

## Supplementary file 1: Search terms and flowcharts

### Assessing scientific soundness and translational value of animal studies on DPP4 inhibitors for treating type 2 diabetes mellitus

Nuno Henrique Franco <sup>1,2</sup>, Sonia Miranda Batista <sup>1,2</sup>, Nóra Kovács <sup>3</sup>, Attila Nagy <sup>4</sup> Bùi Quốc Thiện <sup>5</sup>, Flávio Reis <sup>6-8</sup> and Orsolya Varga <sup>3,9\*</sup>

<sup>1</sup> Laboratory Animal Science group, IBMC – Instituto de Biologia Molecular e Celular, Universidade do Porto, Rua Alfredo Allen 208, 4200-135 Porto, Portugal; [nfranco@ibmc.up.pt](mailto:nfranco@ibmc.up.pt); [soniabatistamiranda@outlook.com](mailto:soniabatistamiranda@outlook.com)

<sup>2</sup> Instituto de Investigação e Inovação da Universidade do Porto, Rua Alfredo Allen 208, 4200-135 Porto, Portugal; [nfranco@ibmc.up.pt](mailto:nfranco@ibmc.up.pt); [soniabatistamiranda@outlook.com](mailto:soniabatistamiranda@outlook.com)

<sup>3</sup> Department of Public Health and Epidemiology, Faculty of Medicine, University of Debrecen, Kassai út 26, 4028 Debrecen, Hungary; [kovacs.nora@med.unideb.hu](mailto:kovacs.nora@med.unideb.hu); [varga.orsolya@med.unideb.hu](mailto:varga.orsolya@med.unideb.hu)

<sup>4</sup> Faculty of Public Health, University of Debrecen, Kassai út 26, 4028 Debrecen, Hungary; [nagy.attila@sph.unideb.hu](mailto:nagy.attila@sph.unideb.hu)

<sup>5</sup> Faculty of Medicine, University of Debrecen, Egyetem square 1, 4032 Debrecen, Hungary 4032; [buiquochien1996@gmail.com](mailto:buiquochien1996@gmail.com)

<sup>6</sup> Institute of Pharmacology & Experimental Therapeutics, & Coimbra Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine, University of Coimbra, 3000-548 Coimbra, Portugal.; [freis@fmed.uc.pt](mailto:freis@fmed.uc.pt)

<sup>7</sup> Center for Innovative Biomedicine and Biotechnology (CIBB), University of Coimbra, 3004-504 Coimbra, Portugal.; [freis@fmed.uc.pt](mailto:freis@fmed.uc.pt)

<sup>8</sup> Clinical Academic Center of Coimbra (CACC), 3004-504 Coimbra, Portugal.; [freis@fmed.uc.pt](mailto:freis@fmed.uc.pt)

<sup>9</sup> Office for Research Groups Attached to Universities and Other Institutions, Hungarian Academy of Sciences, 1051 Budapest, Hungary.; [varga.orsolya@med.unideb.hu](mailto:varga.orsolya@med.unideb.hu)

**A. Search terms**

**Human search terms**

"Vildagliptin"[Mesh] AND (("placebos"[MeSH Terms] OR "placebos"[All Fields] OR "placebo"[All Fields]) AND controlled[All Fields]) AND (("glucose"[MeSH Terms] OR "glucose"[All Fields]) OR ("glycated hemoglobin a"[MeSH Terms] OR "glycated hemoglobin a"[All Fields] OR "hba1c"[All Fields])) AND Clinical Trial[ptyp] 62

'non insulin dependent diabetes mellitus'/exp AND 'vildagliptin'/exp AND ('glucose'/exp OR 'hemoglobin a1c'/exp) AND 'clinical trial'/exp AND placebo AND controlled AND ('human'/de OR 'randomized controlled trial'/de) AND 'article'/it AND 'placebo'/de

placebo | Completed Studies | Type 2 Diabetes | Vildagliptin | glucose OR HbA1c

//

((("placebos"[MeSH Terms] OR "placebos"[All Fields] OR "placebo"[All Fields]) AND controlled[All Fields]) AND ((("Sitagliptin Phosphate"[Mesh] AND "Diabetes Mellitus, Type 2"[Mesh]) AND ("Glucose"[Mesh] OR "Glycated Hemoglobin A"[Mesh])) AND Clinical Trial[ptyp] 86

'non insulin dependent diabetes mellitus'/exp AND 'sitagliptin'/exp AND ('glucose'/exp OR 'hemoglobin a1c'/exp) AND 'clinical trial'/exp AND placebo AND controlled AND ('human'/de OR 'randomized controlled trial'/de) AND 'article'/it AND 'placebo'/de

placebo | Completed Studies | Type 2 Diabetes | Sitagliptin | glucose OR HbA1c

//

((("placebos"[MeSH Terms] OR "placebos"[All Fields] OR "placebo"[All Fields]) AND controlled[All Fields]) AND ((alogliptin AND "Diabetes Mellitus, Type 2"[Mesh]) AND ("Glucose"[Mesh] OR "Glycated Hemoglobin A"[Mesh]))

