**Table S1: EMBASE Search Strategy (Embase 1974 to 2023 February 10)**

|  |  |  |
| --- | --- | --- |
| **#** | **Searches** | **Results** |
| 1 | exp renal cell carcinoma/ | 32669 |
| 2 | ((renal or kidney) adj2 cell adj2 (carcinoma or cancer\* or cancer\* or malignan\* or tumor\* or tumour\* or neoplas\* or adenocarcinoma\*)).ti,ab. | 71377 |
| 3 | (renal cell cancer or RCC or renal cell carcinoma or kidney cancer or kidney carcinoma).ti,ab. | 78474 |
| 4 | or/1-3 | 93138 |
| 5 | (von Hippel Lindau Disease or Familial Cerebello-Retinal Angiomatosis or Angiomatoses, Familial Cerebello-Retinal or Angiomatosis, Familial Cerebello-Retinal or Cerebello-Retinal Angiomatoses, Familial or Cerebello-Retinal Angiomatosis, Familial or Familial Cerebello Retinal Angiomatosis or Familial Cerebello-Retinal Angiomatoses or Hippel-Lindau Disease or Hippel Lindau Disease or VHL Syndrome or VHL Syndromes or Lindau's Disease or Lindau's Diseases or Lindaus Disease or von Hippel-Lindau Syndrome or von Hippel Lindau Syndrome or Angiomatosis Retinae or Cerebelloretinal Angiomatosis, Familial or Angiomatoses, Familial Cerebelloretinal or Angiomatosis, Familial Cerebelloretinal or Cerebelloretinal Angiomatoses, Familial or Familial Cerebelloretinal Angiomatoses or Familial Cerebelloretinal Angiomatosis or Lindau Disease).mp. | 6341 |
| 6 | 4 and 5 | 5833 |
| 7 | Clinical Trial/ | 1065024 |
| 8 | Randomized Controlled Trial/ | 761178 |
| 9 | controlled clinical trial/ | 467929 |
| 10 | multicenter study/ | 361183 |
| 11 | Phase 3 clinical trial/ | 67062 |
| 12 | Phase 4 clinical trial/ | 5232 |
| 13 | exp RANDOMIZATION/ | 98090 |
| 14 | Single Blind Procedure/ | 49948 |
| 15 | Double Blind Procedure/ | 205182 |
| 16 | Crossover Procedure/ | 73344 |
| 17 | PLACEBO/ | 396172 |
| 18 | randomi?ed controlled trial$.tw. | 311641 |
| 19 | rct.tw. | 51375 |
| 20 | (random$ adj2 allocat$).tw. | 53047 |
| 21 | single blind$.tw. | 30743 |
| 22 | double blind$.tw. | 240314 |
| 23 | ((treble or triple) adj blind$).tw. | 1761 |
| 24 | placebo$.tw. | 359809 |
| 25 | Prospective Study/ | 837673 |
| 26 | or/7-25 | 2860632 |
| 27 | Case Study/ | 95237 |
| 28 | case report.tw. | 516684 |
| 29 | abstract report/ or letter/ | 1293133 |
| 30 | Editorial.pt. | 754788 |
| 31 | Note.pt. | 916776 |
| 32 | or/27-31 | 3556000 |
| 33 | 26 not 32 | 2722719 |
| 34 | Clinical study/ | 161350 |
| 35 | case control study/ | 198682 |
| 36 | Family study/ | 25702 |
| 37 | Longitudinal study/ | 184643 |
| 38 | Retrospective study/ | 1383093 |
| 39 | Prospective study/ | 837673 |
| 40 | Cohort analysis/ | 965401 |
| 41 | (Cohort adj (study or studies)).mp. | 451310 |
| 42 | (Case control adj (study or studies)).tw. | 163716 |
| 43 | (follow up adj (study or studies)).tw. | 72231 |
| 44 | (observational adj (study or studies)).tw. | 240852 |
| 45 | (epidemiologic$ adj (study or studies)).tw. | 120346 |
| 46 | (cross sectional adj (study or studies)).tw. | 320093 |
| 47 | or/34-46 | 3739559 |
| 48 | 33 or 47 | 5408531 |
| 49 | 6 and 48 | 707 |

