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Targeted therapy for metastatic renal cell carcinoma (Protocol)

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
BACKGROUND	1
OBJECTIVES	3
METHODS	3
ACKNOWLEDGEMENTS	8
REFERENCES	8
ADDITIONAL TABLES	10
APPENDICES	11
HISTORY	13
CONTRIBUTIONS OF AUTHORS	13
DECLARATIONS OF INTEREST	14
SOURCES OF SUPPORT	14
NOTES	15

Targeted therapy for metastatic renal cell carcinoma

Fabian Hofmann¹, Lorenzo SO Marconi², Fiona Stewart³, Thomas BL Lam⁴, Axel Bex⁵, Steven E Canfield⁶, Börje Ljungberg⁷

¹Department of Urology, Sunderby Sjukhus, Umeå University, Luleå, Sweden. ²Department of Urology and Renal Transplantation, Centro Hospitalar e Universitario de Coimbra, Coimbra, Portugal. ³c/o Cochrane Incontinence Group, Institute of Health & Society, Newcastle University, Newcastle Upon Tyne, UK. ⁴Academic Urology Unit, University of Aberdeen, Aberdeen, UK. ⁵Division of Surgical Oncology, Department of Urology, The Netherlands Cancer Institute, Amsterdam, Netherlands. ⁶Division of Urology, Department of Surgery, The University of Texas Medical School at Houston, Houston, Texas, USA. ⁷Department of Surgical and Perioperative Sciences, Umeå University, Umeå, Sweden

Contact address: Fabian Hofmann, Department of Urology, Sunderby Sjukhus, Umeå University, Sjukhusvägen 10, Luleå, Norrbotten, 97180, Sweden. fhofmann@trigonum.se.

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To compare the effects of targeted agents in the systemic therapy of people with metastatic renal cell carcinoma.

BACKGROUND

Description of the condition

Renal cell carcinoma (RCC) incidence represents about 2.4% of all invasive cancers and has a projected 2012 population age-standardised mortality rate of 1.8 per hundred thousand worldwide and in the USA (GLOBOCAN 2012; Howlader 2017). Two-thirds of cases occur in men. These figures include both renal cell carcinoma and the less common urothelial carcinoma of the renal pelvis; the latter is biologically related to bladder cancer and not further considered here. Renal cell carcinoma is divided into different pathologic subtypes, of which the clear cell subtype represents about 75% (Srigley 2013). The more uncommon subtypes are collectively referred to by clinicians as non-clear renal cell carcinomas which respond differently to treatment as compared to clear cell renal cell carcinoma (Fernández-Pello 2017). Death from

renal cell carcinoma is usually from metastases, either detected during staging of newly-diagnosed patients (Stage IV) or detected during follow-up after nephrectomy. A minority of patients are diagnosed with locally advanced disease which is too advanced for surgical resection but without metastatic findings. The term 'advanced renal cell carcinoma' has been used by authors to include both metastatic and locally advanced disease that have aspects that require separate consideration.

There has been great interest in finding more effective treatments for metastatic renal cell carcinoma. The search for specific targets for therapy goes back at least to Paul Ehrlich's "magic bullet" over a century ago (Strebhardt 2008). This concept has recently received an enormous boost with the knowledge explosion of molecular targets and the potential for associated therapies that are target-specific and therefore might have greater efficacy with less toxicity (Sawyers 2004). Clinical proof of concept came with the remarkable success of single-agent imatinib for chronic myeloid leukaemia

(Deininger 2005). Here we review the subsequent development of targeted therapy for metastatic renal cell carcinoma.

Description of the intervention

Prior to the development of targeted agents, renal cell carcinoma was one of the most drug-resistant malignancies. Hormonal and cytotoxic chemotherapy agents have not been demonstrated to improve overall survival for this condition, and remissions with those agents occur at a frequency similar to that seen with no therapy or with placebo (Gleave 1998; Oliver 1989). Until the past decade, immunotherapy was the main focus of the search for an effective drug therapy for renal cell carcinoma and was the main initial comparator for targeted therapy; it is the subject of a companion Cochrane Review (Coppin 2004), currently being updated. In summary, classic immunotherapy, e.g. interferon-alpha or interleukin-2, has been associated with very modest survival benefit at best. When targeted agents were first being evaluated, the immunotherapy agent interferon-alpha was considered the standard comparator for first-line therapy of metastatic renal cell carcinoma (Mickisch 2003; Motzer 2002); placebo-controlled trials have been appropriate in the second-line setting. One should be aware that the distribution of prognostic risk strata in clinical trials is changing to a more favourable profile, such that direct comparisons of interventions through head-to-head clinical trials remain essential (Patil 2010).