'non insulin dependent diabetes mellitus'/exp AND 'alogliptin'/exp AND ('glucose'/exp OR 'hemoglobin a1c'/exp) AND 'clinical trial'/exp AND placebo AND controlled AND ('human'/de OR 'randomized controlled trial'/de) AND 'article'/it AND 'placebo'/de

placebo | Completed Studies | Type 2 Diabetes | Alogliptin | glucose OR HbA1c

//

((("placebos"[MeSH Terms] OR "placebos"[All Fields] OR "placebo"[All Fields]) AND controlled[All Fields]) AND ((("linagliptin"[MeSH Terms] AND "Diabetes Mellitus, Type 2"[Mesh]) AND ("Glucose"[Mesh] OR "Glycated Hemoglobin A"[Mesh])) AND Clinical Trial[ptyp]

'non insulin dependent diabetes mellitus'/exp AND 'linagliptin'/exp AND ('glucose'/exp OR 'hemoglobin a1c'/exp) AND 'clinical trial'/exp AND placebo AND controlled AND ('human'/de OR 'randomized controlled trial'/de) AND 'article'/it AND 'placebo'/de

placebo | Completed Studies | Type 2 Diabetes | Linagliptin | glucose OR HbA1c

//

((("placebos"[MeSH Terms] OR "placebos"[All Fields] OR "placebo"[All Fields]) AND controlled[All Fields]) AND (((("saxagliptin"[Supplementary Concept] OR "saxagliptin"[All Fields]) AND "Diabetes Mellitus, Type 2"[Mesh]) AND ("Glucose"[Mesh] OR "Glycated Hemoglobin A"[Mesh])) AND Clinical Trial[ptyp]

'non insulin dependent diabetes mellitus'/exp AND 'saxagliptin'/exp AND ('glucose'/exp OR 'hemoglobin a1c'/exp) AND 'clinical trial'/exp AND placebo AND controlled AND ('human'/de OR 'randomized controlled trial'/de) AND 'article'/it AND 'placebo'/de

placebo | Completed Studies | Type 2 Diabetes | Saxagliptin | glucose OR HbA1c

**Animal search terms**

Embase: sitagliptin AND animal experiment AND glucose OR hemoglobin a1c

PubMed: sitagliptin AND ("Hemoglobin A, Glycosylated"[Mesh] OR "Blood Glucose"[Mesh]) AND "animals"[MeSH Terms:noexp] AND (Animals[Mesh:noexp])

Web of Science: Topic=(sitagliptin) AND Topic=(blood glucose OR hemoglobin A) AND

Topic=(animal). Search filter for animals suggested by Carlijn R Hooijmans.

//

Embase: saxagliptin AND animal experiment AND glucose OR hemoglobin a1c  
PubMed: saxagliptin AND ("Hemoglobin A, Glycosylated"[Mesh] OR "Blood Glucose"[Mesh])) AND  
"animals"[MeSH Terms:noexp] AND (Animals[Mesh:noexp])  
Web of Science: Topic=(saxagliptin) AND Topic=(blood glucose OR hemoglobin A) AND  
Topic=(animal). Search filter for animals suggested by Carlijn R Hooijmans.  
////////////////////////////////////  
Embase: linagliptin AND animal experiment AND glucose OR hemoglobin a1c  
PubMed: linagliptin AND ("Hemoglobin A, Glycosylated"[Mesh] OR "Blood Glucose"[Mesh])) AND  
"animals"[MeSH Terms:noexp] AND (Animals[Mesh:noexp])  
Web of Science: Topic=(linagliptin) AND Topic=(blood glucose OR hemoglobin A) AND  
Topic=(animal). Search filter for animals suggested by Carlijn R Hooijmans.  
////////////////////////////////////  
Embase: vildagliptin AND animal experiment AND glucose OR hemoglobin a1c  
PubMed: vildagliptin AND ("Hemoglobin A, Glycosylated"[Mesh] OR "Blood Glucose"[Mesh])) AND  
"animals"[MeSH Terms:noexp] AND (Animals[Mesh:noexp])  
Web of Science: Topic=(vilagliptin) AND Topic=(blood glucose OR hemoglobin A) AND  
Topic=(animal). Search filter for animals suggested by Carlijn R Hooijmans.  
////////////////////////////////////  
Embase: alogliptin AND animal experiment AND glucose OR hemoglobin a1c  
PubMed: alogliptin AND ("Hemoglobin A, Glycosylated"[Mesh] OR "Blood Glucose"[Mesh])) AND  
"animals"[MeSH Terms:noexp] AND (Animals[Mesh:noexp])  
Web of Science: Topic=(alogliptin) AND Topic=(blood glucose OR hemoglobin A) AND Topic=(animal).  
Search filter for animals suggested by Carlijn R Hooijmans

