Neuroepidemiological methods

Carol Brayne

Content

- Basic approaches to studies and inference
- Measurement – diagnosis, lifecourse trajectories
- Reporting our research for maximum later value
- Summary

Designs for questions

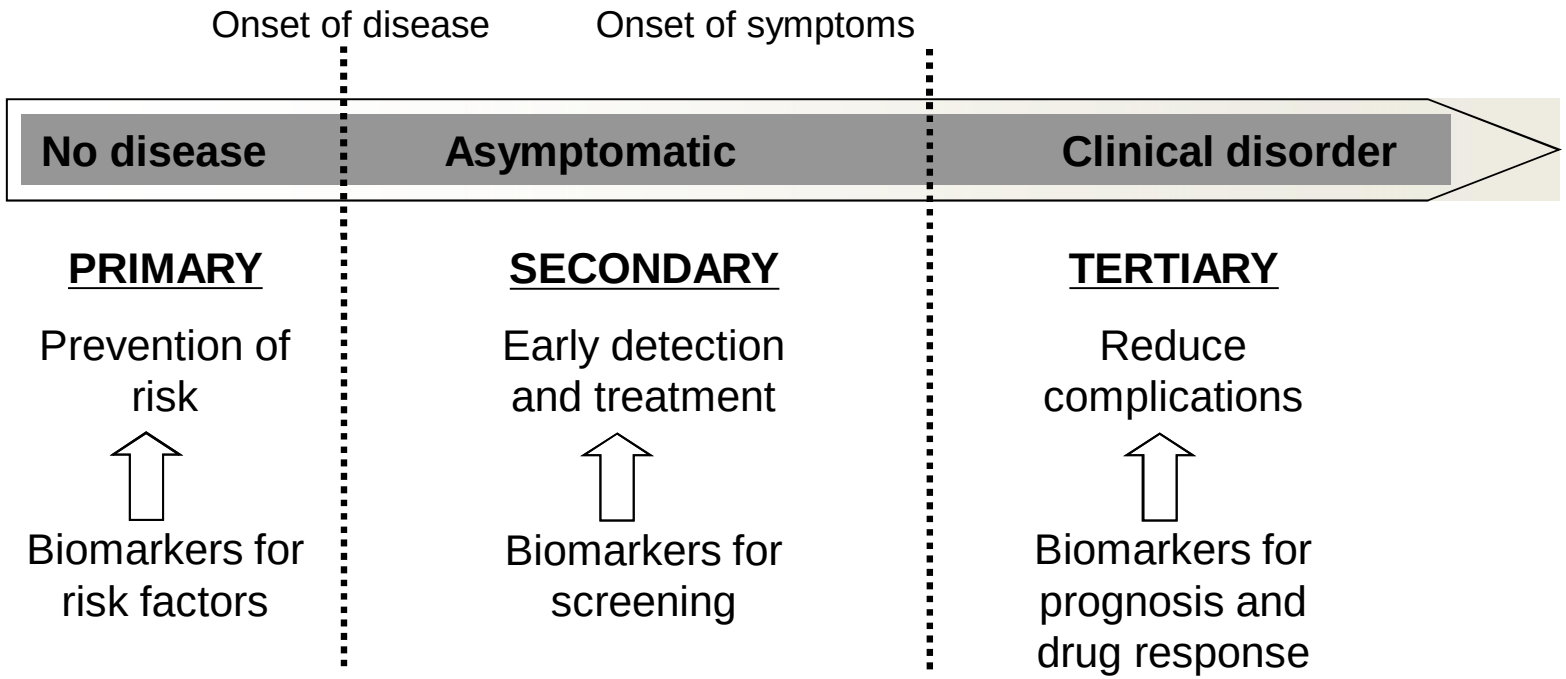
- First specify the question which needs to be answered
- Then choose the appropriate (and sufficient) design
- And build from there –