Molecular pathways with multiple targets that are of particular interest in renal cell carcinoma currently fall into two major groups: angiogenesis (Rini 2005), and intracellular signal transduction pathways (Adjei 2005). The presence of a target may or may not translate into benefit from a targeted agent (Bergsland 2006). Some agents have activity against multiple targets. Classic immunotherapies such as interferon-alpha may have anti-angiogenic activity but are considered a separate class of agent (Coppin 2004). Suitably large randomised controlled trials have a high financial and resource cost, so that selection of agents for Phase III testing requires strategic decision-making (Roberts 2003).

A recent new class of drugs has been introduced into the treatment paradigm of clear cell RCC (Motzer 2015). Immune checkpoint inhibitors are a new type of targeted immunotherapy and have been very successfully tested in other immunogenic tumours such as melanoma.

Since neither multikinase inhibitors nor immune checkpoint inhibitors are necessarily cytotoxic, it is possible that tumour shrinkage may not be a reliable indicator of drug activity (Stadler 2006); for example, objective stabilisation of previously progressive disease might result in extension of overall survival. This is especially the case for immune checkpoint inhibition which in second-line RCC treatment leads to prolonged overall survival without benefit in progression-free survival.

Drug therapy for metastatic renal cell carcinoma has yet to demonstrate curative potential. Improvement in overall survival is the

preferred and definitive outcome of interest to patients, and is a realistic outcome if there is only one effective intervention for an incurable cancer, as was the situation for metastatic renal cell carcinoma at the beginning of the targeted era (i.e. from 2000 onwards). However, when participants with progressive cancer in one arm of a randomised trial are permitted cross-over to the other arm, as is commonly done for ethical reasons or to enhance recruitment, then any survival benefit (or detriment) of the investigational agent might be obscured; the same problem might happen if sequential active therapies are applied. For these reasons and as in other cancer sites, the duration of freedom from cancer progression may be accepted by regulatory bodies as adequate evidence of benefit for drug approval purposes (Johnson 2011). Surrogate endpoints such as progression-free survival should preferably be accompanied by patient-reported outcomes.

How the intervention might work

Molecular analysis of renal cell carcinoma has shown that this cancer is not a homogeneous condition (Hacker 2010; Linehan 2005). A high proportion of sporadic clear cell renal cell carcinomas have biallelic abnormalities of the Von Hippel-Lindau (VHL) tumour-suppressor gene (Young 2009), whereas other subtypes do not. Absence of the active VHL gene produces results in unregulated activation of the hypoxia-inducible system and accumulation of growth factors such as vascular endothelial growth factor (VEGF). In subtypes such as papillary and chromophobe RCC other pathways such as MET proto-oncogene (MET) and tuberous sclerosis (TSC) alterations have been identified through investigation of hereditary and sporadic forms. Therefore the mainstays of first-line therapy until now are multikinase inhibitors targeting predominantly the VEGF-receptor kinases but other targets are included to various degrees, such as MET, AXL receptor tyrosine kinase (AXL), platelet derived growth factor receptor (PDGFR) and epidermal growth factor receptor (EGFR). Immune checkpoint inhibitors targeting the programmed death-ligand (PD-L1) or its receptor (PD-1) have been tested successfully in second- and third-line treatments after failure of one or two lines of VEGFR-targeting therapies (Motzer 2015). These drugs counteract the tumour-driven inhibition of T-cell receptor-mediated activation of IL-2 production and T-cell proliferation which leads to a successful anti-tumour T-cell mediated immune activity. Currently, these drugs are tested in first-line trials in combination with either multikinase inhibitors or other monoclonal antibodies targeting circulating VEGF or anti-CTLA4 against the current first-line monotherapy with VEGFR-targeted therapies. With more treatment options being approved and investigated, it will be necessary to distinguish the impact of therapy on different molecularly-defined tumour types as well as on tumours which have been treated with previous lines of therapy to better select patients for a given drug based on their predicted outcome. Although available, the necessary technology is not yet used in clinical routine. The molec-

ular complexities of both the disease (renal cell carcinoma) and the treatment (targeted therapy) are resulting in a rapidly-evolving and exciting phase in the history of the treatment of metastatic disease. According to [Uzzo 2003](#), “an understanding of the basic biology of renal cell carcinoma is more advanced than that of any other solid malignancy”. Further molecular subclassification within clear cell renal cell carcinoma may well become feasible ([Kaelin 2008](#)).