## B. Flow charts

### Alogliptin

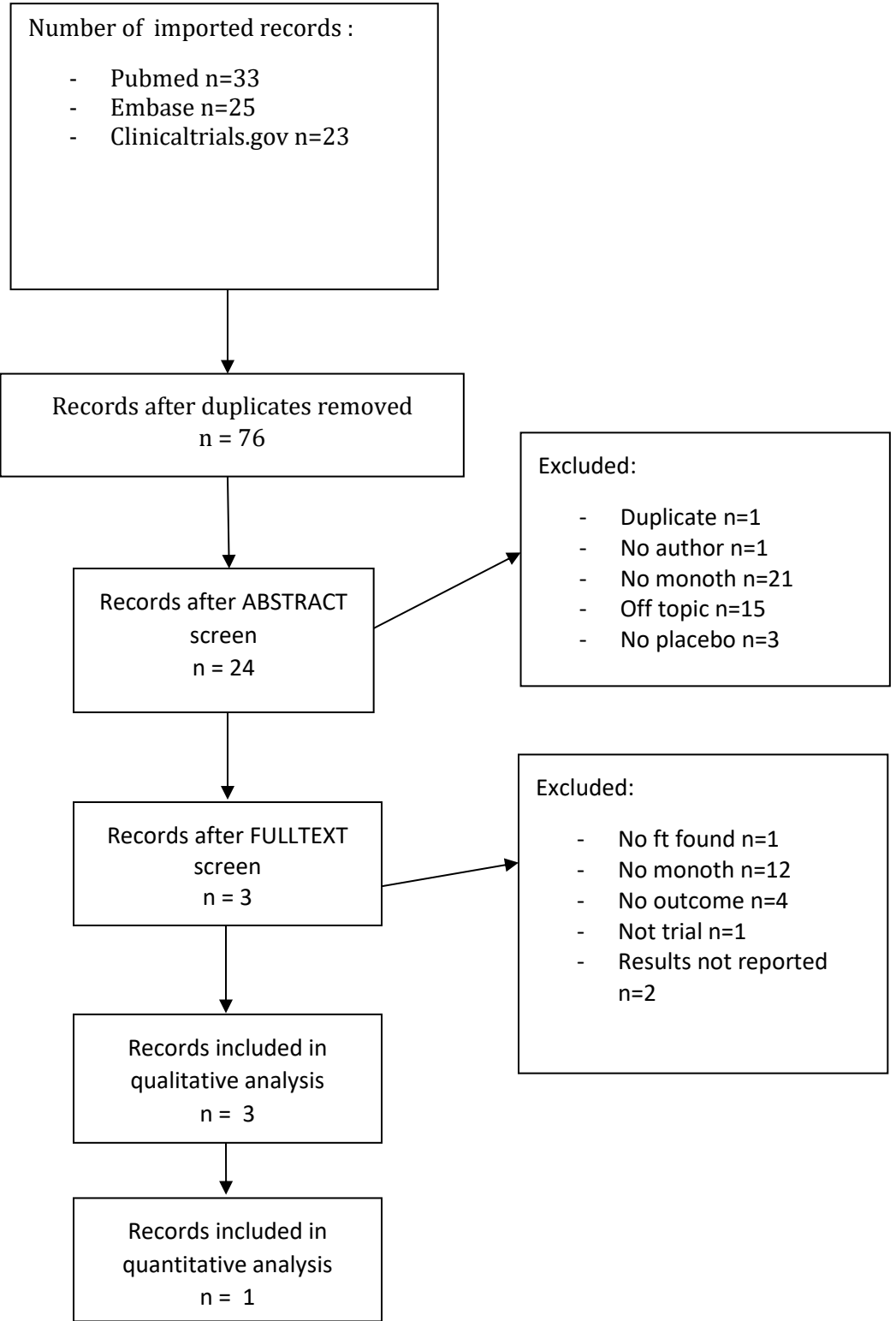


Identification

Screening

Eligibility

Included



# Linagliptin

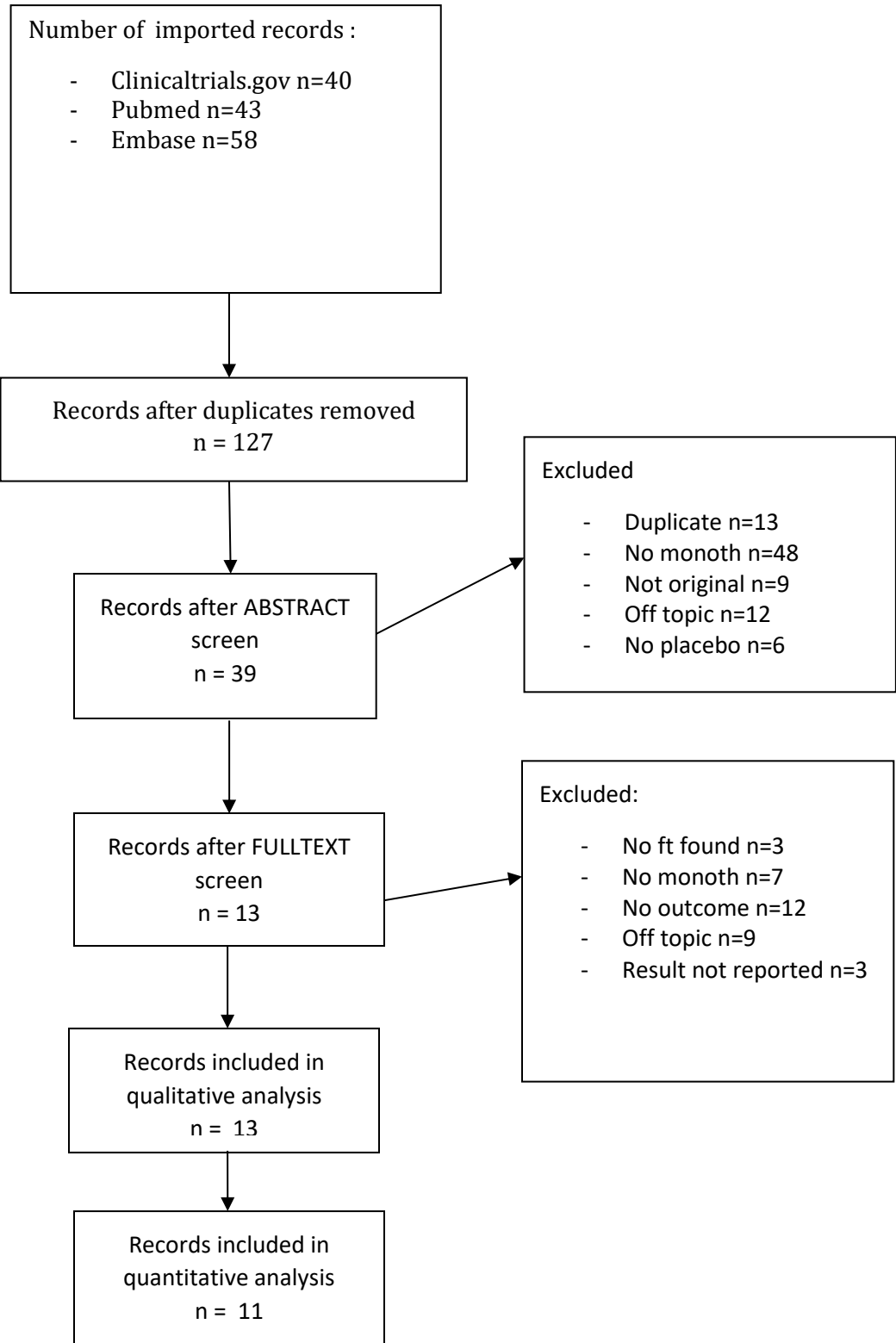


Identification

Screening

Eligibility

Included



# Saxagliptin



Identification

Screening

Eligibility

Included

Number of imported records :

- Clinicaltrials.gov n=32
- Pubmed n=37
- Embase n= 44

Records after duplicates removed  
n = 100

Records after ABSTRACT  
screen  
n = 26

Excluded

- Duplicate n=15
- No monoth n=45
- Not original n=6
- Off topic n=7
- No placebo n=1

Records after FULLTEXT  
screen  
n = 9

Excluded:

- No ft found n=1
- No outcome n=9
- Off topic n=2
- No monoth n=3
- Result not reported n=2
- 

