

Appendices

Appendices to *The moral efficiency of clinical trials in anti-cancer drug development*

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Table of Contents

Appendix A. Database search strategy.....	2
Clinical Search Strategy Generic Embase.....	2
Clinical Search Strategy Generic Medline.....	3
Drug-specific search strategy.....	4
Appendix B. Codebook for extraction.....	6
A. Basic information.....	6
B. Rationale for investigation.....	8
C. Methods.....	8
1. Hypothesis.....	8
2. Design.....	8
3. Treatment.....	9
4. Time.....	9
5. Population.....	10
D. Results.....	10
E. Discussion.....	13
Appendix C. PRISMA diagram (chapter 2).....	14
Appendix D. PRISMA diagram (chapter 3).....	15
Appendix E. PRISMA diagram (chapter 4).....	16
Appendix F. NCCN recommendations (chapter 4).....	17
Appendix G. Software developed for this project.....	18
Drug trial visualiser.....	18
Numbat systematic review manager.....	18

Supplementary data sets in attached files:

Name	Related chapter	Description
Appendix H	1	Per-trial data set for monotherapy and combination
Appendix I	2	Per-trial data set for imatinib, dasatinib and nilotinib
Appendix J	3	Per-trial data set for all drugs (monotherapy)
Appendix K	3	Per-trajectory data set for all drugs (monotherapy)
Appendix L	4	Per-trial data set for all drugs (combination therapy)
Appendix M	4	Per-pairing data set for all drugs (combination therapy)
Appendix N	4	Overall survival HR (combination therapy)
Appendix O	4	Progression-free survival HR (combination therapy)
Appendix P	4	Grade 3-4 SAE (combination therapy)
Appendix Q	4	Grade 5 SAE (combination therapy)

Appendix A. Database search strategy

Clinical Search Strategy Generic Embase

1. exp "randomized controlled trial"/
2. exp "randomized controlled trial (topic)"/
3. exp "controlled clinical trial"/
4. exp "controlled clinical trial (topic)"/
5. exp randomization/
6. double blind procedure/
7. exp placebo/
8. "controlled clinical trial".tw.
9. (random* or RCT\$1 or placebo*).tw.
10. ((singl* or doubl* or trebl* or tripl*) and (mask* or blind* or dumm*)).tw.
11. or/1-10
12. exp clinical trial/
13. "clinical trial".tw.
14. (volunteer or volunteers or open label* or nonrandom* or non random* or quasirandom* or quasi-random*).tw.
15. (longitudinal or prospective).tw.
16. ((follow-up or followup) adj stud*).tw.
17. ((multicenter adj stud*) or (multi-center adj stud*) or (multicentr* adj stud*) or (multi-centr* adj stud*)).tw.
18. ((comparative adj study) or (comparative adj studies)).tw.
19. "head-to-head".tw.
20. (pilot\$1 or feasibility or "Proof of principle").tw.
21. or/12-20
22. 11 or 21
23. (editorial or letter or note).pt.

24. 22 not 23

25. exp Animal/ not (exp Animal/ and Human/)

26. 24 not 25

Clinical Search Strategy Generic Medline

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

1. (controlled clinical trial or randomized controlled trial).pt.

2. exp randomized controlled trials as topic/ or exp controlled clinical trials as topic/ or exp random allocation/ or exp double-blind method/ or exp single-blind method/ or exp placebos/

3. "controlled clinical trial".tw.

4. (random* or RCT\$1 or placebo*).tw.

5. ((singl* or doubl* or trebl* or tripl*) and (mask* or blind* or dumm*)).tw.

6. or/1-5

7. clinical trial.pt.

8. (clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.

9. exp Clinical Trial/

10. exp Clinical Trials as Topic/

11. "clinical trial".tw.

12. (volunteer or volunteers or open label* or nonrandom* or non random* or quasirandom* or quasi-random*).tw.