Why it is important to do this review

The topic of this review is now the main systemic therapy of an important type of malignancy, metastatic renal cell carcinoma, for which the therapy has changed greatly over the past decade and continues to be a strong focus of development of new agents and comparative studies. This review is needed to provide an objective and up-to-date resource for researchers, clinicians and consumers. This will be an update of a Cochrane review first published in 2008 and previously updated in 2011 ([Coppin 2008](#); [Coppin 2011](#)). Since the last date of full literature search, a number of additional studies have been published and there is an evolving shift to using previously validated targeted agents as the comparator rather than placebo, quasi-placebo such as hormone therapy, or immunotherapy such as interferon-alpha. There is also increasing emphasis on second-line therapy now that targeted agents are established for first-line therapy of metastatic renal cell carcinoma. In addition, new agents such as immune checkpoint inhibitors are increasingly being compared against first-line standard therapies ([Kuusk 2017](#)). This updated protocol reflects a restriction of scope in order to focus on metastatic renal cell carcinoma within the broader category of ‘advanced disease’ that additionally included locally-advanced cancers without metastases. The main reason for this change of scope is because the management of locally-advanced disease may include both systemic and surgical interventions, and therefore the complex interaction between the two modalities as well as additional outcomes such as resectability and local control rates. Other reasons include lack of criteria for inoperability that include both cancer and patient factors, and the possibility that drug response to the primary tumour might be different from the response of its metastases. This review also now reflects the development of a collaboration between the previous Cochrane Review authorship and the Renal Cell Carcinoma Guideline Panel of the European Association of Urology (EAU panel). Preliminary discussions with the EAU panel representative Thomas Lam demonstrated a high level of overlap between the protocols of the two groups. This protocol is designed to minimise residual differences.

OBJECTIVES

To compare the effects of targeted agents in the systemic therapy of people with metastatic renal cell carcinoma.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials, including randomised discontinuation trials in which treatment was stopped early because of obvious benefits or harms ([Stadler 2005](#)). Quasi-randomised trials such as alternate allocation are eligible for consideration. We will exclude randomised Phase I trials as well as cross-over trials, cluster-randomised trials or trials of factorial design.

Types of participants

Participants are eligible: if older than 18 years of age; have metastatic renal cell carcinoma which is histologically or pathologically verified at presentation or relapse; have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2 or equivalent. Participants who are evaluated in second- or later lines therapy must have had at least one prior systemic treatment. For individuals who are analysed in first-line therapy no prior systemic treatment is allowed.

Exclusion criteria are: the presence of symptomatic brain metastases; a life expectancy of less than 12 weeks; a serious acute or chronic illness or recent history of cardiac event.

Studies which allow solid tumours other than renal cell carcinoma will be eligible only if participants with renal cell carcinoma are stratified and reported separately from other tumour types.

Diagnosis should be reported using the standard criteria (e.g. TNM-classification) valid at the time that the trial began.

All histologic subtypes of renal cell carcinoma are eligible. We will document individuals with clear cell and non-clear cell subtypes, and will analyse them separately if data are available.

We will exclude studies for analysis of oncological outcomes that are designed for or include more than 20% of participants without metastases, i.e. locally-advanced disease or unfit for nephrectomy. However, we will include evaluation of adverse events if reported.

Types of interventions

Agents with known or presumed molecular targets must have been part of the therapeutic regimen of at least one study arm. Non-specific agents considered previously are no longer eligible, as they are of historic interest only, including ABT-510, AE-941, and carboxyaminoimidazole. We exclude classic immunotherapy agents, including recombinant cytokines and their predecessors, from this definition of targeted therapy, but they may have been included as part of the regimen in any study arm. See [Table 1](#) for a list of targeted agents to be sought, although we may identify additional

targeted agents during the search process. Studies in which maintenance therapy by a targeted agent was the randomised variable will be eligible. Studies of dose or schedule of a targeted agent will be eligible. There are no eligibility restrictions on drug route, dose, or schedule.