Records included in  
qualitative synthesis  
n = 9

Records included in  
quantitative synthesis  
n = 5

# Sitagliptin

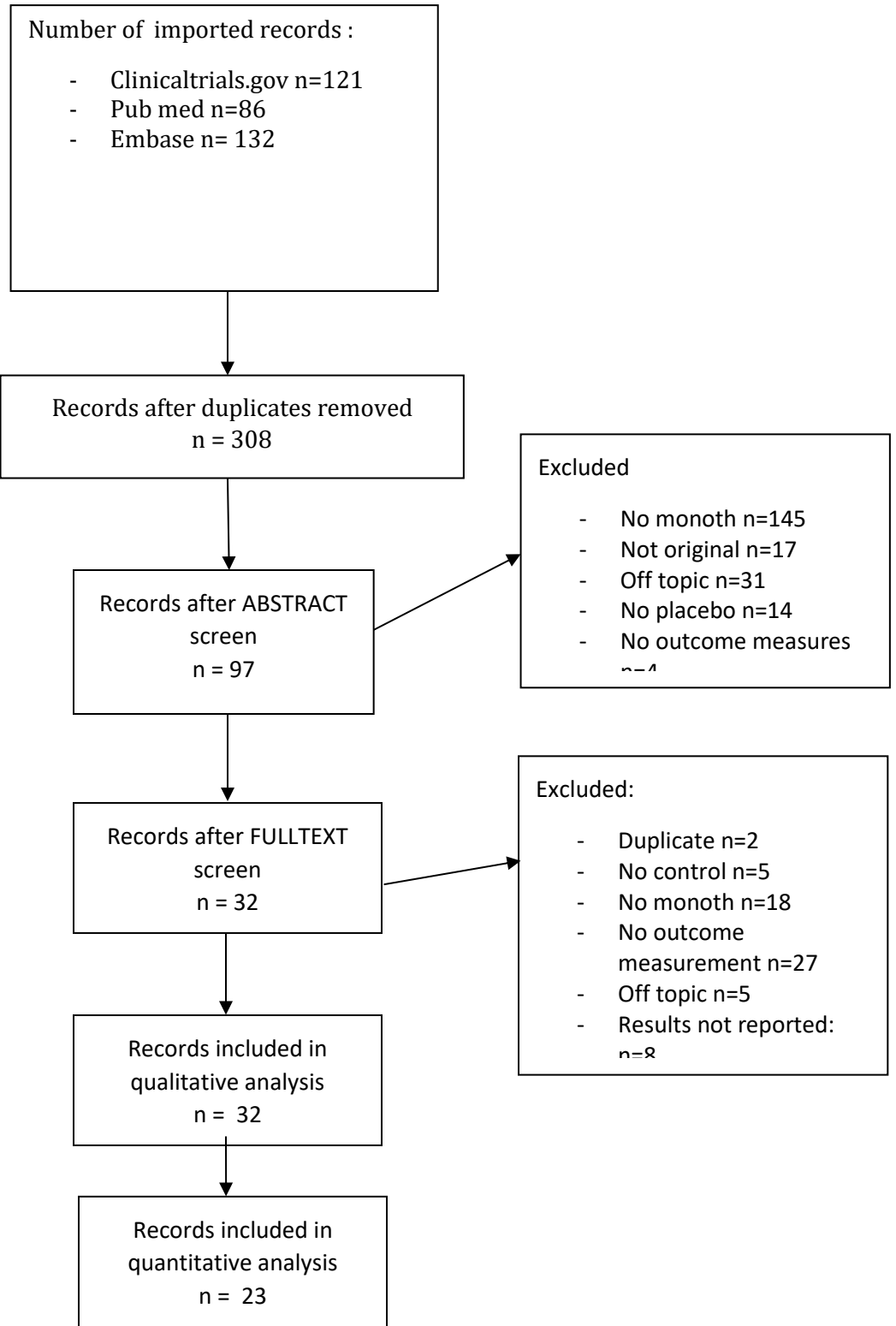