13. exp Longitudinal Studies/ or exp Prospective Studies/ or exp Follow-Up Studies/

14. (longitudinal or prospective).tw.

15. ((follow-up or followup) adj stud*).tw.

16. Multicenter Study.pt.

17. exp Multicenter Study/ or exp Multicenter Studies as Topic/

18. ((multicenter adj stud*) or (multi-center adj stud*) or (multicentr* adj stud*) or (multi-centr* adj stud*)).tw.

19. Comparative Study.pt.

20. ((comparative adj study) or (comparative adj studies)).tw.
21. "head-to-head".tw.
22. exp Pilot Projects/ or exp Feasibility Studies/
23. (pilot\$1 or feasibility or "Proof of principle").tw.
24. or/7-23
25. 6 or 24
26. (comment or editorial or guideline or practice guideline or interview or letter).pt.
27. 25 not 26
28. exp Animals/ not (exp Animals/ and Humans/)
29. 27 not 28

Drug-specific search strategy

("(alpha-(4-methyl-1-piperazinyl)-3'-((4-(3-pyridyl)-2-pyrimidinyl)amino)-p-tolu-p-toluidide" or CGP 57148 or CGP-57148 or CGP57148B or Gleevec or Glivec or imatinib or "imatinib mesylate" or "imatinib methanesulfonate" or "ST 1571" or ST1571 or "STI 571" or STI-571 or STI571).tw. [6086 EB results]

(dasatinib or sprycel or "BMS-354825" or sprycel or dasatinibum or BMS 354825" or bms354825).tw. [1099 EB results]

(nilotinib or tassigna or amn107 or "amn 107" or "amn-107").tw. [784 EB results]

(arxoxifene or "2-(4-Methoxyphenyl)-3-[4-(2-piperidin-1-ylethoxy)phenoxy]-1-benzothiophen-6-ol" or E569WG6E60 or "UNII-E569WG6E60" or "4F-DMA" or "LY 353381" or "LY-353381" or "LY353381" or "LY353381 hydrochloride" or "LY353381hydrochloride" or "LY-353381 hydrochloride" or "LY 353381 hydrochloride" or "182133-25-1").tw. [140 EB results]

(bendamustine or bendamustinum or bendamustina or "16506-27-7" or "SDX 105" or "SDX-105" or bendamustin or "Zimet 3393" or AC1123nb).tw. [299 EB results]

(degarelix or "214766-78-6" or "CHEBI:337139" or DNC006645 or D08901 or ChEMBL264089 or "CHEBI:416818" or DNC005341 or firmagon or FE200486 or DB06699 or "UNII-SX0XJI3A11").tw. [81 EB results]

(Certican or everolimus or afinitor or zortress or "sdz-rad" or "rad 001" or "rad-001" or "159351-69-6").tw. [2772 EB results]

(efaproxiral or efaproxyn or "131179-95-8" or "2-Dacmpp" or RSR13 or "RSR 13" or "RSR-13" or J81E81G364 or "UNII-J81E81G364" or "2-[4-[2-(3,5-dimethylanilino)-2-oxoethyl]phenoxy]-2-methylpropanoic acid" or "2-(4-(2-((3,5-dimethylphenyl)amino)-2-oxoethyl)phenoxy)-2-

methylpropanoic acid" or "RSR13 cpd" or "RSR 13 cpd" or "RSR-13 cpd" or RSR56 or "RSR-56" or "RSR 56").tw. [84 EB results]

(ixabepilone or "Azaepothilone B" or ixempra or "BMS-247550" or "BMS 247550-1" or "azaepothilone B").tw. [508 EB results]

(Lapatinib or "Lapatinib Ditosylate" or Tykerb or Tyverb or tycerb or "GW572016" or "GW-572016" or "GW 572016").tw. [1265 EB results]

