# Evidence based clinical trial design

## Hypothermia for acute ischaemic stroke

Malcolm Macleod
Centre for Clinical Brain Sciences, University of Edinburgh
Co-Chief Investigator, EuroHYP-1

# Developing new treatments for old diseases

**Understand**

- Understand what causes the disease
- Understand which biological processes are pivotal and which are not

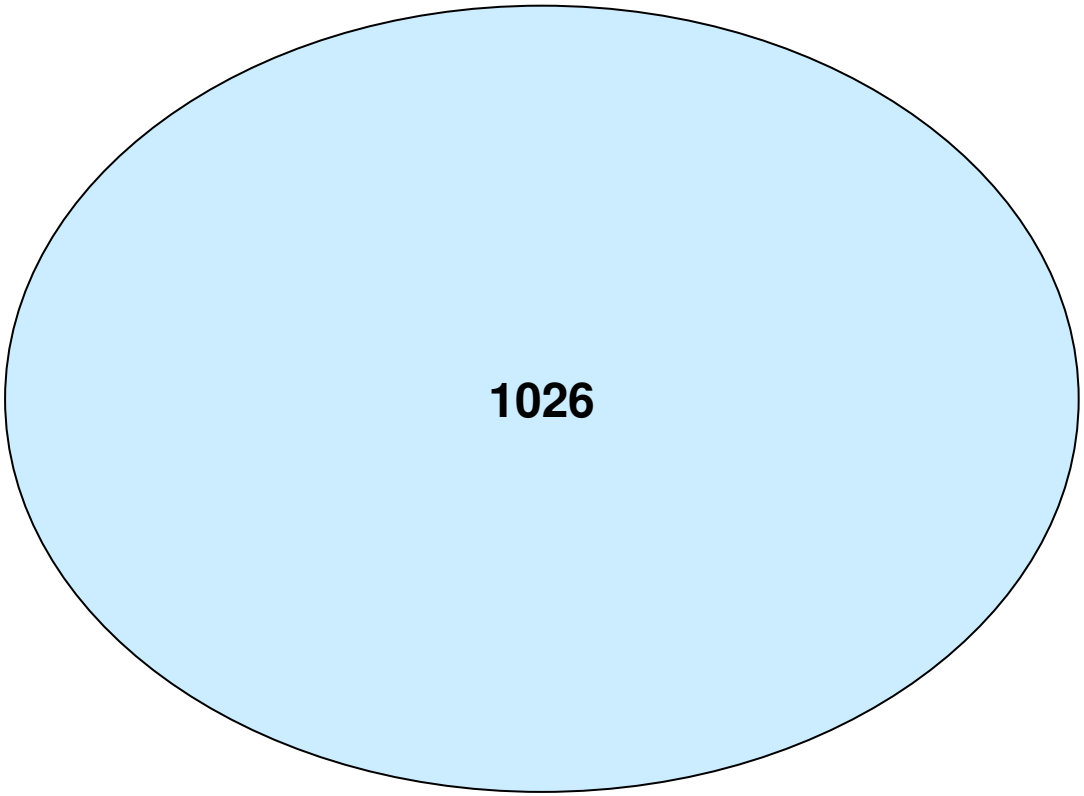
**Influence in models**

- Be able to change these processes in experiments
- Be able to change outcome in disease models
- Know your treatment is probably safe

**Prevent in real life**

- Show, in clinical trials, that the treatment changes outcome
- Show that the treatment works in the real world

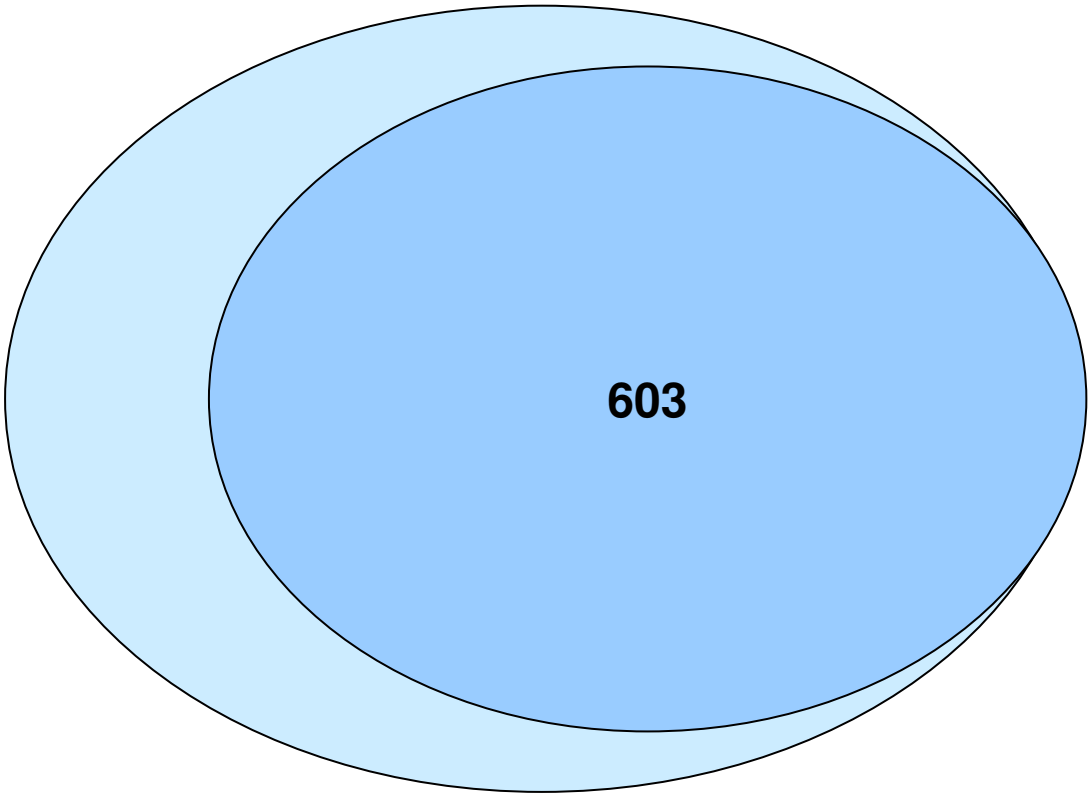
# 1026 interventions in experimental stroke




**Tested in experiments**

O'Collins et al, 2006

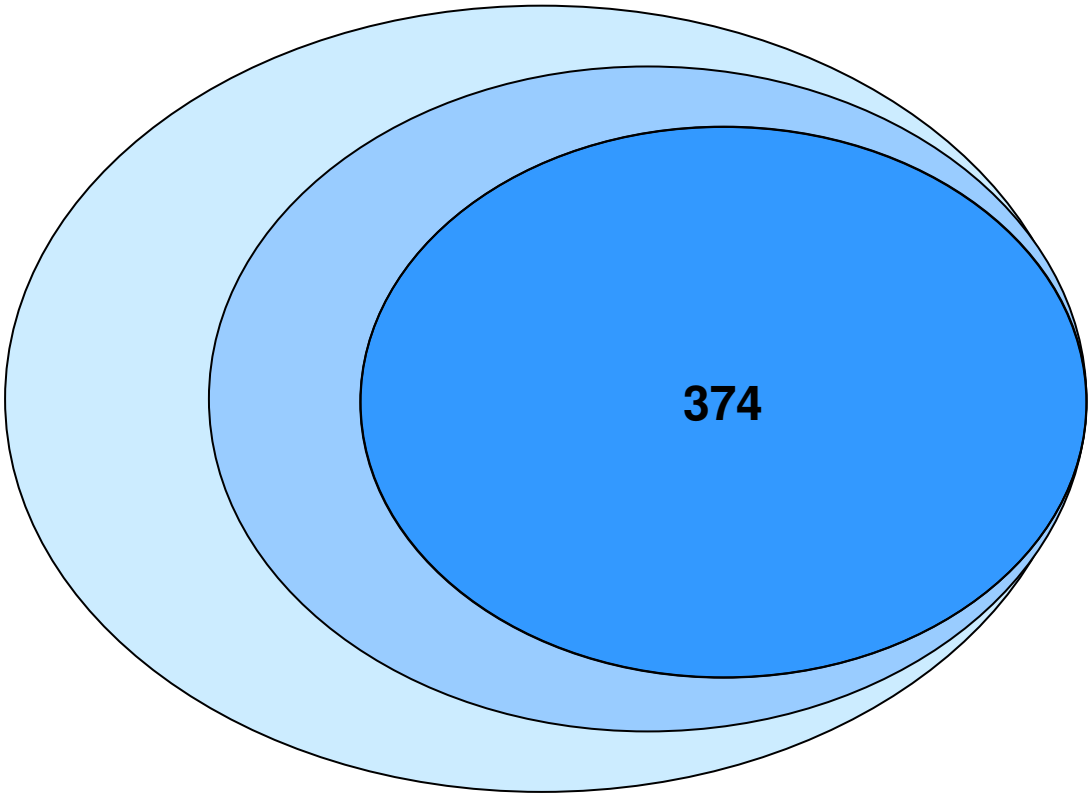
# 1026 interventions in experimental stroke