Identification

Screening

Eligibility

Included



# Vildagliptin

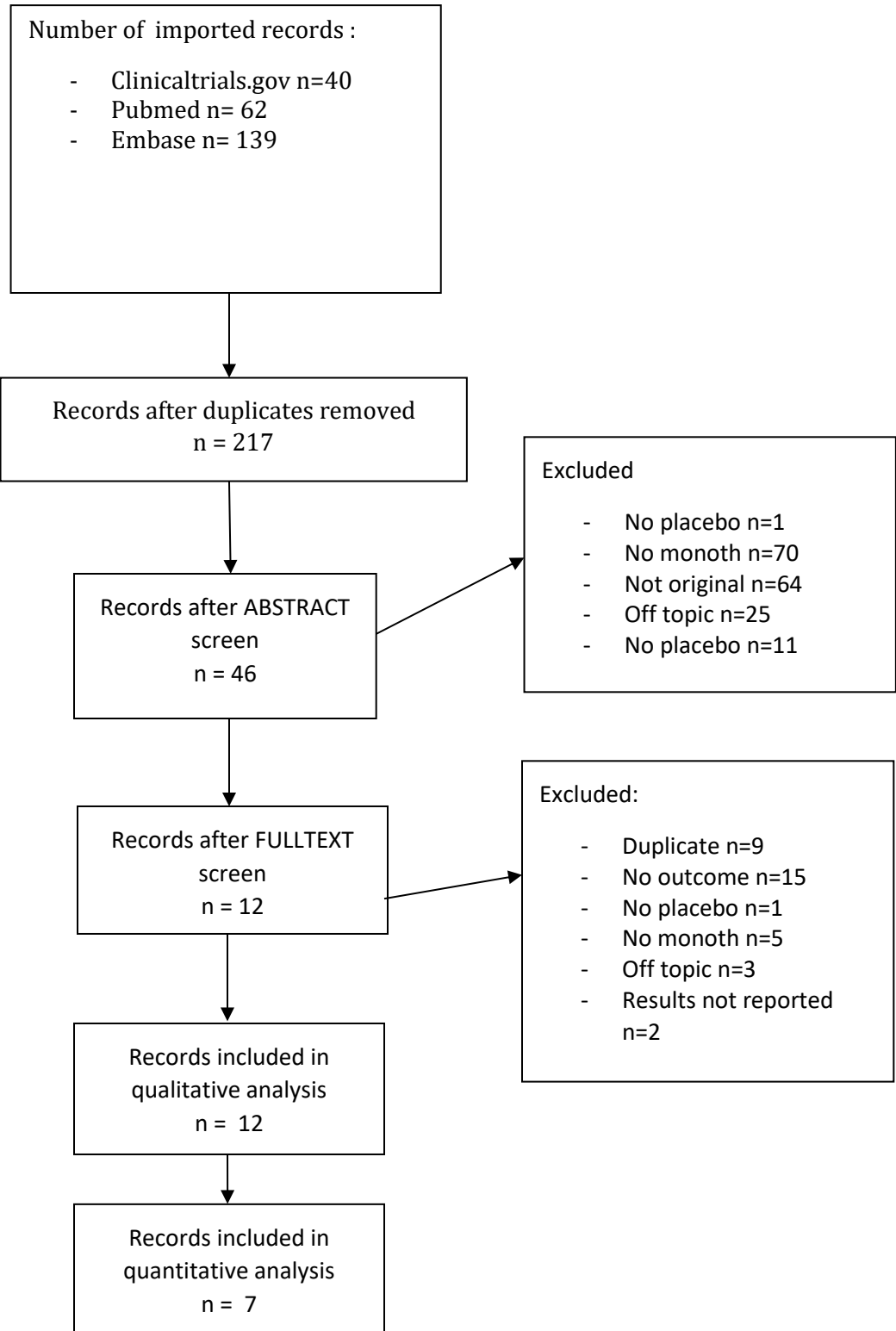


Identification

Screening

Eligibility