(nelzarabine or nelarabine or arranon or ariance or arranonG or AC1mhtjs or "GW-506u78" or "GW 506u78" or GW506u78 or 506U78 or "s1213_Selleck").tw. [90 EB results]

(nolatrexed or "nolatrexed dihydrochloride" or "2-Amino-6-methyl-5-(4-pyridylthio)-1H-quinazolin-4-one" or "4-dihydro-2-amino-6-methyl-4-oxo-5-(4-pyridylthio)quinazoline dihydrochloride" or AG337 or "AG-337" or "AG 337" or Thymitaq or "UNII-K75ZUN743Q" or K75ZUN743Q).tw. [83 EB results]

(pazopanib or "444731-52-6" or "kinome_3790" or "GW-786034" or "GW7 86034" or "UNII-7RN5DR86CK" or ChEMBL477772).tw. [456 EB results]

(pralatrexate or folotyn or "10-propargyl-10-deazaaminopterin" or "14646-95-1" or "NSC754230" or "NSC 754230" or "NSC-754230").tw. [61 EB results]

(romidepsin or istodax or chromadax or FK228 or "FR901228" or "FR 901228" or "FR-901228").tw. [271 EB results]

(sorafenib or Nexavar or sofafenibum or "BAY 43-9006" or "BAY-43-9006" or "BAY 439006" or "BAY43-9006").tw. [3292 EB results]

(sunitinib or sutent or "SU-11248" or "Su-011248" or SU11248 or "SU 11248").tw. [2945 EB results]

(temsirolimus or torisel or "CCI 779" or "CCI-779" or cci779 or "S1044_Selleck" or NSC683864 or "NSC-683864" or "NSC 683864").tw. [1560 EB results]

(panitumumab or Vectibix or "ABX-EGF" or L01XC08 or "E7.6.3").tw.

(vorinostat or Zolinza or "18F-SAHA" or Vorinostatium or "Suberoylanilide hydroxamic acid" or "SAHA").tw.

Appendix B. Codebook for extraction

A. Basic information

- Location of corresponding author
- Registration number
 - From www.clinicaltrials.gov, if given in the text only.
- Publication date
 - Earliest publication date, including e-publication, if available.
- Stated goal: Safety, Dosage, Efficacy, Pharmacodynamics, Pharmacokinetics, Other
 - All articulated goals, anywhere in the manuscript. Often will occur in methods or intro as a list of primary and secondary endpoints. Avoid imputing goals.
 - Do not put safety, unless safety is explicitly mentioned as a goal before the results section.
- Sponsor: Government, Biotech, Pharma, Nonprofit, Not stated
 - Provided any funding to support study. Criteria for sponsorship: named explicitly as supplying funding in article.
 - Criteria for "Biotech:" Involved primarily in discovery as opposed to manufacture, or manufactures products primarily using biological processes. Some biotech companies are owned by big pharma, but ownership is irrelevant for classification. Hence, some common biotech firms include: Amgen, Biogen, Genentech, Genzyme, etc.
 - Pharma includes Merck, Pfizer, etc. When there is doubt, add to directory of companies.
 - Criteria for dividing ambiguous entity should be whether main revenue stream is a biotech derived product (e.g. recombinant protein) or a small molecule. "Develops and markets" means that it's a pharma.
- What is the phase of the trial? Case, Phase 1, Phase 1-2, Phase 2, Phase 2-3, Phase 3
 - If the phase number is not explicitly stated:
 - Phase 1: healthy volunteers OR patients lacking target disorder, OR dose escalation where safety, dosage, OR PK are primary endpoints. Typically < 50 patients.
 - Phase 2: in patients with target disorder, AND primary endpoint not specified OR primary endpoint is specified, and it is a surrogate (i.e. tumor response), ... other pieces of evidence: call for large randomized trials