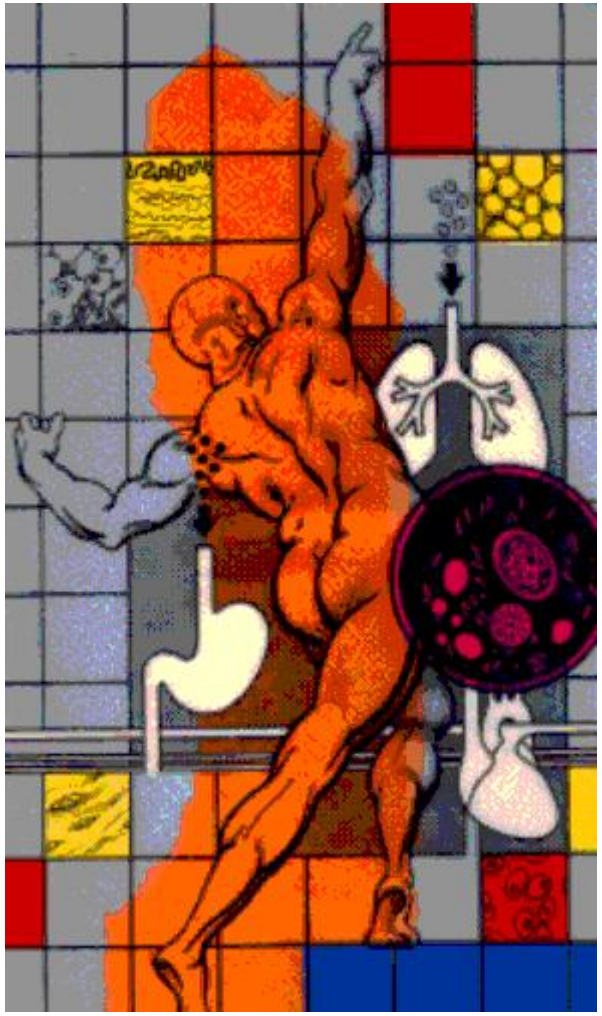
  appropriate sample

  appropriate definitions of disorders

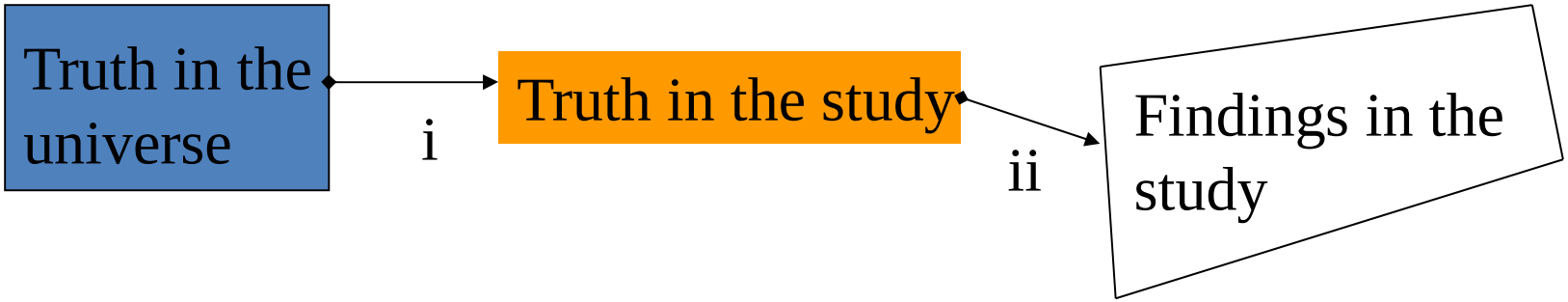
  appropriate measures

In the new world of Big Data these may need to be studies within large assembled datasets, but provenance, numerators and denominators will still be necessary as will meaningful outcomes for people in their ‘lived’ lives


Onset of disease
Onset of symptoms
No disease
Asymptomatic
Clinical disorder
PRIMARY
Prevention of risk
Biomarkers for risk factors
SECONDARY
Early detection and treatment
Biomarkers for screening
TERTIARY
Reduce complications
Biomarkers for prognosis and drug response

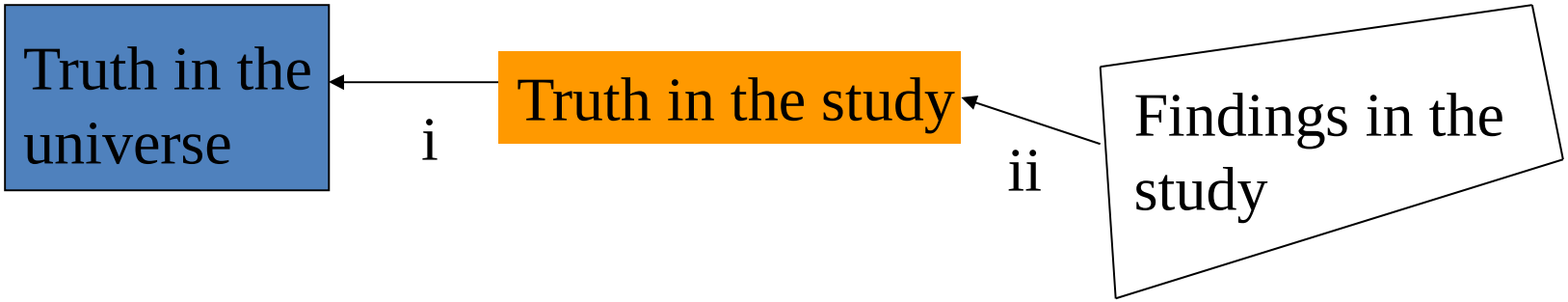


Moving from the truth about we wish to learn to the study we wish to carry out and the actual results we get.