**Tested in focal ischaemia**

O'Collins et al, 2006

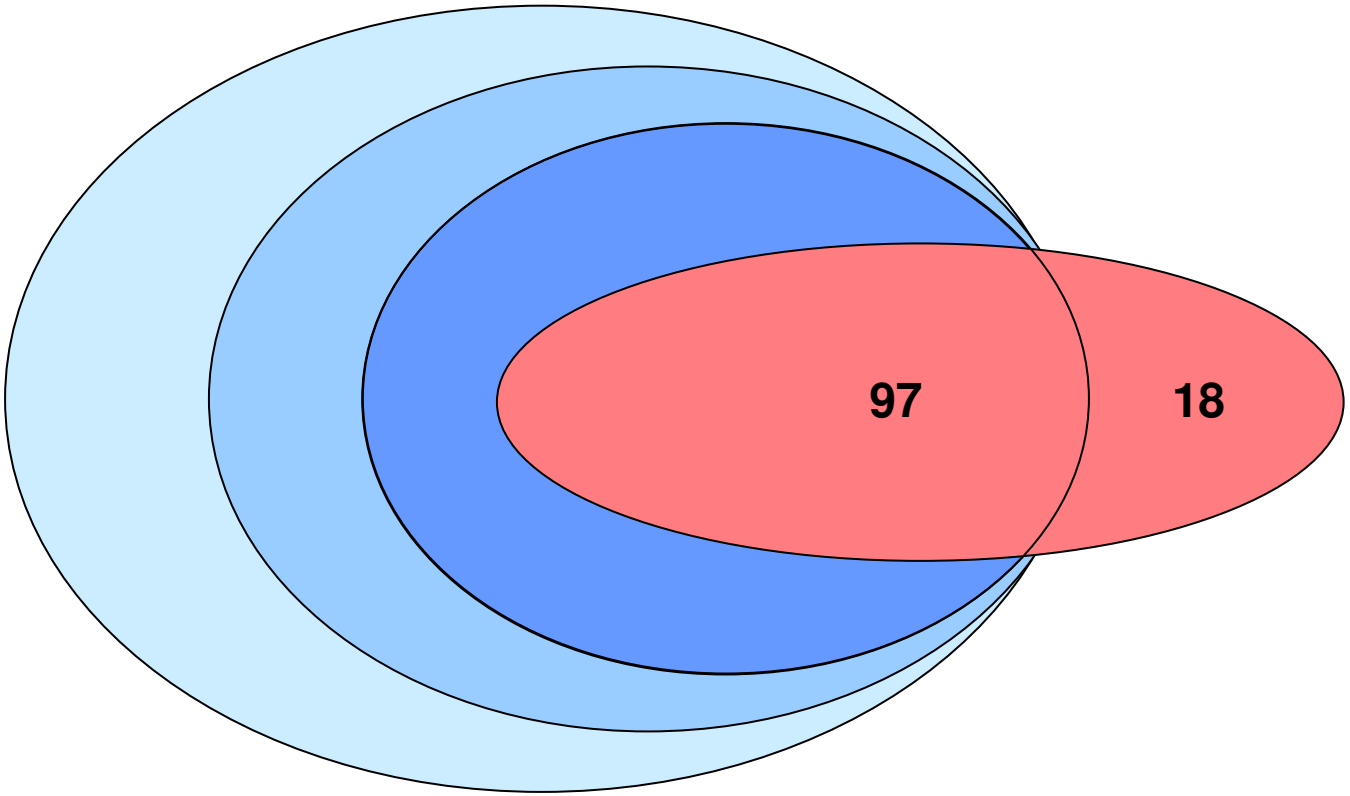
# 1026 interventions in experimental stroke




**Effective in focal ischaemia**

O'Collins et al, 2006

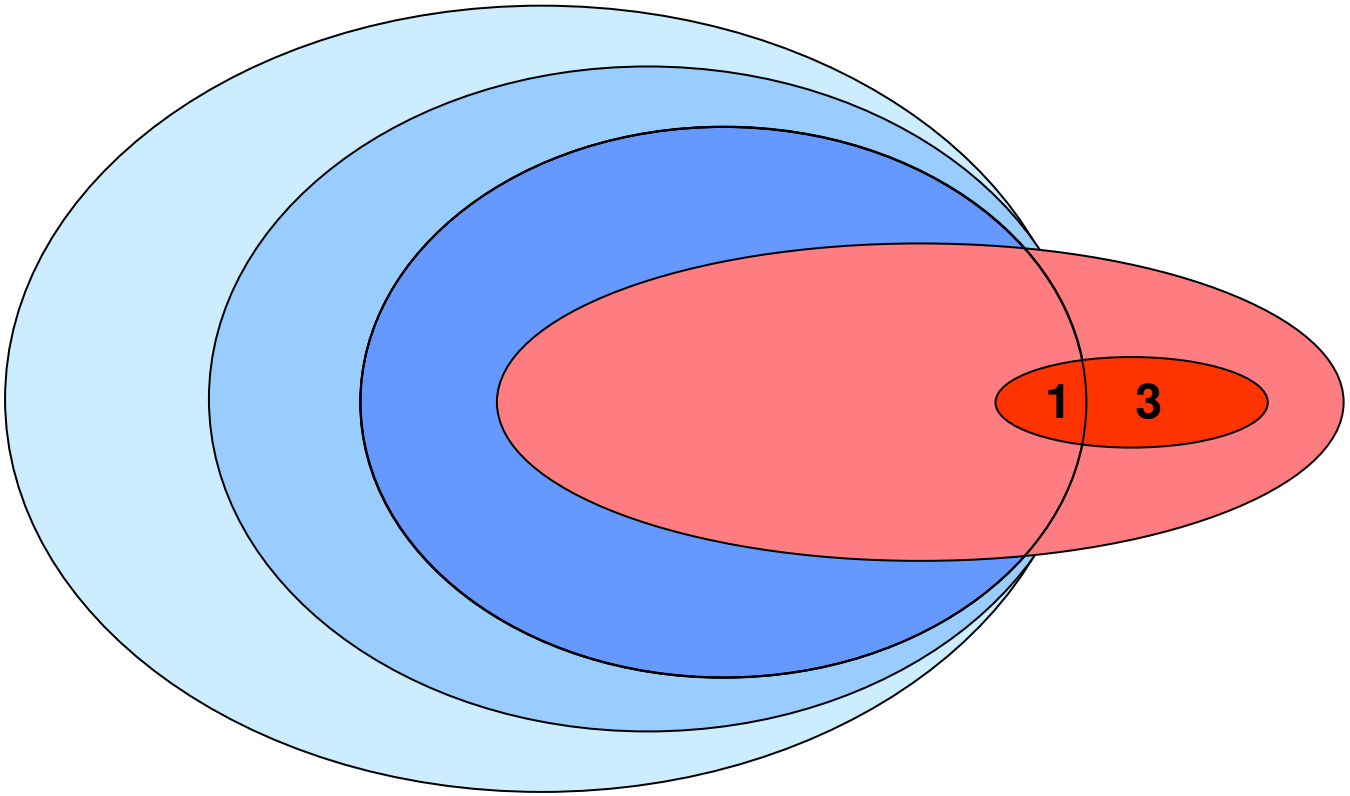
# 1026 interventions in experimental stroke




**Tested in clinical trial**

O'Collins et al, 2006

# 1026 interventions in experimental stroke



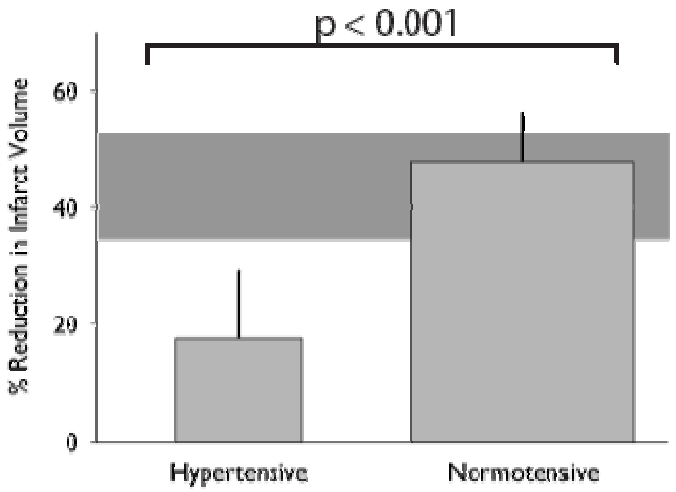

**Effective in clinical trial**

O'Collins et al, 2006

# High blood pressure in animal stroke studies – NXY-059

**Hypertension:**

- 7% of animal studies
- 77% of patients in the (neutral) SAINT II study



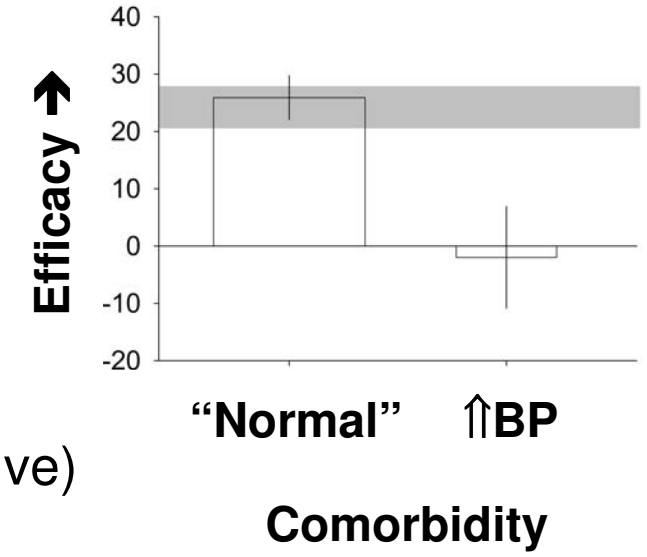
# High blood pressure in animal stroke studies – tPA