We plan to investigate the following comparisons of target agents listed in [Table 1](#) versus control/comparator:

Intervention

- Targeted agent (a)
- Targeted agent in combination with another targeted agent (b)
- Targeted agent in combination with cytokine (c)
- Sequencing of targeted agent A and targeted agent B (d)

Comparator

- Placebo compared to (a), (b) or (c)
- Targeted agent other than intervention compared to (a), (b) or (c)
 - Targeted agent other than intervention in combination with cytokine or hormonal treatment or both, compared to (a), (b) or (c)
 - Cytokine(s) compared to (a), (b) or (c)
 - Hormonal treatment compared to (a), (b) or (c)
 - Same agent as intervention in different dose or schedule or both, compared to (a), (b) or (c)
 - Reversed sequence of targeted agent A and targeted agent B compared to (d)

We will distinguish comparisons in first-line therapy from comparisons in subsequent therapy.

We will consider whether the control arm has been validated by a prior randomised study.

Minimum duration of intervention

Minimum duration of intervention will be four weeks.

Minimum duration of follow-up

Minimum duration of follow-up will be 12 weeks. We will evaluate extended follow-up periods after the trial termination only for adverse events.

Specific exclusion criteria

Studies observing neoadjuvant or adjuvant treatment or both with targeted agents are not eligible for analysis.

Types of outcome measures

To be eligible for inclusion, studies must assess at least one efficacy outcome by allocation arm. We will examine 'quality of life' outcomes where available, with reference to minimally important clinical differences where known for the assessment tools used. We will evaluate adverse events in all studies. The selection of outcomes for GRADE assessment was based on discussions amongst an expert panel (EAU panel) and authors of the previous review, and reflects outcomes of importance to stakeholders including patients, clinicians and healthcare providers.

Primary outcomes

1. Progression-free survival
2. Overall survival
3. Serious adverse events (Grade 3 or 4)

Secondary outcomes

1. Health-related quality of life
2. Response rate
3. Minor adverse events (Grade 1 or 2)

Method and timing of outcome measurement

- Progression-free survival: time from date of randomisation to date of clinical or radiological progression
- Overall survival: length of time from date of randomisation that participants are still alive
- Serious adverse events: all adverse events measured at any time that needed surgical, endoscopic, radiological or anaesthesiological intervention, as well as any life-threatening complications after participants received at least one treatment in intervention or comparator groups, classified by Common Terminology Criteria for Adverse Events (CTCAE 2009)
 - Quality of life: evaluated by validated instrument such as Supplementary Quality of Life Questionnaire (SQLQ), Functional Assessment of Cancer Therapy (FACT), Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI) or European Quality of Life-5 Dimensions (EQ-5D). If they are available we will focus on data of pre- to post-treatment evaluation
 - Response rate: measured by RECIST or modified RECIST criteria (Eisenhauer 2009)
 - Minor adverse events: all adverse events measured at any time that could be managed by observation or pharmacological treatment after participants received at least one treatment in intervention or comparator groups, classified by Common Terminology Criteria for Adverse Events (CTCAE)

If time-to-event data are not available, we will try to assess the number of events per total for dichotomised outcomes at certain time points (e.g. at one, two, three, four, five years, or at the longest reported follow-up).

Main outcomes for 'Summary of findings' table

1. Progression-free survival
2. Overall survival
3. Health-related quality of life
4. Serious adverse events

Search methods for identification of studies

Overall time frame: we will conduct a new search from 1 January 2000 (we found no earlier studies in the previous version of this review) to an agreed cut-off date to be at least one month before the date of search, to allow for indexing. We may assemble duplicate searches from separate time segments, for example the EAU panel has completed a search to 30 November 2012 using the algorithm in [Appendix 1](#), and the Canadian authors have searched to 30 June 2010 as described previously ([Coppin 2008](#), electronically updated to 30 June 2011 for [Coppin 2011](#)).

There will be no restriction by language or publication status.

Electronic searches

We will search the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, and LILACS databases, as well as trial registers [ClinicalTrials.gov](#) and the WHO International Clinical Trials Registry Platform ([apps.who.int/trialsearch/](#)).

We will use [Review Manager 2014](#) as reference management software to initially remove duplicate records.

Searching other resources

1. Handsearching of abstracts in the proceedings of the annual meetings of the American Urological Association, the European Cancer Conference (ECCO), the European Society of Medical Oncology (ESMO), and the American Society of Clinical Oncology (ASCO), all from 2000 to current year; and the annual ASCO genitourinary meeting (2008 to current year)
2. Handsearching of the bibliographies of included primary studies and of recent systematic reviews of targeted therapies for metastatic or advanced renal cell carcinoma
3. We will consult clinical experts (EAU panel) to identify additional potentially important or seminal studies which may have been missed by the electronic searches
4. We will try to identify other potentially eligible trials or ancillary publications by searching the reference lists of included trials, systematic reviews, meta-analyses and health technology assessment reports. We will also contact authors of included trials to identify any additional information on the retrieved trials, and to determine if further trials exist that we may have missed. We will also search databases from regulatory agencies (European Medicines Agency (EMA) and US Food and Drugs Administration (FDA)) ([Hart 2012](#); [Schroll 2015](#)).