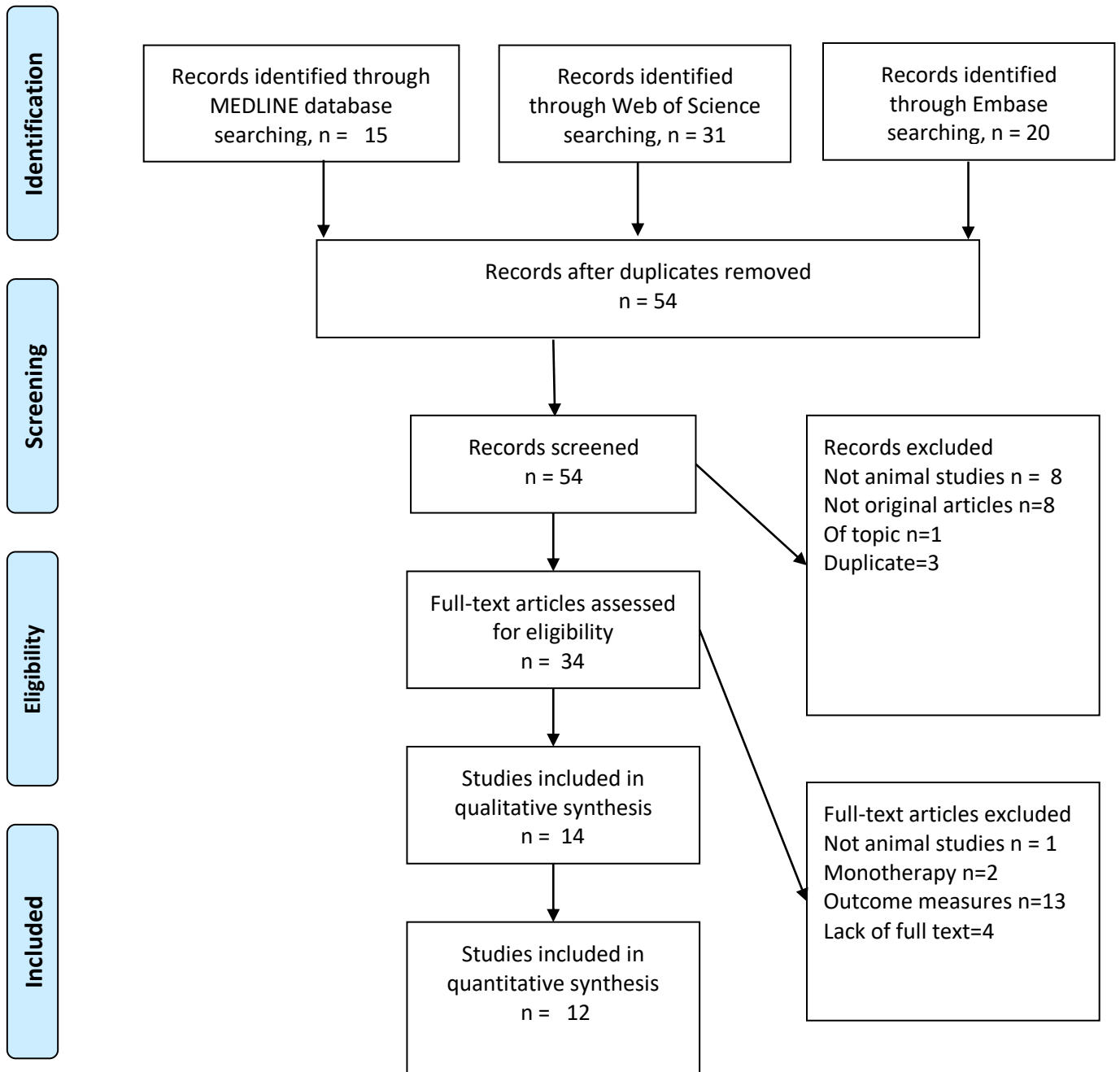
Included





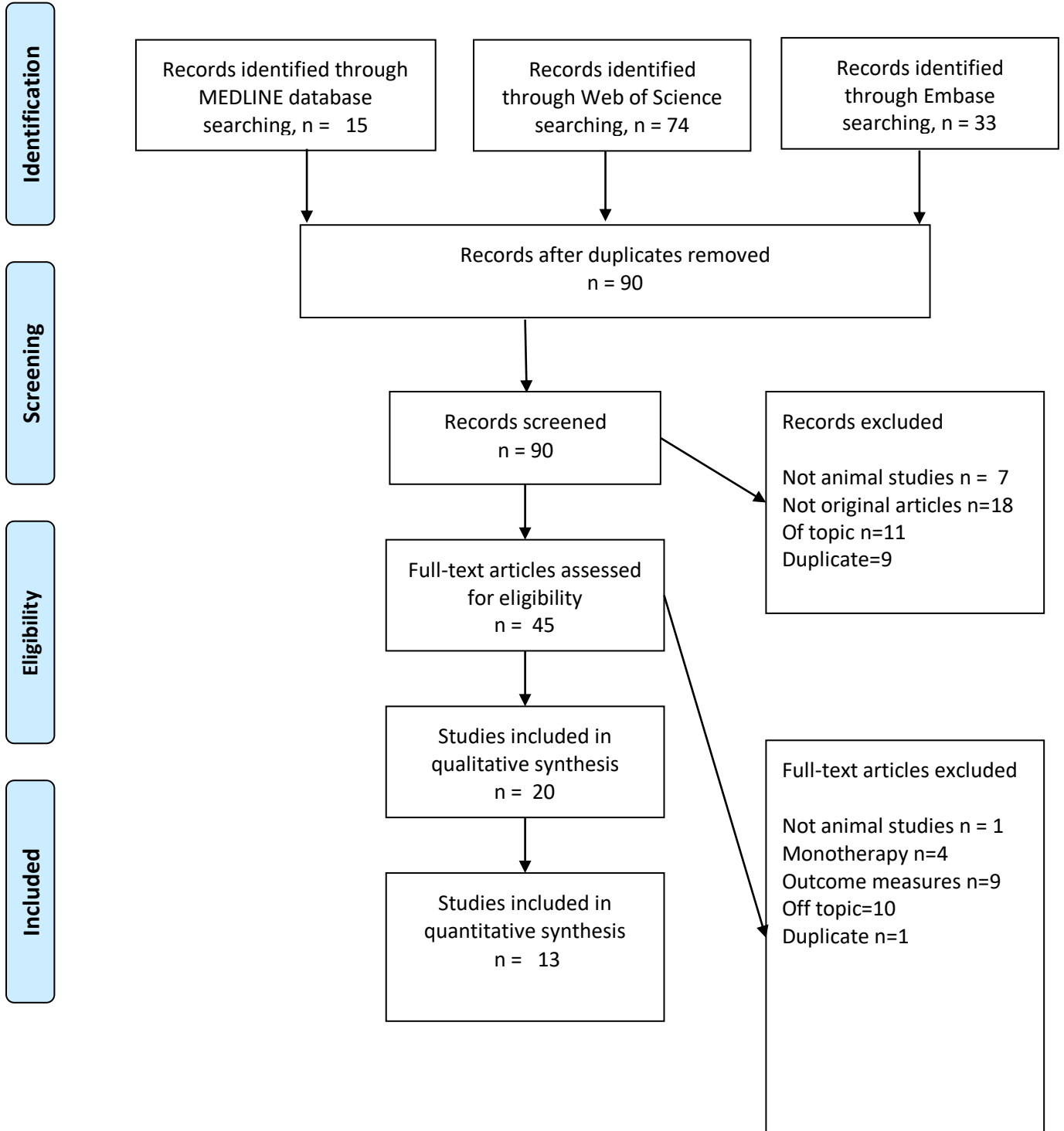


## ALOGLIPTIN animal studies



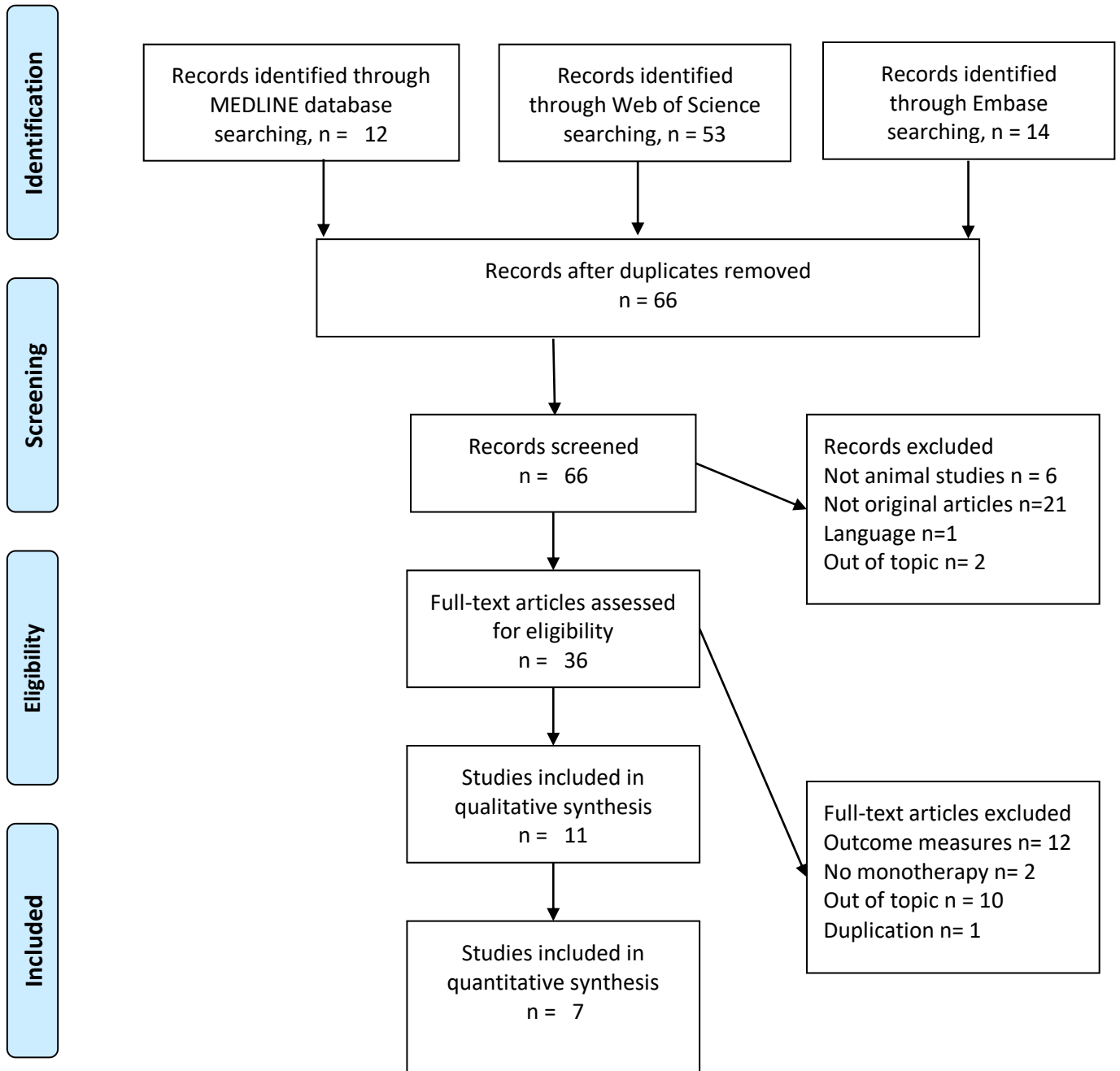