Table S2: MEDLINE Search Strategy Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to February 10, 2023

|  |  |  |
| --- | --- | --- |
| **#** | **Searches** | **Results** |
| 1 | exp renal cell carcinoma/ | 39277 |
| 2 | ((renal or kidney) adj2 cell adj2 (carcinoma or cancer\* or cancer\* or malignan\* or tumor\* or tumour\* or neoplas\* or adenocarcinoma\*)).ti,ab. | 47550 |
| 3 | (renal cell cancer or RCC or renal cell carcinoma or kidney cancer or kidney carcinoma).ti,ab. | 50937 |
| 4 | or/1-3 | 60423 |
| 5 | (von Hippel Lindau Disease or Familial Cerebello-Retinal Angiomatosis or Angiomatoses, Familial Cerebello-Retinal or Angiomatosis, Familial Cerebello-Retinal or Cerebello-Retinal Angiomatoses, Familial or Cerebello-Retinal Angiomatosis, Familial or Familial Cerebello Retinal Angiomatosis or Familial Cerebello-Retinal Angiomatoses or Hippel-Lindau Disease or Hippel Lindau Disease or VHL Syndrome or VHL Syndromes or Lindau's Disease or Lindau's Diseases or Lindaus Disease or von Hippel-Lindau Syndrome or von Hippel Lindau Syndrome or Angiomatosis Retinae or Cerebelloretinal Angiomatosis, Familial or Angiomatoses, Familial Cerebelloretinal or Angiomatosis, Familial Cerebelloretinal or Cerebelloretinal Angiomatoses, Familial or Familial Cerebelloretinal Angiomatoses or Familial Cerebelloretinal Angiomatosis or Lindau Disease).mp. | 4026 |
| 6 | 4 and 5 | 1057 |
| 7 | Randomized Controlled Trials as Topic/ | 160370 |
| 8 | randomized controlled trial/ | 586563 |
| 9 | Random Allocation/ | 106907 |
| 10 | Double Blind Method/ | 174274 |
| 11 | Single Blind Method/ | 32486 |
| 12 | clinical trial/ | 537062 |
| 13 | clinical trial, phase i.pt. | 24612 |
| 14 | clinical trial, phase ii.pt. | 39275 |
| 15 | clinical trial, phase iii.pt. | 21395 |
| 16 | clinical trial, phase iv.pt. | 2381 |
| 17 | controlled clinical trial.pt. | 95186 |
| 18 | randomized controlled trial.pt. | 586563 |
| 19 | multicenter study.pt. | 330598 |
| 20 | clinical trial.pt. | 537062 |
| 21 | exp Clinical Trials as topic/ | 380382 |
| 22 | or/7-21 | 1550215 |
| 23 | (clinical adj trial$).tw. | 463458 |
| 24 | ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. | 194579 |
| 25 | placebos/ | 35925 |
| 26 | placebo$.tw. | 243149 |
| 27 | randomly allocated.tw. | 35439 |
| 28 | (allocated adj2 random$).tw. | 39144 |
| 29 | or/23-28 | 763327 |
| 30 | 22 or 29 | 1883695 |
| 31 | case report.tw. | 384881 |
| 32 | letter/ | 1207271 |
| 33 | historical article/ | 369044 |
| 34 | or/31-33 | 1942607 |
| 35 | 30 not 34 | 1841583 |
| 36 | Epidemiologic studies/ | 9255 |
| 37 | exp case control studies/ | 1390411 |
| 38 | exp cohort studies/ | 2446313 |
| 39 | Case control.tw. | 150265 |
| 40 | (cohort adj (study or studies)).tw. | 300787 |
| 41 | Cohort analy$.tw. | 11252 |
| 42 | (Follow up adj (study or studies)).tw. | 55393 |
| 43 | (observational adj (study or studies)).tw. | 153670 |
| 44 | Longitudinal.tw. | 311627 |
| 45 | Retrospective.tw. | 714986 |
| 46 | Cross sectional.tw. | 490540 |
| 47 | Cross-sectional studies/ | 456145 |
| 48 | or/36-47 | 3699082 |
| 49 | 35 or 48 | 5049175 |
| 50 | 6 and 49 | 163 |