Data collection and analysis

Selection of studies

Inclusion and exclusion of studies

Two review authors (FH, LM) will independently conduct searches, assess full-text records, and independently map records to potentially eligible studies for inclusion/exclusion. We will resolve discrepancies by discussion or by arbitration from additional review authors (TL, AB) as necessary.

We will refer to trials by their eight-digit NCT number where known. We will classify studies as included studies, excluded studies, studies awaiting classification, or ongoing studies, in accordance with the criteria for each provided in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011a](#)). We will document the search process in a study flow diagram.

We will document reasons for exclusion of identified studies not suitable for this review in a 'Characteristics of excluded studies' table. We will include studies that do not report on our primary or secondary outcomes, and will consider them for qualitative analysis.

Data extraction and management

Two review authors (FH, LM) will independently extract data using an agreed template, which we will pilot, and will resolve any discrepancies by consensus, with recourse to a third review author (TL, AB) if needed. We will construct a master database of consensus-agreed data, which will be available to all review authors. Data extraction fields for each study will include:

1. Basic study design features (e.g. parallel-group randomised trial);
2. Dates when the study was conducted;
3. Study setting;
4. Participant eligibility criteria and actual accrual by arm for age, race, gender, performance status, prior nephrectomy, prior systemic therapy, histologic subtype, and prognostic risk method and distribution;
5. Stratification parameters, if any;
6. Detailed interventions, including criteria for discontinuing therapy and cross-over to the investigational arm;
7. The sample size for each included study and for each intervention/comparator group;
8. Details (such as dose, route, frequency, duration, as applicable) of each intervention/comparator relevant to this review;
9. Treatment delivery evaluation such as time point of administration and masking of treatment in interventional/comparator groups;

10. Frequency and protocol status (e.g. planned versus later protocol modification) of cross-over to the investigational arm;
11. Details of the outcome definition for outcomes relevant to this review that were assessed in each study, method of outcome measurement for each outcome, timing of outcome measurement for each outcome, subgroups relevant to this review that were assessed for each outcome;
12. Reported statistics for each time-dependent outcome, i.e. hazard ratio and two-sided log rank P value;
13. All adverse events reported by allocation;
14. Study funding sources;
15. Details of declarations of interest among the trialists.

We will attempt to contact study investigators to obtain missing data for primary outcomes for eligible studies.

We will report identified studies in a 'Characteristics of included studies' table. If an eligible trial is still ongoing and not reporting any results, we will collect information in a 'Characteristics of ongoing studies' table.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents or multiple reports of a primary trial, we will maximise the information yield by collating all available data and will use the most complete data set aggregated across all known publications. We will list duplicate publications, companion documents, multiple reports of a primary trial and trial documents of included trials (such as trial registry information) as secondary references under the study ID of the included trial. We will also list duplicate publications, companion documents, multiple reports of a trial and trial documents of excluded trials (such as trial registry information) as secondary references under the study ID of the excluded trial.

Data from clinical trial registers

In cases where data of included trials are available as study results in clinical trial registers such as ClinicalTrials.gov or similar resources, we will make full use of this information and extract data. If there is also a full publication of the trial, we will collate and critically appraise all available data. If an included trial is marked as a completed study in a clinical trial register but no additional information (study results, publication or both) is available, we will add this trial to the table 'Characteristics of studies awaiting classification'.

Assessment of risk of bias in included studies

Two review authors (FH, LM) will independently use the latest version of the Cochrane tool for assessing risk of bias to construct a 'Risk of bias' table for each study, resolving discrepancies by consensus ([Higgins 2011b](#)). If needed, a third review author (TL,

AB) will be involved. We will rate the following domains at low, high, or unclear risk of bias:

1. Random sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective reporting
7. Other potential sources of bias.

We will assess the 'Risk of bias' domains 'blinding of participants and personnel', 'blinding of outcome assessment', and 'incomplete outcome data' on an outcome-specific basis, grouping subjective outcomes and objective outcomes for the blinding domains, and grouping outcomes according to similar completeness of data for the outcome-specific assessments of 'incomplete outcome data'. We regard all outcomes as susceptible to performance bias, whereas all outcomes except for 'overall survival' are regarded as susceptible to detection bias. We will summarise the risk of bias across domains for each outcome in each included study. We will assess the risk of attrition bias in three combined outcome groups that are defined by oncological, adverse event and quality-of-life outcomes. We will present our judgements in a 'Risk of bias' graph and a 'Risk of bias' summary figure.

