

1 Background

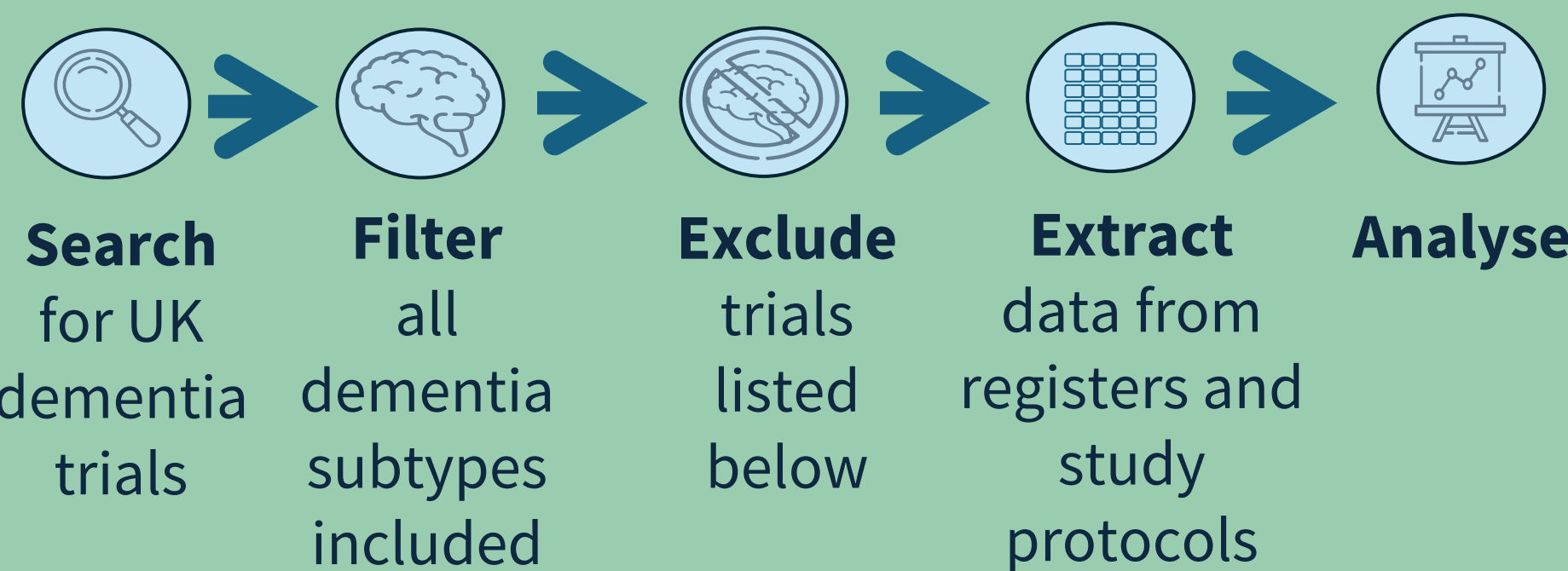
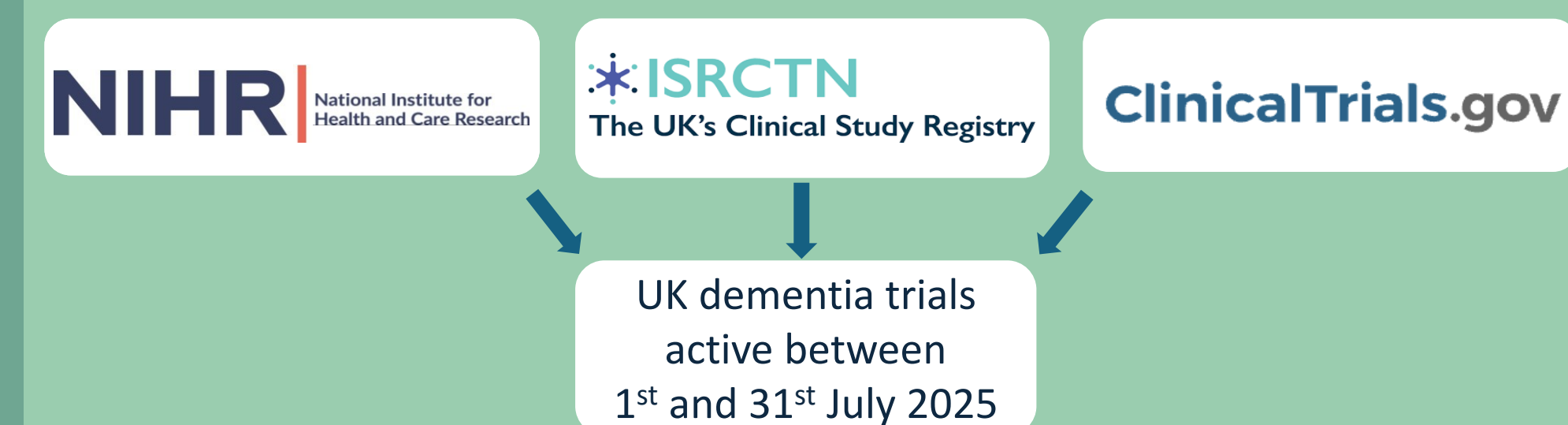
Introduction: Most people with dementia have additional diagnoses. Comorbidities affect their clinical care, including their response to, and tolerance of, pharmacological treatment and the interpretation of emerging blood-based biomarkers.