- Phase 3: "confirmatory," "pivotal", OR randomized trial enrolling > 200 patients where primary endpoint is clearly specified, and it is a clinical endpoint. Typically uses 1 or perhaps 2 dose arms.
- Is the phase of the trial stated in the paper itself? Phase is explicitly stated, Phase is not stated
- Single or multi centre?
- What is the indication for the trial?
 - Short phrase capturing broad clinical indication. Do not include criteria for classification. E.g. "RCC," "partial onset seizures," "Parkinson's." For cancer, indication might be "NSCLC."
 - Non-solid indications will be grouped as follows:
 - CP-CML / AP-CML
 - BC-CML / Ph+ ALL / Ph+ AML
 - AML (Ph-, unspecified, or mixed Ph status)
 - ALL (Ph-, unspecified, or mixed Ph status)
 - Other non-solid (e.g. HES/CEL/DFSP/MDS/MPD/etc.)
- Subindication
 - Subset or clinical characteristic of disease, like "Recent onset Parkinson's" or "familial PD." For cancer, subindication might be "EGFR positive NSCLC."
- Stage: First line, Second line, Refractory, Mixed
 - 1st line: no prior therapy
 - 2nd line: refractory to / relapsed after at least one prior therapy
 - Refractory: "inadequately controlled," "advanced," or "metastatic"
- Are investigator conflicts of interest disclosed?
 - Discloses anywhere in the manuscript the existence or nonexistence of a financial relationship with sponsor.
- Is there a conflict of interest?
 - If yes, this means that there is a significant relationship among any of authors and sponsor. All conflicts of interest count, including funding, consultancies, etc.
 - "Supported by Pfizer" would not be a conflict of interest. This only includes relationships between the sponsor and investigators.

B. Rationale for investigation

- Introduction citations
 - This section records the stated evidentiary rationale supporting the clinical trial at hand, based on references supplied by the author. We are not seeking citations to articles on chemistry, manufacturing, etc. Rather, grounds for believing drug will modulate particular effect.
 - Citations: list each citation of experimental evidence that seems to include live animals (preclinical or clinical) used to support the trial. We will later code this according to evidence type.
 - Begin by typing an author's name or part of the title of the citation. When you have found the citation you're looking for, click "Add citation" and this will attach it to this extraction. If you can't find the citation in the list of suggestions that appears, choose "Add a new reference" from the panel at the left.
 - Indication in the text: Look at the sentence preceding the citation, and record indications that are referred to in that sentence. Don't go looking at the article being cited.
 - Efficacy / safety / dosage: Indicate why the article is being cited.
 - Cited as positive (P / N / I): Indicate if the article is cited as positive, negative or inconclusive.

C. Methods

1. Hypothesis

- Randomization: Randomized, Not randomized
 - With respect to the drug in question
- Primary outcome blinding
- Allocation blinding
- Description of withdrawals
 - Withdrawals described: any description of withdrawals
 - Withdrawals not described: no description of withdrawals at all

2. Design

- Design: Dose escalation, Dose finding, Dose ranging, Historical control, Parallel group, Futility, Simon two-stage, Placebo, Crossover, Invasv PD/BM, Other (specify)

- Dose finding: mainly to cause side-effects, titrates dose to pre-specified optimum based on bio or clinical specifications.
- Dose ranging: tests specified doses.
- Dose escalation: determines doses for subsequent cohorts.

3. Treatment

- Experimental arms
 - N: number of patients at baseline. Do not record patients screened. Typically, this is number randomised, though if there is a 2 week wash-out before randomization, N would be recorded at start of wash-out.
 - Not the number of patients assessable or the number enrolled, generally the number that started the treatment.
 - D: day. W: week, M: month, X: cycle
 - Ex: "Pts received DRUG 14 mg/m² as a 4-hour intravenous infusion on days 1, 8, and 15 of each 28-day cycle for up to six cycles" would be coded as: "D 1, 8, 15 / 28 d X 6"
 - If "combination" is selected, please indicate the other drug being used in the combination therapy. Leave blank if none.
 - Route: Oral, IV, Surgical, Other