Measures of treatment effect

When at least two included trials are available for a comparison and a given outcome, we will try to express dichotomous data as a risk ratio (RR) or odds ratio (OR) with 95% confidence interval (CI). For continuous outcomes measured on the same scale we will estimate the intervention effect using the mean difference (MD) with 95% CI. For continuous outcomes measuring the same underlying concept but using different measurement scales, we will calculate the standardised mean difference (SMD). We will express time-to-event data as a hazard ratio with a 95% CI. We will use RevMan software ([Review Manager 2014](#)) for the 'Risk of bias' analysis.

Unit of analysis issues

If more than one comparison from the same trial is eligible for inclusion in the same meta-analysis, we will either combine groups to create a single pair-wise comparison or appropriately reduce the sample size so that the same participants do not contribute to multiple comparisons (splitting the 'shared' group into two or more groups). While the latter approach offers some solution to adjusting the precision of the comparison, it does not account for correlation arising from the same set of participants being in multiple comparisons ([Higgins 2011a](#)).

Dealing with missing data

We plan to perform intention-to-treat analyses where data are available; however, we will not impute missing data and will otherwise perform an available-case analysis. We will include studies that combine outcomes from metastatic and locally-advanced disease in tabulations if the locally-advanced subgroup is documented as less than 20% of the total participants randomised; we will consider other studies separately.

If possible, we will obtain missing data from the authors of the included trials. We will carefully evaluate important numerical data such as screened, randomly-assigned participants as well as intention-to-treat, and as-treated and per-protocol populations. We will investigate attrition rates (e.g. dropouts, losses to follow-up, withdrawals), and we will critically appraise issues concerning missing data and use of imputation methods (e.g. last observation carried forward).

Assessment of heterogeneity

In the event of substantial clinical or methodological heterogeneity, we will not report trial results as the pooled effect estimate in a meta-analysis. We will identify heterogeneity (inconsistency) by visually inspecting the forest plots and by using a standard Chi^2 test with a significance level of $\alpha = 0.1$. In view of the low power of this test, we will also consider the I^2 statistic, which quantifies inconsistency across trials, to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003). We will interpret the I^2 statistic as follows:

- 0% to 40%, may not be important
- 30% to 60%, represents moderate heterogeneity
- 50% to 90%, represents substantial heterogeneity
- 75% to 100%, represents considerable heterogeneity

When we find heterogeneity, we will attempt to determine possible reasons for it by examining individual study and subgroup characteristics.

Assessment of reporting biases

If we include 10 or more trials that investigate a particular outcome, we will use funnel plots to assess small-trial effects. Several explanations may account for funnel plot asymmetry, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials) and publication bias, so we will be cautious in our interpretation of results (Sterne 2011).

Data synthesis

We plan to undertake (or display) a meta-analysis only if we judge participants, interventions, comparisons and outcomes to be sufficiently similar to ensure an answer that is clinically meaningful. Unless good evidence shows homogeneous effects across trials, we

will primarily summarise low risk of bias data using a random-effects model (Wood 2008). We will interpret random-effects meta-analyses with due consideration for the whole distribution of effects, ideally by presenting a prediction interval (Higgins 2009). This specifies a predicted range for the true treatment effect in an individual trial (Riley 2011). For rare events such as event rates below 1% we will use the Peto odds ratio, provided that there is no substantial imbalance between intervention and comparator group sizes, and that intervention effects are not exceptionally large. We will also perform statistical analyses according to the statistical guidelines presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

Quality of evidence

We will present the overall quality of the evidence for each outcome according to the GRADE approach, which takes into account five criteria not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias), but also to external validity, such as directness of results (Guyatt 2008). For each comparison, two review authors (FH, LM) will independently rate the quality of evidence for each outcome as 'high', 'moderate', 'low', or 'very low', using GRADEpro GDT. We will resolve any discrepancies by consensus, or, if needed by recourse to a third review author (TL, AB). For each comparison, we will present a summary of the evidence for the main outcomes in a 'Summary of findings' table, which provides key information about the best estimate of the magnitude of the effect in relative terms and absolute differences for each relevant comparison of alternative management strategies; numbers of participants and studies addressing each important outcome; and the rating of the overall confidence in effect estimates for each outcome (Guyatt 2011; Schünemann 2011).