Aims and Hypothesis: To characterise the inclusion and exclusion of people with comorbidities in active dementia trials, with the hypothesis that common chronic conditions are exclusion criteria for many studies.



A study of nearly 5,000 primary care patients in the UK with a diagnosis of dementia found that 91.7% had at least one other chronic condition¹

2 Methods



We searched the National Institute for Health and Care Research Clinical Research Network's Open Data Platform, International Standard Randomised Controlled Trial Number registry, and ClinicalTrials.gov registration database and included all dementia trials. Trials focusing only on mild cognitive impairment, preclinical dementia, delirium, or dementia prevention were excluded.

Data on the diagnosis, type of intervention, inclusion and exclusion criteria, and projected sample size were extracted.

3 Results

We found 68 trials, representing a combined target sample size of 29,955 participants. Over half of these focused on Alzheimer's disease, with the other types shown in **Table 1**. Most were clinical trials of investigational medicinal products, and the remaining interventions are shown in **Table 2**.

Table 1: Types of dementia studied

Dementia subtype	Number of trials (%)
Alzheimer's disease	39 (57)
All-cause dementia	21 (31)
Frontotemporal	6 (9)
Lewy body	5 (7)
Vascular	1 (1)

Table 2: Types of intervention studied

Intervention	Number of trials (%)
Drug	38 (56)
Behavioural	14 (21)
Imaging	4 (6)
Device	3 (4)
Other, e.g. audio media, app	9 (13)

The most common contraindication to trial participation was a concomitant neurological disease, as shown in **Figure 1**. Around half of the studies listed broad exclusion criteria, such as "any clinically relevant comorbidity" or "unstable illnesses", with investigator discretion an important factor in the application of eligibility criteria.

Top 3 exclusion criteria:

1. Other neurological condition (85%)
2. Mental health condition (81%)
3. Cardiovascular condition (74%)

Four studies excluding renal disease referred to specific estimated glomerular filtration rate cut-offs, but most excluded any "clinically significant" renal disease

Only one study excluding patients with diabetes mellitus referred to specific haemoglobin A1c levels, while others excluded "poorly controlled" diabetes or simply "diabetes"