**Infarct Volume:**

- 113 publications
- 212 experiments
- 3301 animals
- Improved outcome by 24% (20-28)

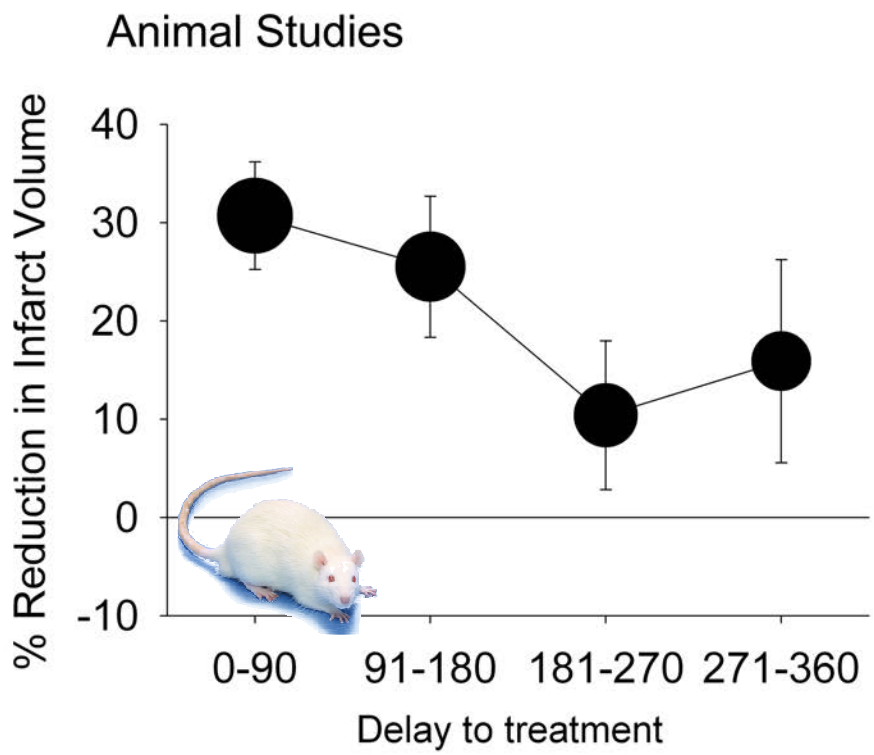
**Hypertension:**

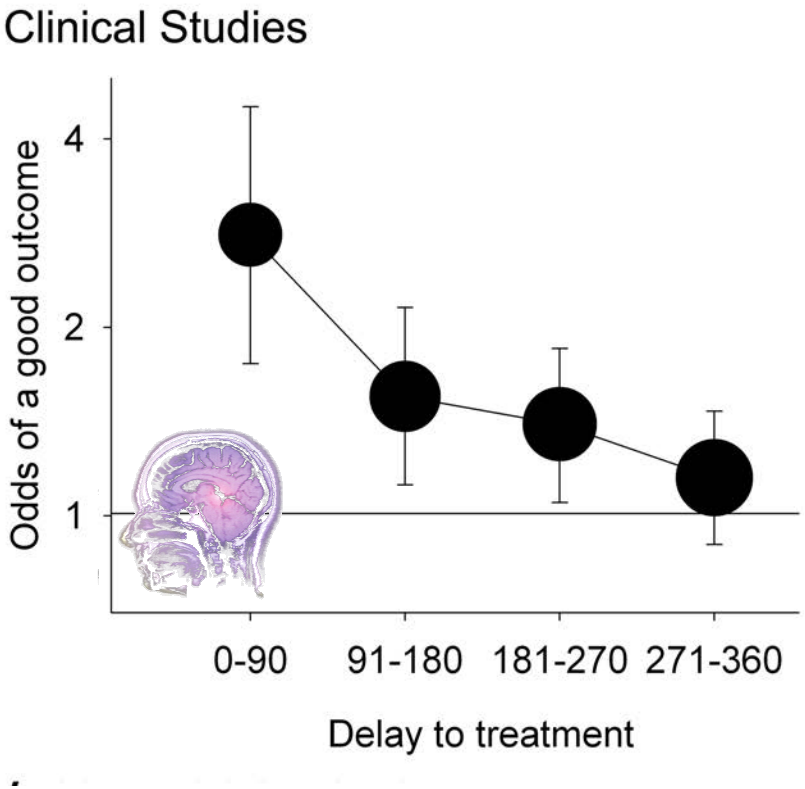
- 9% of animal studies
- Specifically exclusion criterion in (positive) NINDS study



# Time to treatment in animal stroke studies

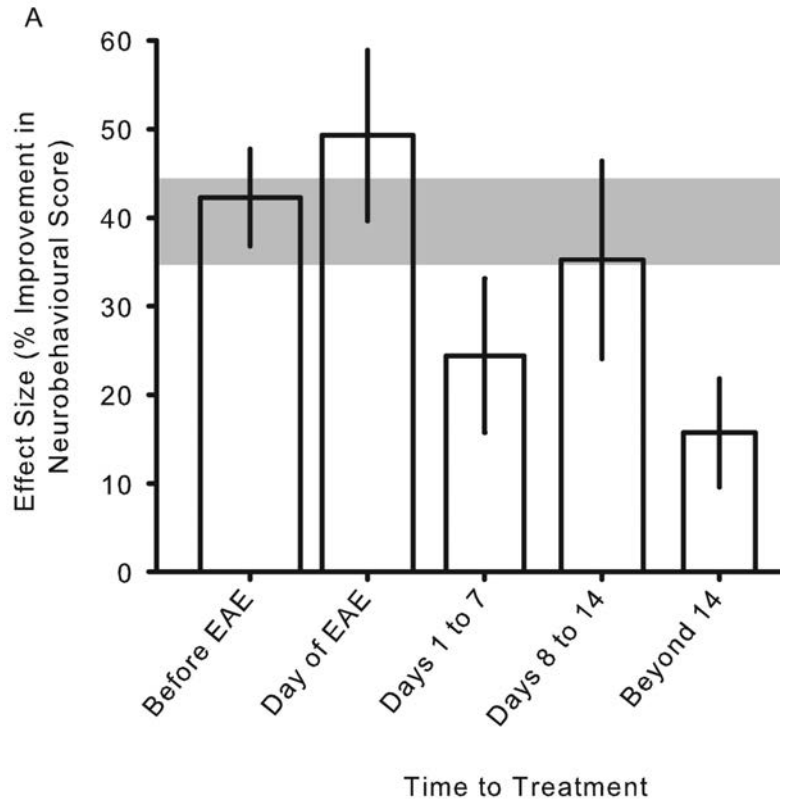
- Both tPA and tirilazad appear to work in animals
- tPA works in humans but tirilazad doesn't
- Time to treatment: tPA:
  - Animals – median 90 minutes
  - Clinical trial – median 90 minutes
- Time to treatment: tirilazad
  - Animals – median 10 minutes
  - Clinical trial - >3 hrs for >75% of patients




**CAMARADES: Bringing evidence to translational medicine**

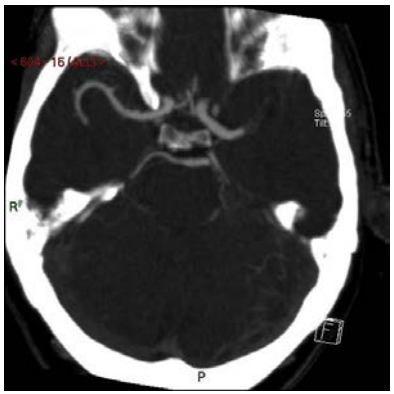
# External validity in Multiple Sclerosis models

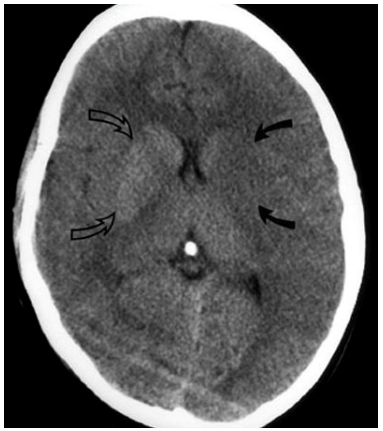


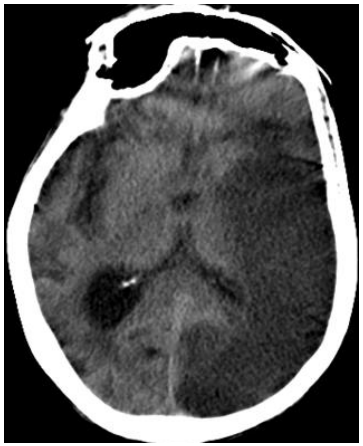
# Cooling for stroke

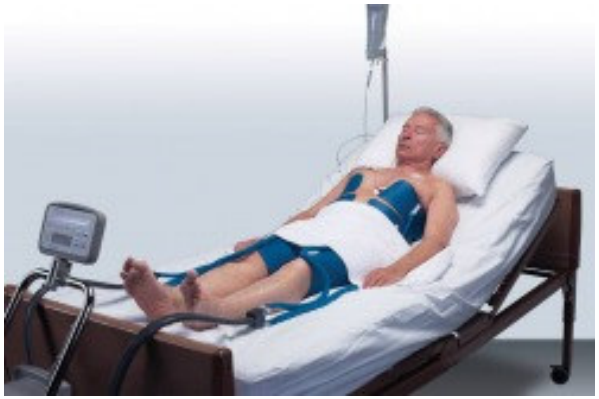
- Cooling seems to work in patients who have brain injury due to cardiac arrest
- There's lots of stories about individual patients who should have extensive brain damage but don't
- Many labs use cooling as a positive control in their animal studies
- Preliminary evidence from clinical trials in stroke is encouraging