Statistical analysis

We anticipate analysis of four types of outcomes: categorical outcomes, such as tumour remission; single time-dependant outcomes, such as overall survival; quality-of-life surveys; and toxicity tables. Of these, methods for analysis of dichotomous outcomes are fully covered by standard Cochrane procedures (Deeks 2011). We will consider multidimensional quality-of-life and toxicity outcomes individually. Time-dependent outcomes are potentially problematic. Where only a single study is available for a comparison, we will accept any standard statistical analysis, such as the log-rank test used by the author, but we will prefer the hazard ratio and log-rank testing. For meta-analysis of multiple studies of the same type, we will use extraction of a dichotomous endpoint such as survival at one year from randomisation (see also *Measures of treatment effect* above).

Subgroup analysis and investigation of heterogeneity

We plan to perform a subgroup analysis if data are available for the following:

1. Nephrectomy done or not done prior to treatment
2. ECOG performance status (0,1 or 2)
3. Clear cell versus non-clear cell renal cell carcinoma

Sensitivity analysis

We plan sensitivity analysis for studies that are at a high risk of bias for sequence generation, allocation concealment and blinding versus studies at low risk of bias. We will conduct a separate meta-analysis for validation of results studies at low risk of bias only.

Summary of findings table

We will create the 'Summary of findings' table based on the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* by means of RevMan's tables editor ([Review Manager 2014](#)). We will include an appendix entitled 'A checklist to aid consistency and reproducibility of GRADE assessments', developed by [Meader 2014](#) to help with standardisation of the 'Summary of findings' tables ([Higgins 2011a](#)). Alternatively, we will

use the GRADEpro Guideline Development Tool (GDT) software ([GRADEpro GDT](#)) and present evidence profile tables as an appendix. We will present results for the outcomes as described in the [Types of outcome measures](#) section. If meta-analysis is not possible, we will present the results in a narrative format in the 'Summary of findings' table. We will justify all decisions to downgrade the quality of trials using footnotes, and we will make comments to aid the reader's understanding of the Cochrane Review where necessary.

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* Indicates the major publication for the study

ADDITIONAL TABLES

Table 1. Individual targeted agents to be searched

Axitinib
Bevacizumab
Dovitinib
Erlotinib
Everolimus
Lapatinib
Pazopanib
Sorafenib
Sunitinib
Temsirolimus
Thalidomide
Tivozanib
Other agents identified during search

APPENDICES

Appendix I. EAU panel search strategy

Courtesy of the EAU panel, reproduced with permission.

MEDLINE 1946 to November week 3 2014

MEDLINE-In-Process and other Non-Indexed Citations December 11 2014

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomi?ed.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8

10. Carcinoma, Renal Cell/
11. (metastas* adj5 ((kidney or renal) adj2 (cancer* or carcinoma* or neoplasm* or tum?or* or mass*))).tw.
12. or/10-11
13. Chemotherapy, Cancer, Regional Perfusion/
14. thalidomide/
15. exp Antineoplastic Protocols/
16. exp Antineoplastic agents/
17. (axitinib or bevacizumab or dovitinib or erlotinib or everolimus or lapatinib or pazopanib or sorafenib or sunitinib or temsirolimus or thalidomide or tivozanib).tw.
18. antineoplastic\$.tw.
19. or/13-18
20. 9 and 12 and 19
21. (conference or letter or editorial or comment*).pt.
22. exp animals/ not humans/
23. 20 not (21 or 22)
24. Limit 23 to yr="2001 -Current"

Embase 1974 to 2014 December 22

1. kidney carcinoma/
2. (metastas* adj5 ((kidney or renal) adj2 (cancer* or carcinoma* or neoplasm* or tum?or* or mass*))).tw.
3. 1 or 2
4. exp cancer chemotherapy/
5. exp Antineoplastic agent/
6. sorafenib/
7. sunitinib/
8. bevacizumab/
9. axitinib/
10. pazopanib/
11. everolimus/
12. temsirolimus/
13. interferon/
14. interleukin 2/
15. dovitinib/
16. tivozanib/
17. erlotinib/
18. (axitinib or bevacizumab or dovitinib or erlotinib or everolimus or lapatinib or pazopanib or sorafenib or sunitinib or temsirolimus or thalidomide or tivozanib).tw.
19. antineoplastic\$.tw.
20. or/4-19
21. random.tw.
22. placebo.mp.
23. double-blind.tw.
24. or/21-23
25. 3 and 20 and 24
26. exp animals/ not humans/
27. (conference or letter or editorial or comment*).pt.
28. 25 not (26 or 27)
29. Limit 28 to yr="2001 -Current"

Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials
(The Cochrane Library, Issue 11 of 12, November 2014) www.thecochranelibrary.com

1. MeSH descriptor Carcinoma, Renal Cell, this term only
2. (metastas* near/5 ((kidney or renal) near/2 (cancer* or carcinoma* or neoplasm* or tum?or* or mass*)))
3. (#1 OR #2)
4. (#3), from 2001 to current

LILACS

December 2014

<http://lilacs.bvsalud.org/en/>

(tw:(renal cell carcinoma or renal cancer or renal tumour\$ or renal tumor\$ or renal carcinoma\$ or renal neoplasm\$ or renal mass\$ or kidney cancer or kidney tumour\$ or kidney tumor\$ or kidney neoplasm\$ or kidney mass\$)) OR (mh:(kidney neoplasms))

Type of study: Controlled Clinical Trial

Clinicaltrials.gov: <http://clinicaltrials.gov>

Basic search: metastatic renal cell carcinoma

WHO International Clinical Trials Registry Platform <http://apps.who.int/>

Basic search: metastatic renal cell carcinoma

HISTORY

Protocol first published: Issue 9, 2017

Date	Event	Description
1 July 2010	New search has been performed	Complete update with additional studies, revised analysis, risk of bias assessment, and revised conclusions. Specifically, the search has been updated from the end of 2007 to June 2010, with 5 new eligible studies identified; analyses are now based on the nature of the control arm. Targeted agents have now been validated as first and second-line therapy choices for patients with advanced renal cancers of the clear cell subtype
8 April 2010	New search has been performed	Converted to new review format.
14 January 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Contributions to the protocol

This protocol version concept and design: Fabian Hofmann, Thomas BL Lam, Axel Bex
Submitted and revised protocol: final approval by all authors.

Contributions to the review

To be decided after discussion and consensus

DECLARATIONS OF INTEREST

F Hofmann: declares the following relevant activities outside the submitted work: employed as a urologist, serves as guideline associate of European Association of Urology Renal Cell Carcinoma Guideline Panel and reports receiving no compensation for panel membership.

LSO Marconi: none known

F Steward: none known.

C Coppin: declares the following activities related to the submitted work: received support from BC Cancer Agency for travel to a meeting for the study or other purposes. Declares the following relevant activities outside the submitted work: received payment for contracted employment from BC Cancer Agency, a Canadian provincial government cancer agency with treatment policies that include agents described in the submitted work.

TBL Lam: declares the following relevant activity outside the submitted work: serves as member of European Association of Urology Renal Cell Carcinoma Guideline Panel and reports receiving no compensation for panel membership.

A Bex: declares the following relevant activities outside the submitted work: received consultancy support paid to his institution by Pfizer and Novartis for taking part in advisory boards; received payment from Pfizer and GlaxoSmithKline for presenting at Pfizer and GlaxoSmithKline sponsored symposia and conferences. These companies produce interventions (mTOR inhibitors and VEGF-targeting therapy) that are researched in the review. Dr. Bex also reports that he is principal investigator of the European Organisation for Research and Treatment of Cancer (EORTC) SURTIME trial, a randomised phase III trial comparing immediate versus deferred nephrectomy in patients with synchronous metastatic renal cell carcinoma, which is in part supported by a grant from Pfizer to the sponsor (EORTC).

SE Canfield: none known.

B Ljungberg: declares the following relevant activities outside the submitted work: received support from Pfizer, GlaxoSmithKline and Novartis for advisory board attendance, most recently in early 2013, on the topic of renal cell carcinoma. Most interventions assessed in the review are produced by these companies.

SOURCES OF SUPPORT

Internal sources

- BC Cancer Agency, Canada.

External sources

- No sources of support supplied

NOTES

This is a protocol for a Cochrane Review that will serve to update and replace the existing Cochrane Review entitled, “Targeted therapy for advanced renal cell carcinoma” ([Coppin 2008](#)).

We have based parts of the Methods section of this Cochrane protocol on a standard template established by the CMED Group.