## LINAGLIPTIN animal studies



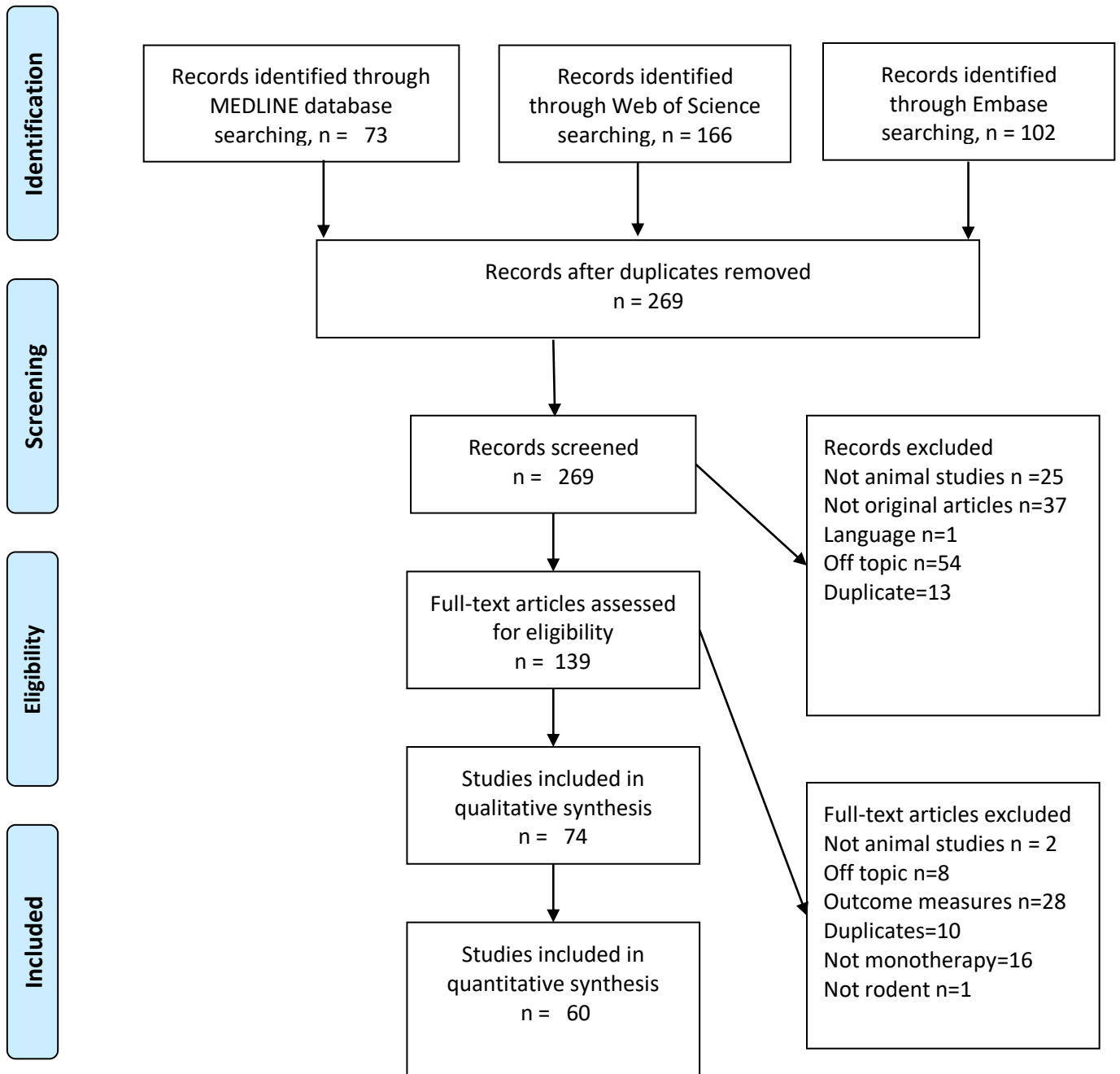


## SAXAGLIPTIN animal studies





## SITAGLIPTIN animal studies





## VILDAGLIPTIN animal studies