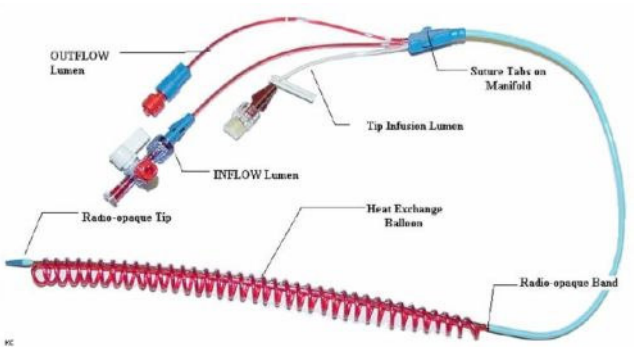
# How to become cool



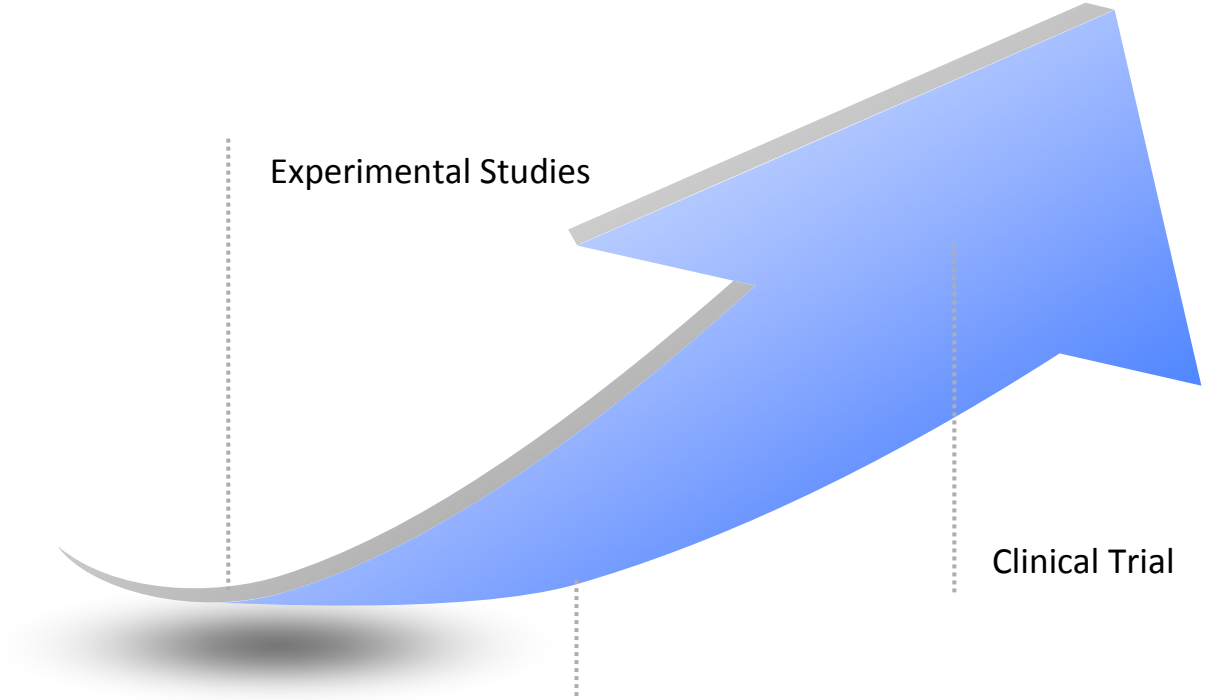








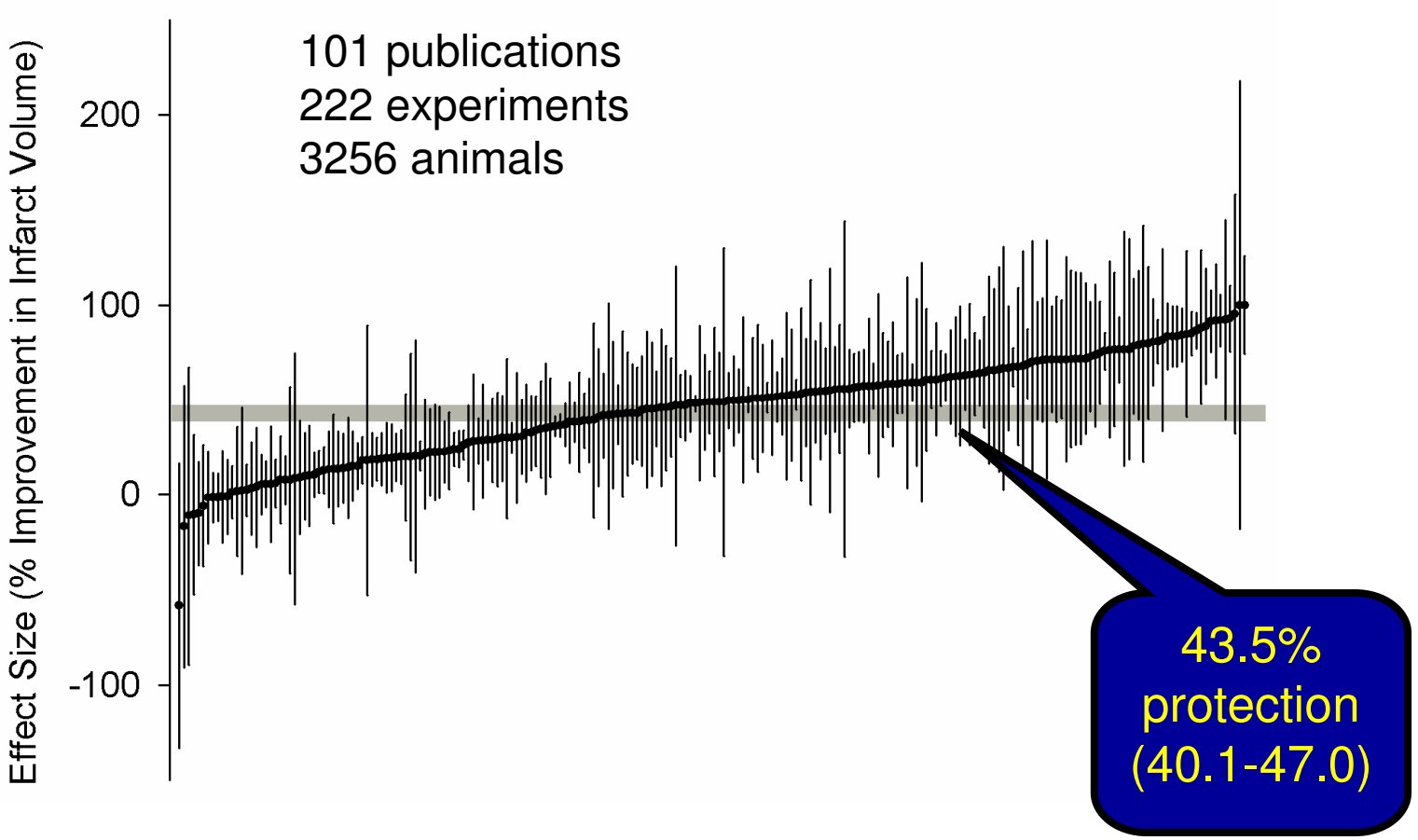
# Evidence based trial design



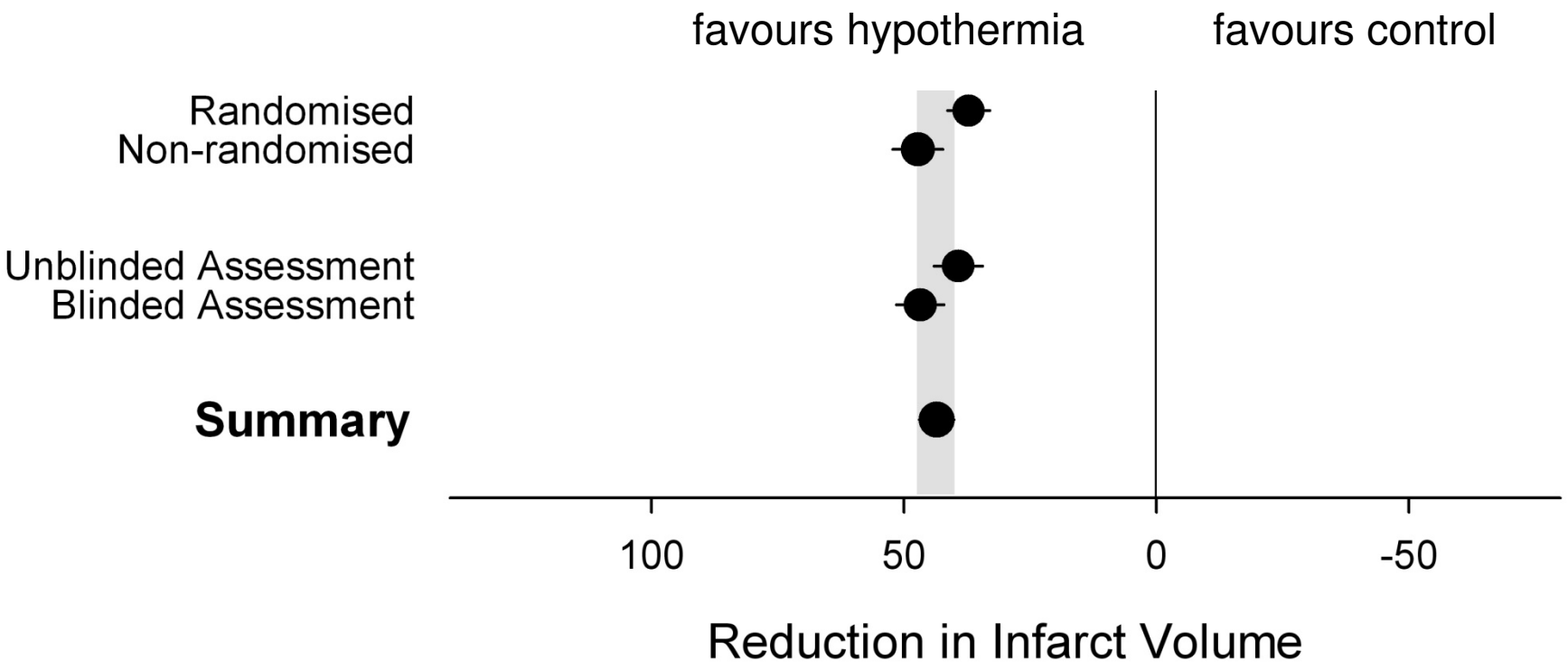

Systematic review and meta-analysis

- how powerful is the treatment?
- what is the quality of evidence?