Table S3: Cochrane Central Register of Controlled Trials Search Strategy (EBM Reviews - Cochrane Central Register of Controlled Trials January 2023)

|  |  |  |
| --- | --- | --- |
| **#** | **Searches** | **Results** |
| 1 | exp Carcinoma, Renal Cell/ | 1286 |
| 2 | ((renal or kidney) adj2 cell adj2 (carcinoma or cancer\* or cancer\* or malignan\* or tumor\* or tumour\* or neoplas\* or adenocarcinoma\*)).ti,ab. | 2903 |
| 3 | (renal cell cancer or RCC or renal cell carcinoma or kidney cancer or kidney carcinoma).ti,ab. | 3314 |
| 4 | or/1-3 | 3499 |
| 5 | (von Hippel Lindau Disease or Familial Cerebello-Retinal Angiomatosis or Angiomatoses, Familial Cerebello-Retinal or Angiomatosis, Familial Cerebello-Retinal or Cerebello-Retinal Angiomatoses, Familial or Cerebello-Retinal Angiomatosis, Familial or Familial Cerebello Retinal Angiomatosis or Familial Cerebello-Retinal Angiomatoses or Hippel-Lindau Disease or Hippel Lindau Disease or VHL Syndrome or VHL Syndromes or Lindau's Disease or Lindau's Diseases or Lindaus Disease or von Hippel-Lindau Syndrome or von Hippel Lindau Syndrome or Angiomatosis Retinae or Cerebelloretinal Angiomatosis, Familial or Angiomatoses, Familial Cerebelloretinal or Angiomatosis, Familial Cerebelloretinal or Cerebelloretinal Angiomatoses, Familial or Familial Cerebelloretinal Angiomatoses or Familial Cerebelloretinal Angiomatosis or Lindau Disease).mp. | 20 |
| 6 | 4 and 5 | 10 |

**Table S4: PICOTS Criteria for Study Inclusion.**

|  |  |
| --- | --- |
| **Criteria** | **Inclusion/Exclusion** |
| **Population** | Inclusion criteria:   * Patients with VHL-associated RCC that has not metastasized   Exclusion criteria:   * Patients with metastatic disease * Stage IV (M1) |
| **Interventions** | Any surgical or pharmacological intervention studied in the population of interest. |
| **Comparisons** | * With respect to comparative evidence (e.g. randomized controlled trials [RCTs], the following comparators are of interest:   + Placebo or best supportive care   + Any intervention of interest * With respect to non-comparative evidence (e.g. ‘single-arm’ trials, observational cohorts), no comparator treatment is required |
| **Outcomes** | * Objective response rate (ORR) * Duration of response (DOR) * Time to response (TTR) * Time to surgery (TTS) * Overall survival (OS) * Progression-free survival (PFS) * Primary failure or re-intervention rates * Drug related adverse events (AEs) * Grade 3-5 AEs (all, drug related) * Discontinuation due to AE (DAEs) * Serious AEs (SAEs) * Surgical complications |
| **Time** | * Not Applicable |
| **Study design** | * Randomized controlled trials * Controlled clinical trials * Non-randomized clinical trials, including ‘single-arm’ prospective interventional trials * Prospective and retrospective cohort studies, including ‘real-world’ studies |