Arm (e.g. sunitinib or placebo)	Arm N	Dose	Schedule	Route	Combination

- Outcomes
 - Only put "safety" if it is the primary endpoint
 - Priority: 1 for primary outcome, 2 for secondary outcome(s)

Outcome	Priority

4. Time

- Duration of patient enrolment from baseline to primary endpoint (weeks)

- Indicate how long a patient must be enrolled in a trial in order for the primary endpoint to be collected. Captures length of time between projected collection of primary endpoint and collection of baseline data.
- If trial is "time to event" (i.e. indeterminate endpoint) use mean or median time to event for overall study.
- Something like PFS-6 would be recorded as "6 months." (Convert to weeks.)
- If not specified, impute by median number of cycles x period of each cycle. If total number of cycles given, divide by number of patients, and multiply by period for each cycle. Round to nearest day (i.e. if trial only runs for 6 hours, round to 1 day).
- If total cycles are given, divide by number of patients and multiply by weeks per cycle.
- Always report in weeks. If given in months, divide by 12 and multiply by 52.
- Is the duration of treatment imputed?
- Date of enrolment
 - Year and month when first patient was enrolled. If not available, check www.clinicaltrials.gov. Otherwise leave blank and query investigators later.
- Date of closure
 - Year and month when last patient was enrolled. Clinicaltrials.gov does not generally record this info. As above, leave blank if not available.

5. Population

- Concomitant medications for managing target disorder?
 - Experimental intervention is added on top of standard treatment for managing disorder. Do not record meds for managing symptoms of disorder (e.g. nausea for a cancer drug), or comorbidities (e.g. high blood pressure in stroke victims). Do not record brief challenge removal of concomitant (gets recorded in wash-out below).
- Paediatric subjects: All, Some, None
 - Pediatric Subjects: Age < 18 yrs
- Burdens: Invasive research procedures, Wash-out, Other, None

D. Results

- Primary endpoint: Negative, Inconclusive trend negative, Inconclusive, Inconclusive trend positive, Positive

- If possible, measure 95% confidence intervals as relate to null hypothesis. Often inferable from text, but may require analysis later on.
- Negative: upper bound of CI does not capture null
- Inconclusive trend negative: favours comparator, but not significant
- Inconclusive: equivalent activity
- Inconclusive trend positive: favours experimental drug, but not significant
- Positive: favours new drug and statistically significant
- Toxicity described as: Acceptable, Unacceptable, Not stated
- Total assessment of risk / benefit: Favourable, Inconclusive, Unfavourable
 - Based on last paragraph of paper
- What is the number of patients to receive the drug in question? (Denominator for response)
 - For example, if you are extracting Sunitinib trials, you would put the total number of patients to receive Sunitinib.
 - In cases of single-arm studies, this number may be the same as the total N, below.
 - In cases of placebo control studies, this may be the same number as the arm N for Sunitinib above.
 - This will differ from the arm N above in cases where there is more than one arm receiving the drug in question. Imagine a study where one arm is testing continuous daily dosing and the other is testing the 4/2 schedule. In this case, you would enter the sum of both.
 - This may differ from the total N below, which is the total number enrolled, where here we're extracting the total number receiving the drug in question
- What is the total N?
 - This is the total number of patient-subjects enrolled. The "arm n" from the table above is the total number randomised and treated.
- Efficacy endpoints table
 - Outcome: record outcome measure used. Usually these will be efficacy measures like response rate or survival. However, occasionally, "safety" is a primary or secondary endpoint, and analyses of safety are different than what is captured in Safety Table. When this occurs, record safety info in this table (i.e. for a drug known to cause headaches, and where a primary or secondary outcome is measure of headache events, record average number of headaches). If resp is measured by > 2 methods (i.e. investigator and independent committee assessment), pick only the best standard [independent committee].