- what is the range of evidence?
- is there evidence of a publication bias?
- What are the conditions of maximum efficacy?

# How powerful is the treatment in animals?



# What is the quality of evidence?



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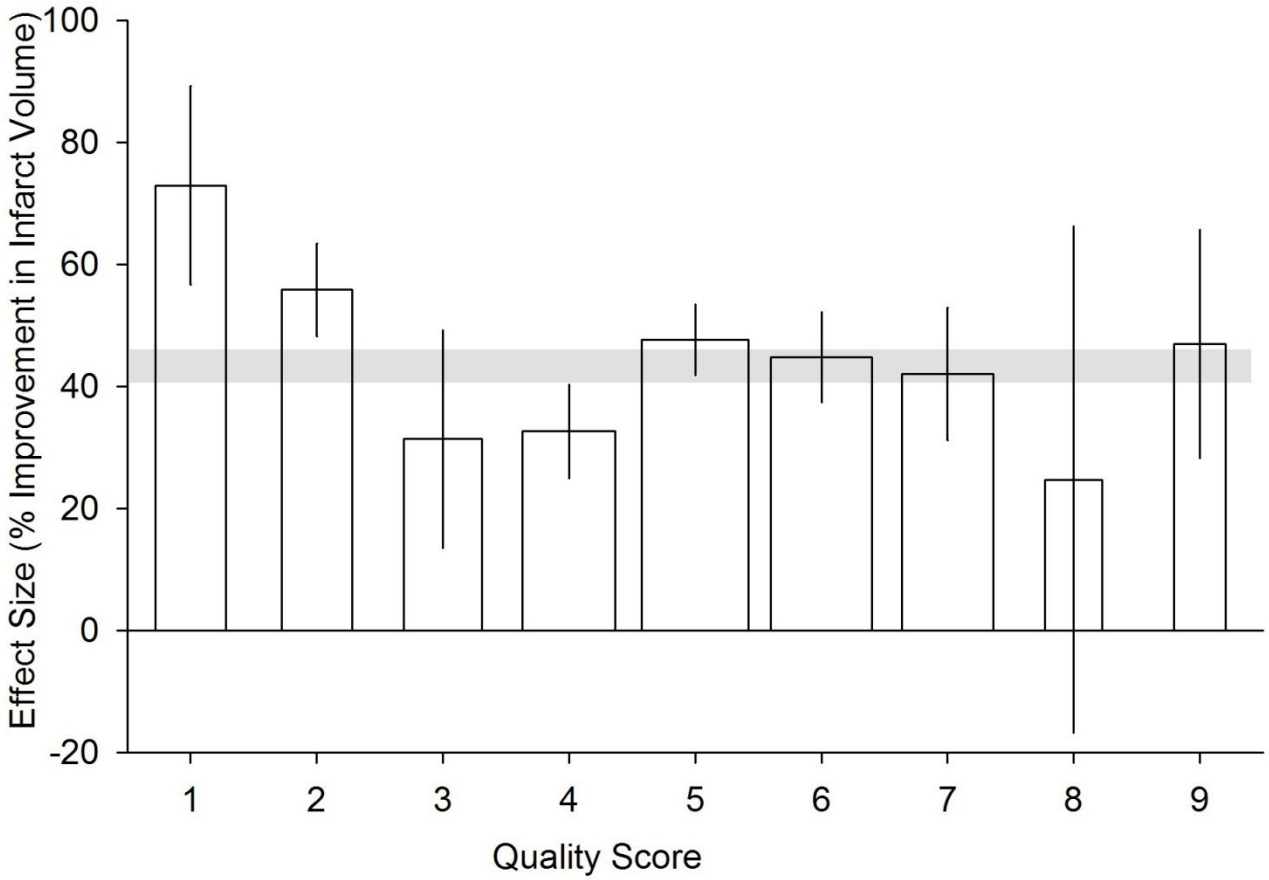
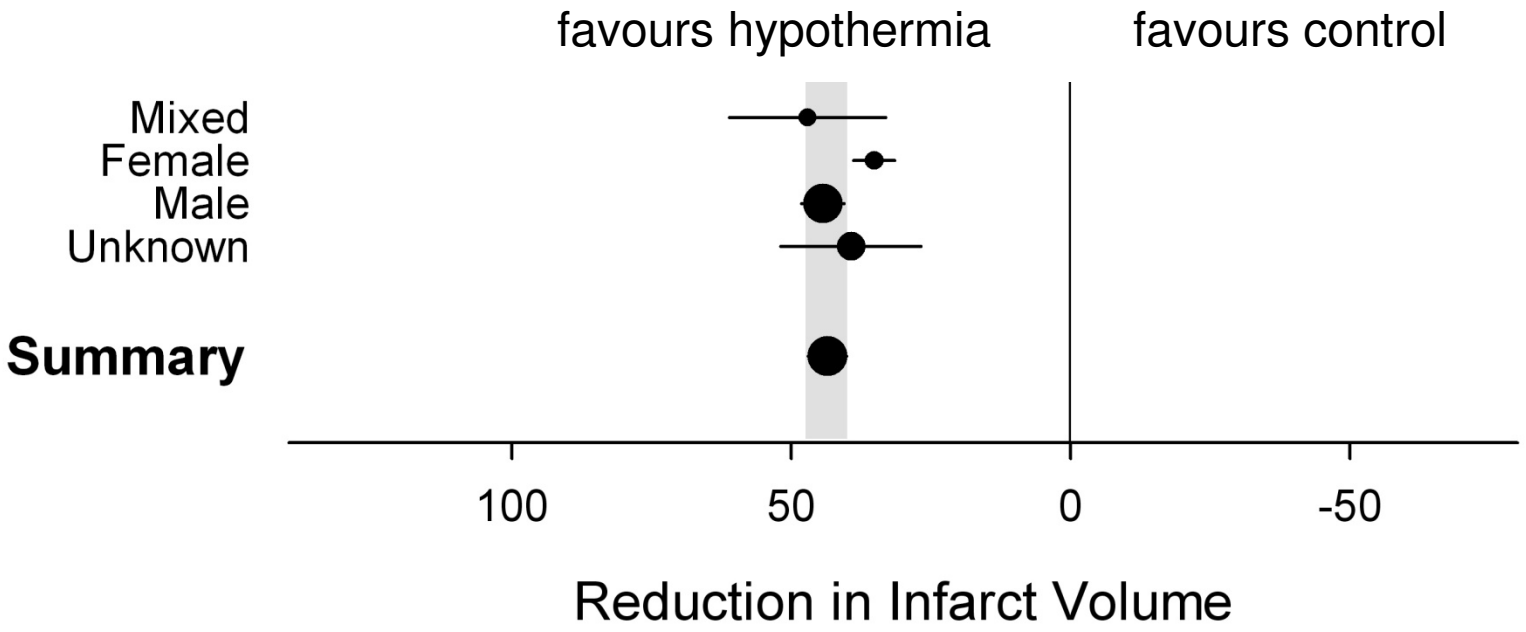