Frequency of exclusion criteria

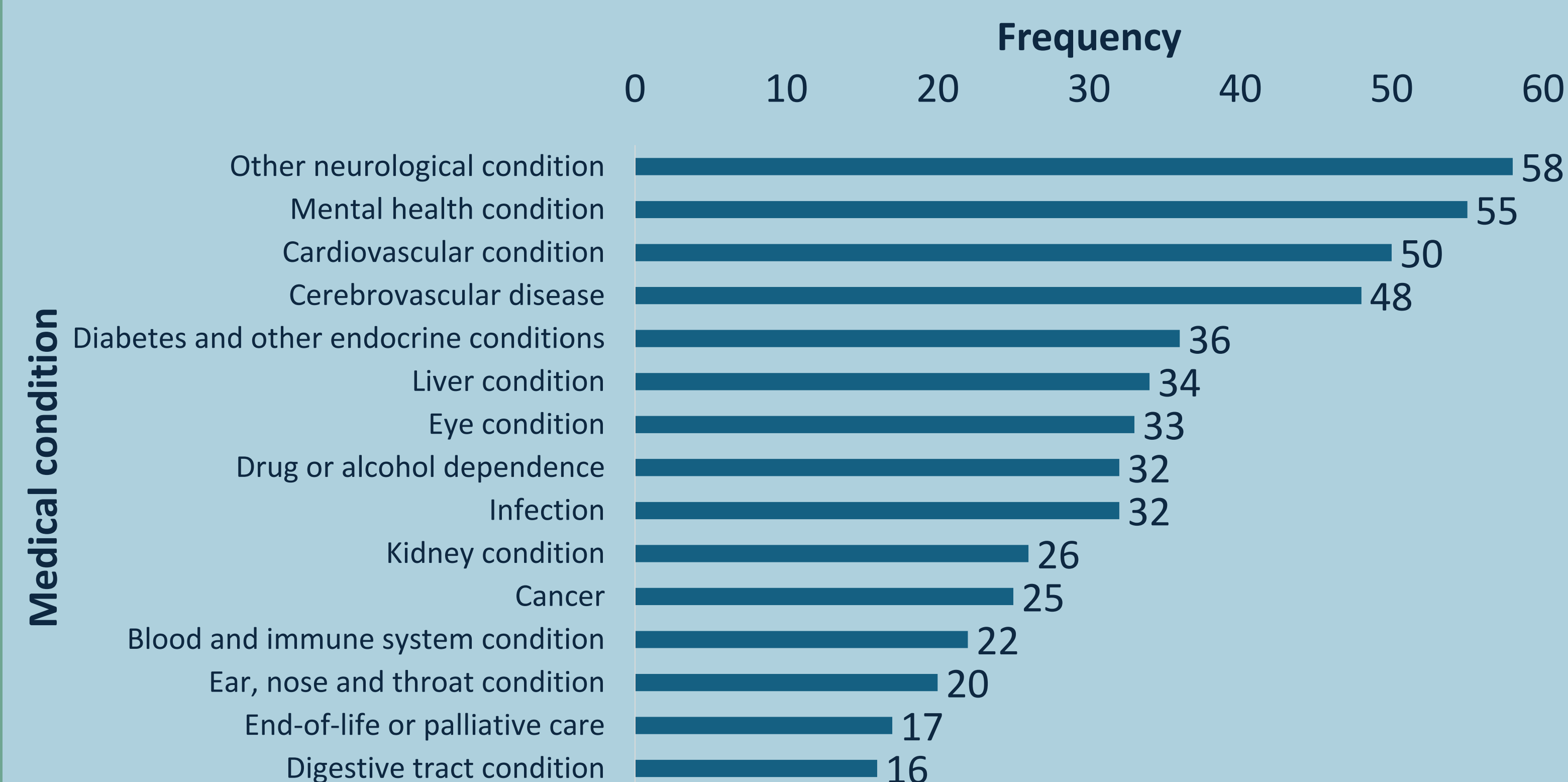
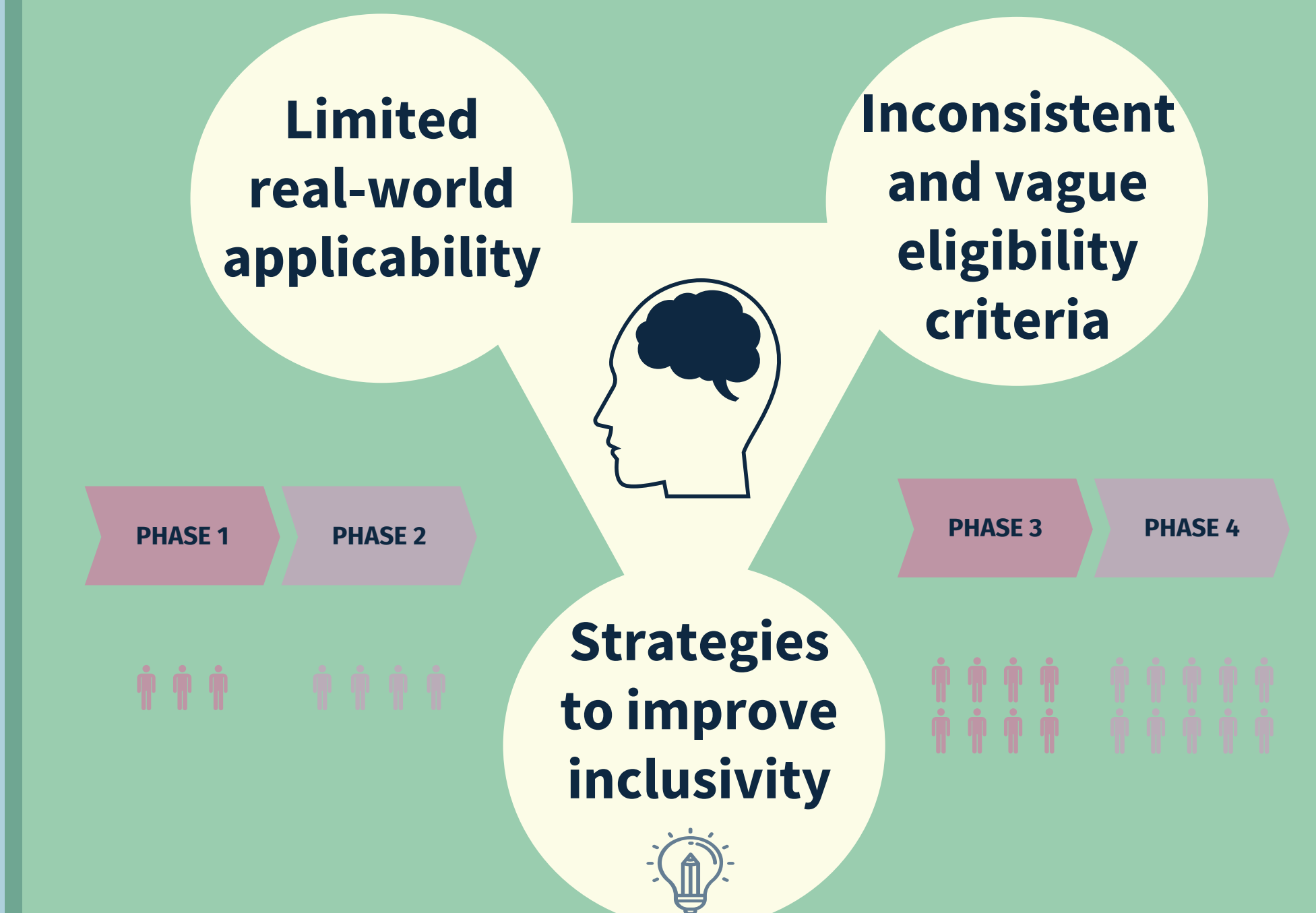


Figure 1: Exclusion criteria in descending order from most to least frequent

4 Discussion

The selective trial populations reduce the external validity of research. Clinical guidelines derived from these trials may therefore not fully apply to real-world patients with multimorbidity.

Trial exclusion criteria often use poorly defined terms and thresholds for clinical measures vary widely. Lack of consensus can lead to unnecessary exclusion and underrepresentation.



Studies recommend clearer disease classifications, broader eligibility in later trial phases, "expansion cohorts" for patients with comorbidities excluded from the main study, and observational studies to investigate effect modification by comorbidity.

5 Conclusions

Dementia trials of all types exclude participants with comorbid conditions. This limits their generalisability to populations with dementia.

Incorporating measures that more holistically reflect a participant's biological resilience, such as frailty, may improve the representativeness of trial participants and the application of results in real-world populations.

6 References

1. Browne J, Edwards DA, Rhodes KM, Brimicombe DJ, Payne RA. Association of comorbidity and health service usage among patients with dementia in the UK: a population-based study. *BMJ Open* 2017;7(3):012546. doi:10.1136/bmjopen-2016-012546

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