- Arm: which intervention arm? For 2 arm studies, put "Tx" and "control." Record nature of each arm if > 2 (i.e. dose arm)
-
- Total N: number of patients at baseline. Do not record patients screened. Typically, this is number randomised, though if there is a 2 week wash-out before randomization, N would be recorded at start of wash-out.
- N: number in each arm. Rules as above.
- Mean: record value at specified endpoint in trial. This might be an average measure (-4.3 on UPDRS scale). Or it might be a number of pts (5 objective responses).
- Aggregated: measures that combine results in treatment and comparator arms. These include: odds ratios, etc.
- Dir: direction with respect to experimental drug
 - + favors experimental drug
 - 0 equivalent
 - - disfavors experimental drug
- Sig: statistical tests run
 - + significant
 - 0 NS
 - - insignificant

Outcome	Arm	Treated mean value	Stats	Agg. Value	Agg. Var	Agg. Units	Dir	Sig

- What is the statistical measure used to report error? Standard deviation, *p*-value, 95% confidence interval, Standard error, None
- Safety endpoints
 - Probably or definitely treatment related events only
 - SAE: serious adverse events. Grade 3 or 4 adverse events recorded as SAE. Record highest number of SAE in a single category as reported. Look for per-event table. Find highest G3

or G4 SAE row, record the number of events. (E.g. 30 G3 or G4 neutropenia events, record "30".) Do not include deaths.

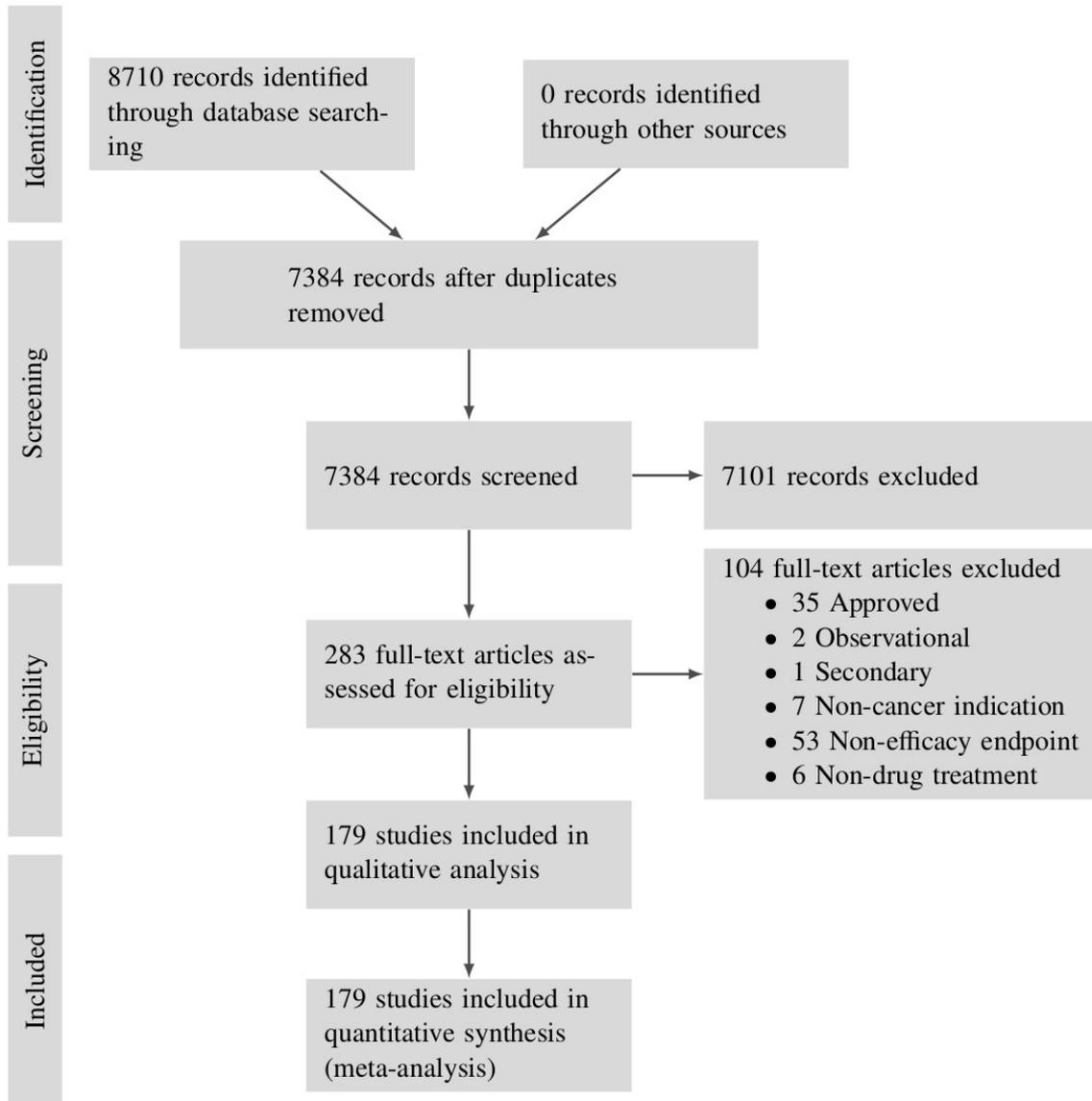
- Withdrawals: Withdrawal or discontinuation due to toxicity