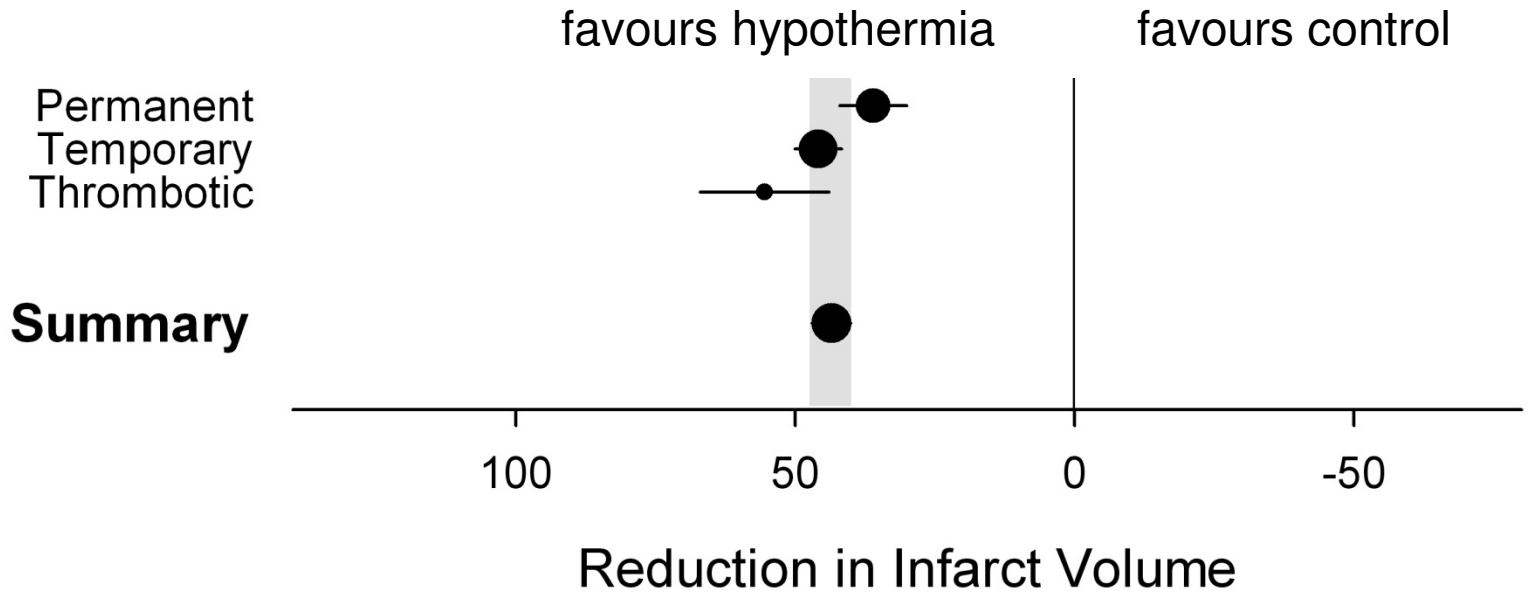
# What is the range of evidence?

sex



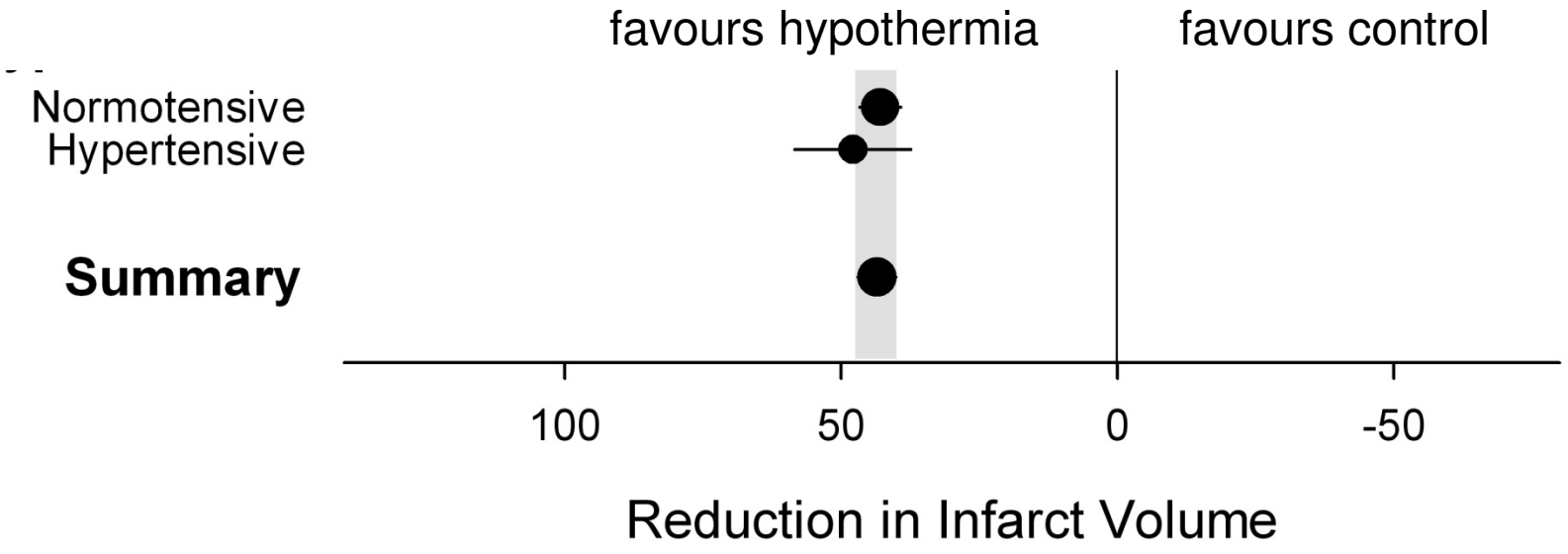
# What is the range of evidence?

duration of ischaemia



# What is the range of evidence?

presence of hypertension

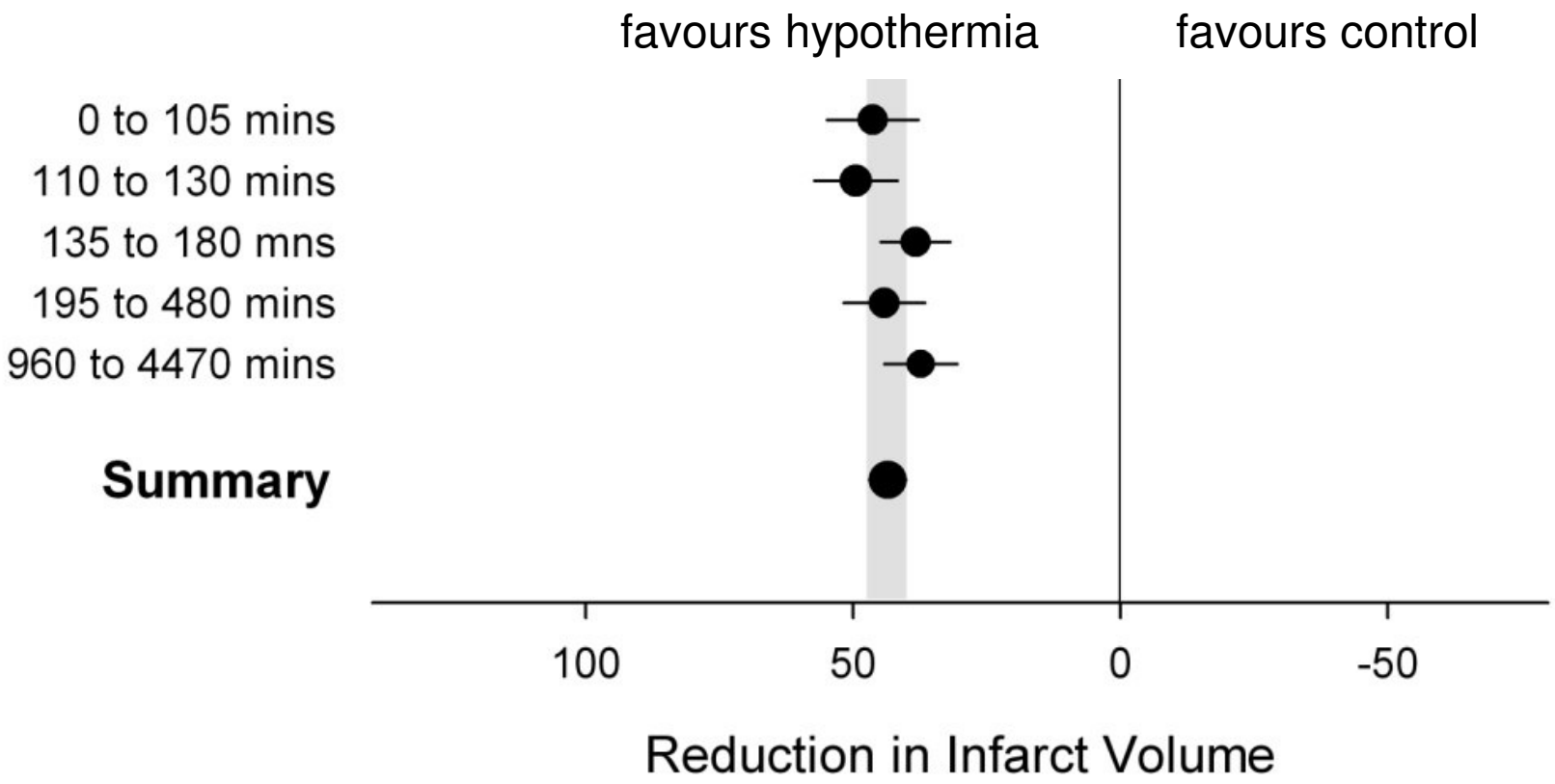


# Is there evidence of a publication bias?

| Intervention | Reported Effect Size (95%CI) | Bias with Egger Regression | Bias with METATRIM | Additional %Studies Considered "Missing" | METATRIM Adjusted Effect Size (95%CI) | Absolute Overstatement of Efficacy | Relative Over-statement of Efficacy |
|---|---|---|---|---|---|---|---|
| Estrogens | 26.7% (20.4%–33.0%) | + | + | 24 | 11.9% (4.6%–19.2%)[a] | 14.8% (8.0%–21.6%) | 124.4% |
| FK506 | 32.0% (27.8%–36.3%) | + | + | 30 | 21.9% (17.5%–26.3%)[a] | 10.1% (5.8%–14.4%) | 46.1% |
| Growth factors | 29.7% (25.9%–33.4%) | + | + | 14 | 25.1% (21.2%–28.9%)[a] | 4.6% (0.9%–8.3%) | 18.3% |
| Hypothermia | 43.5% (40.1%–47.0%) | + | + | 20 | 35.4% (31.7%–39.1%)[a] | 8.1% (4.5%–11.6%) | 22.9% |
| IL1-RA | 38.2% (31.2%–45.1%) | + | + | 36 | 25.4% (18.4%–32.4%)[a] | 12.8% (5.9%–19.7%) | 50.4% |
| Melatonin | 42.1% (35.7%–48.5%) | + | + | 14 | 41.0% (34.8%–47.3%) | 1.1% (−5.1% to 7.4%) | 2.7% |
| Minocycline | 30.9% (24.1%–37.6%) | + | − | 0 | No adjustment | | — |
| Nicotinamide | 29.2% (23.0%–35.5%) | + | + | 24 | 21.8% (14.9%–28.6%)[a] | 7.4% (0.8%–13.9%) | 33.9% |
| NOS donors | 21.4% (13.7%–29.1%) | + | + | 25 | 14.0% (6.4%–21.6%)[a] | 7.4% (−0.1% to 14.9%) | 52.9% |
| NOS inhibitors | 22.2% (17.1%–27.3%) | + | + | 13 | 14.7% (8.9%–20.6%)[a] | 7.5% (2.0%–13.0%) | 51.0% |
| NXY-059 | 43.8% (34.7%–52.8%) | + | − | 0 | No adjustment | | — |
| Piracetam and related compounds | 29.6% (16.1%–44.4%) | + | − | 0 | No adjustment | | |
| Stem cells | 29.6% (23.7%–35.4%) | + | − | 0 | No adjustment | | — |
| Tirilazad | 31.9% (23.1%–40.7%) | + | − | 0 | No adjustment | | — |
| tPA | 22.5% (19.2%–25.9%) | + | + | 5 | 19.9% (16.4%–23.3%) | 2.6% (−0.7% to 6.0%) | 13.1% |
| Other Thrombolytics | 46.6% (35.7%–57.5%) | + | − | 0 | No adjustment | | - |
| **Pooled analysis** | **31.3% (29.7%–32.8%)** | **+** | **+** | **214[b]** | **23.8% (22.2%–25.5)[a]** | **7.5% (5.9%–9.1%)** | **31.1%** |

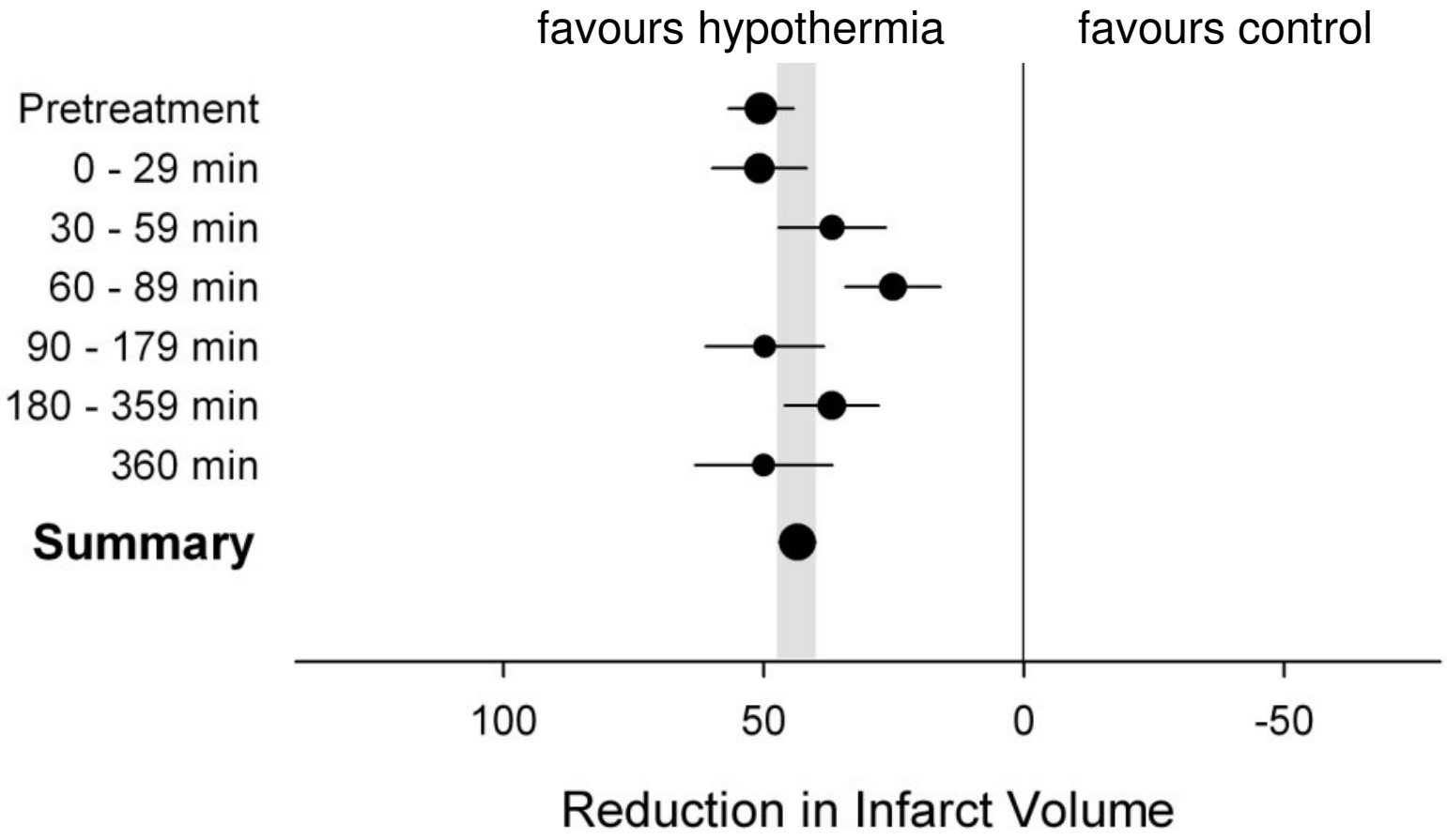
# What are the conditions of maximum efficacy?