Arm	Deaths	Withdrawals	Grade 3-5 SAE

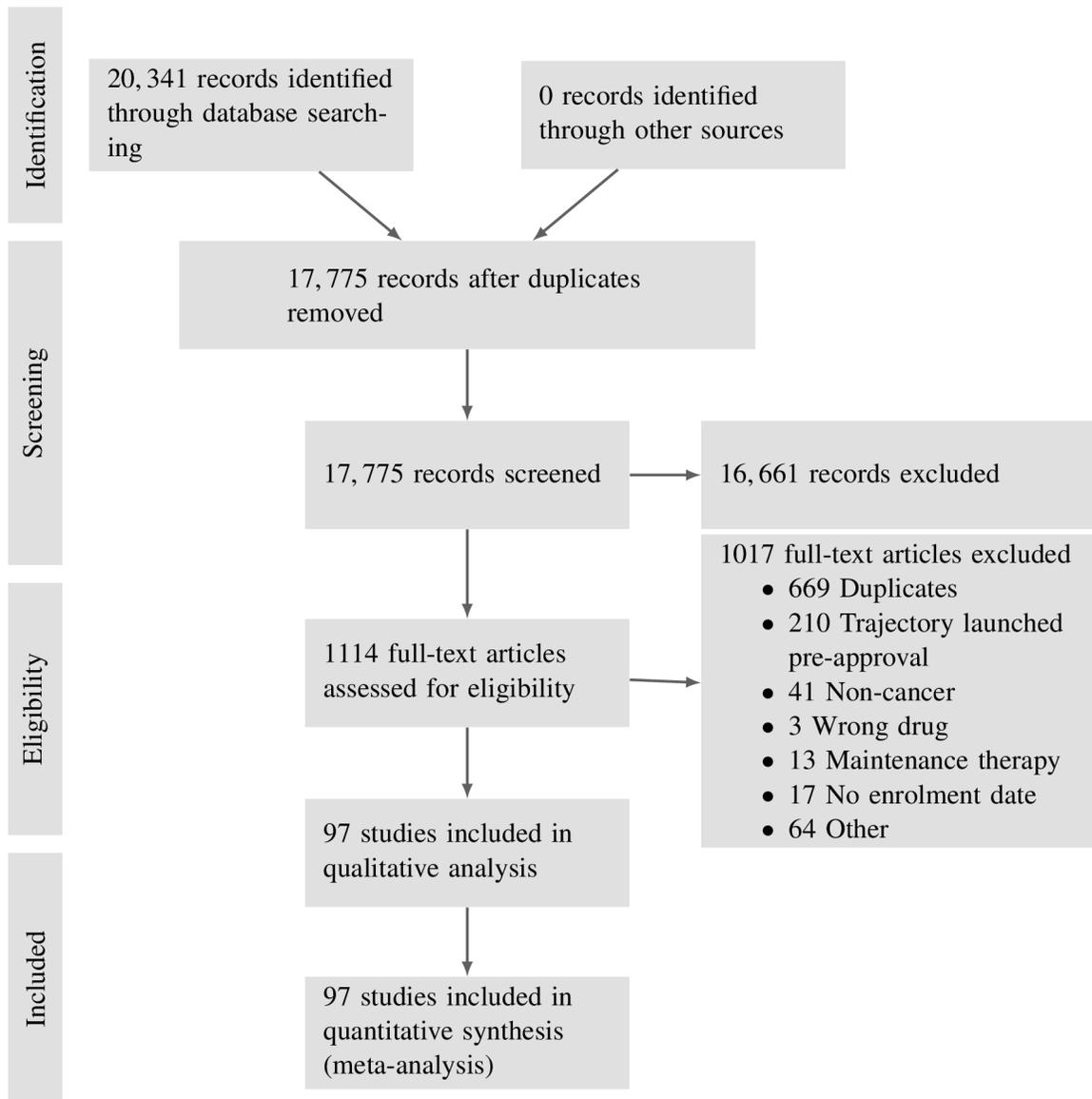
E. Discussion

- Does the paper conclude that the drug is of clinical interest? Concludes drug is of clinical interest, Concludes drug is not of clinical interest, Concludes drug should be re-tested, Unclear
- Discussion citations
 - Include case reports and all studies with live animals, preclinical or clinical.
 - Not negative: "Our study compares favourably."
 - Negative: "This study showed toxicities or lack of efficacy."
 - Leave "Cited as negative?" blank if it is not cited as negative.

Appendix C. PRISMA diagram (chapter 2)



Appendix D. PRISMA diagram (chapter 3)



Appendix F. NCCN recommendations (chapter 4)

Index drug	Combination	Indication	First enrolment date
Panitumumab	Bevacizumab FOLFIRI	Colorectal	2008-09-01
Panitumumab	FOLFOXIRI	Colorectal	2010-03-25
Lapatinib	Trastuzumab	Breast cancer	2008-01-01
Dasatinib	Hyper-CVAD	ALL	2006-09-01
Nilotinib	Daunorubicin Prednisone Vincristine	ALL	2009-01-01

Appendix G. Software developed for this project

Drug trial visualiser

The *Drug Trials Visualiser* is a tool for finding and displaying information about the development of drugs. It was originally designed by Benjamin Gregory Carlisle in 2011 for internal use by the STREAM research group. It downloads trial data from www.clinicaltrials.gov and displays a chronological chart of all the clinical trials in the National Library of Medicine database for the drug in question. FDA approvals, labeling revisions and other regulatory actions are also downloaded, parsed and overlaid on the graph.

Available from: <https://www.bgcarlisle.com/drugs/>

Numbat systematic review manager

Numbat is free software first developed by PhD student Benjamin Gregory Carlisle in 2014 to facilitate meta-analytic work for the *Animals, Humans and the Continuity of Evidence* grant as well as the *Signals, Safety and Success* grant. It was re-written for use with [Beaker Browser](#) in 2017. It is designed for use in meta-analytic projects in an academic context—managing the extraction of large volumes of data from primary sources among multiple users, and then reconciling the differences between them. It is released as free and open-source under a [Creative Commons Attribution 4.0 International License](#).

Available from: <https://www.bgcarlisle.com/blog/numbat3/>