duration of hypothermia



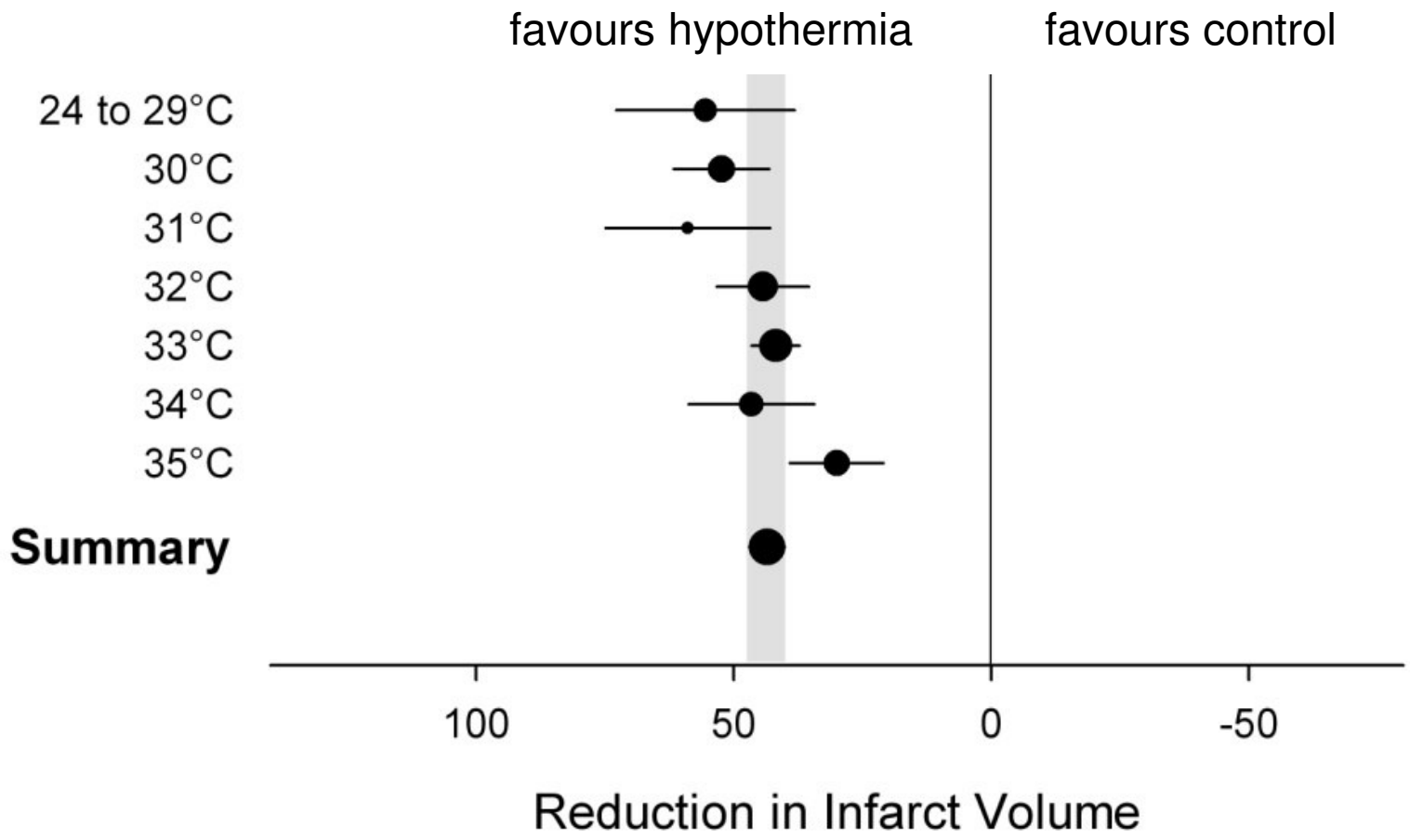
# What are the conditions of maximum efficacy?

delay to treatment



# What are the conditions of maximum efficacy?

depth of hypothermia



# EuroHYP-1

- International randomised controlled clinical trial of modest cooling in patients with stroke
- Evidence based trial design
  - entry within 6 hours of stroke onset
  - Cooling to 34 to 35℃
  - Patients with hypertension allowed
  - Cooling for 24 hours

# EuroHYP-1

- FP7 funding of €11m awarded from 01/02/12
- 50 – 70 centres in more than 15 countries
- First patient to be recruited September 2012
- 1500 patient target over 4 years
- Results late 2017

# Closing thoughts

- Developing treatments for testing in stroke and MS is difficult
- There are opportunities to improve the quality of the science and therefore the prospects of success
- Evidence based clinical trial design is a plausible and feasible approach
- In a few years, we'll also know if it is a successful approach

# Evidence based trial design in MS

- Providing information to support decision making in drug selection
- Identifying long list of candidate drugs from existing literature (MS, PD, AD, MND, HD)
- Assessing against dimensions of quality, safety, efficacy
- Co-presentation of details of efficacy for that drugs from animal studies

# Identification of long list

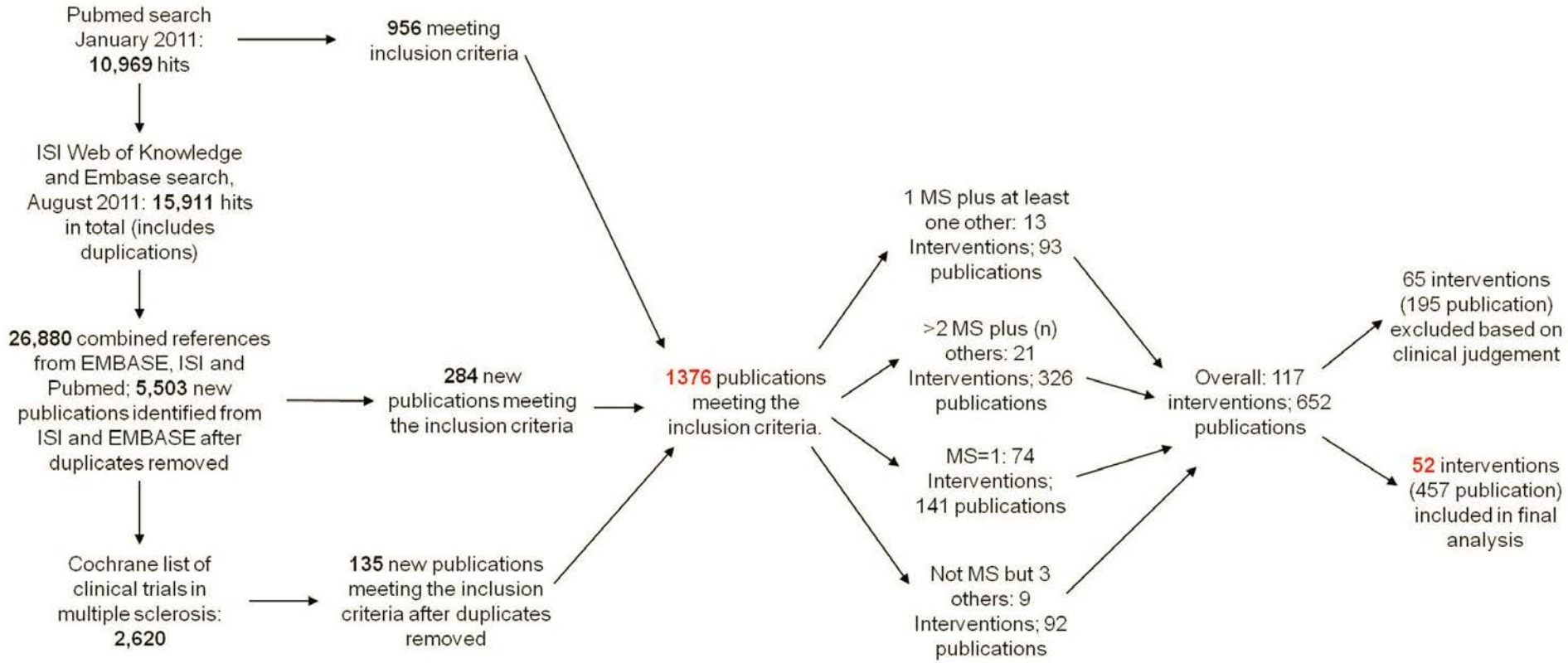



**Figure 1.** Quorum chart of the progression from the literature searches to the final number of relevant hits included in the systematic review.

# Dimensions of assessment

- Safety
  - SUSARs
  - SAEs only
  - AEs only
  - No AEs seen
- Efficacy
  - Definitely worse
  - Neutral
  - Non significant improvement
  - Significant Improvement

# Dimensions of assessment

- Quality
  - Three overlapping scales
    - CAMARADES basics
    - GRADE checklist
    - Atkins et al Delphi derived checklist
  - Score 0-21
  - Categorised by quartiles of quality to score 1-4

- Study size
  - logarithmic

# Heat Maps

| Efficacy Score \ Safety Score | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| 1 | | | 1 | |
| 2 | | 1 | | |
| 3 | | 1 | | |
| 4 | | | | |

| Efficacy Score \ Quality Score | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| 1 | | | 1 | |
| 2 | | | 1 | |
| 3 | | 1 | | |
| 4 | | | | |

| Quality Score \ Safety Score | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| 1 | | | | |
| 2 | | 1 | | |
| 3 | | 1 | 1 | |
| 4 | | | | |

| Efficacy Score \ Safety Score | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| 1 | 2 | 2 | | 1 |
| 2 | 5 | | 3 | 2 |
| 3 | 8 | 3 | 9 | 2 |
| 4 | 3 | 2 | 14 | 1 |

| Efficacy Score \ Quality Score | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| 1 | 3 | 2 | | |
| 2 | 1 | 5 | 4 | |
| 3 | 8 | 5 | 5 | 4 |
| 4 | 2 | 8 | 9 | 1 |

| Quality Score \ Safety Score | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| 1 | 8 | 4 | 3 | |
| 2 | 8 | 2 | 8 | 3 |
| 3 | 2 | 1 | 13 | 2 |
| 4 | | 1 | 4 | 1 |

# EAE data

| Author and Year | Quality Score | Animal | Sex | Time of Admin | Neurobehavioural Score (SE) | Axon Loss (SE) | Demyelination (SE) | Inflammation (SE) |
|---|---|---|---|---|---|---|---|---|
| Jiao,Z. 2008 | 4 | | | | | | | |
| | | Rat | F | 0 | 2.5 (0.6) | | | 2.2 (0.6) |
| | | Rat | F | 10 | 4.8 (1) | | | 2.8 (0.7) |
| Nashold,F. 2000 | 2 | | | | | | | |
| | | Mouse | B | | 2 (0.7) | | | 1.7 (0.7) |

# MS STOP consensus meeting

- Starting with a long list of 52 possible interventions, used the data presented to decide on shorter list of 7 (4 plus 3) attractive candidates for clinical trial
- Protocol currently in development