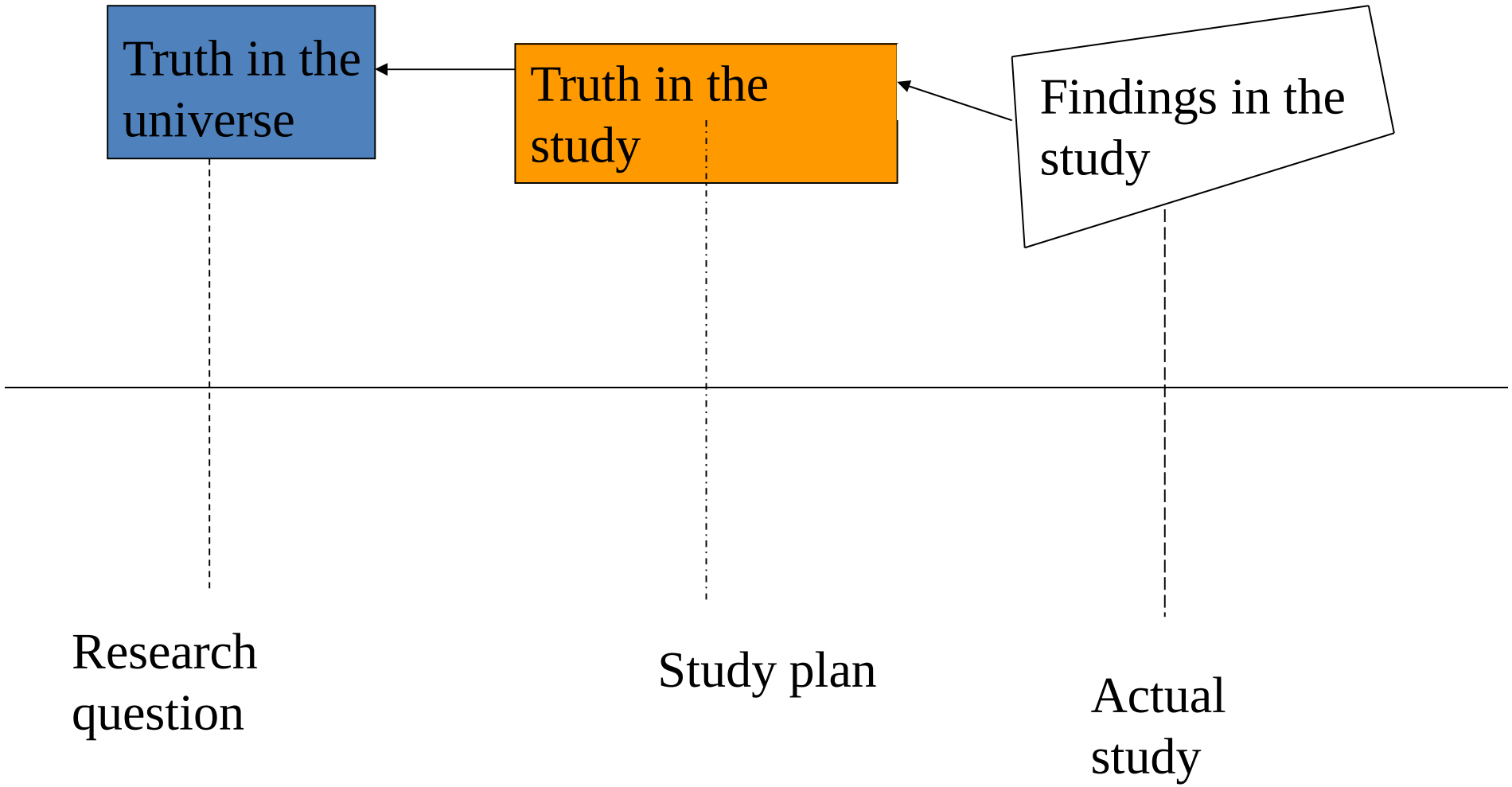
(i) = external validity

(ii) = internal validity

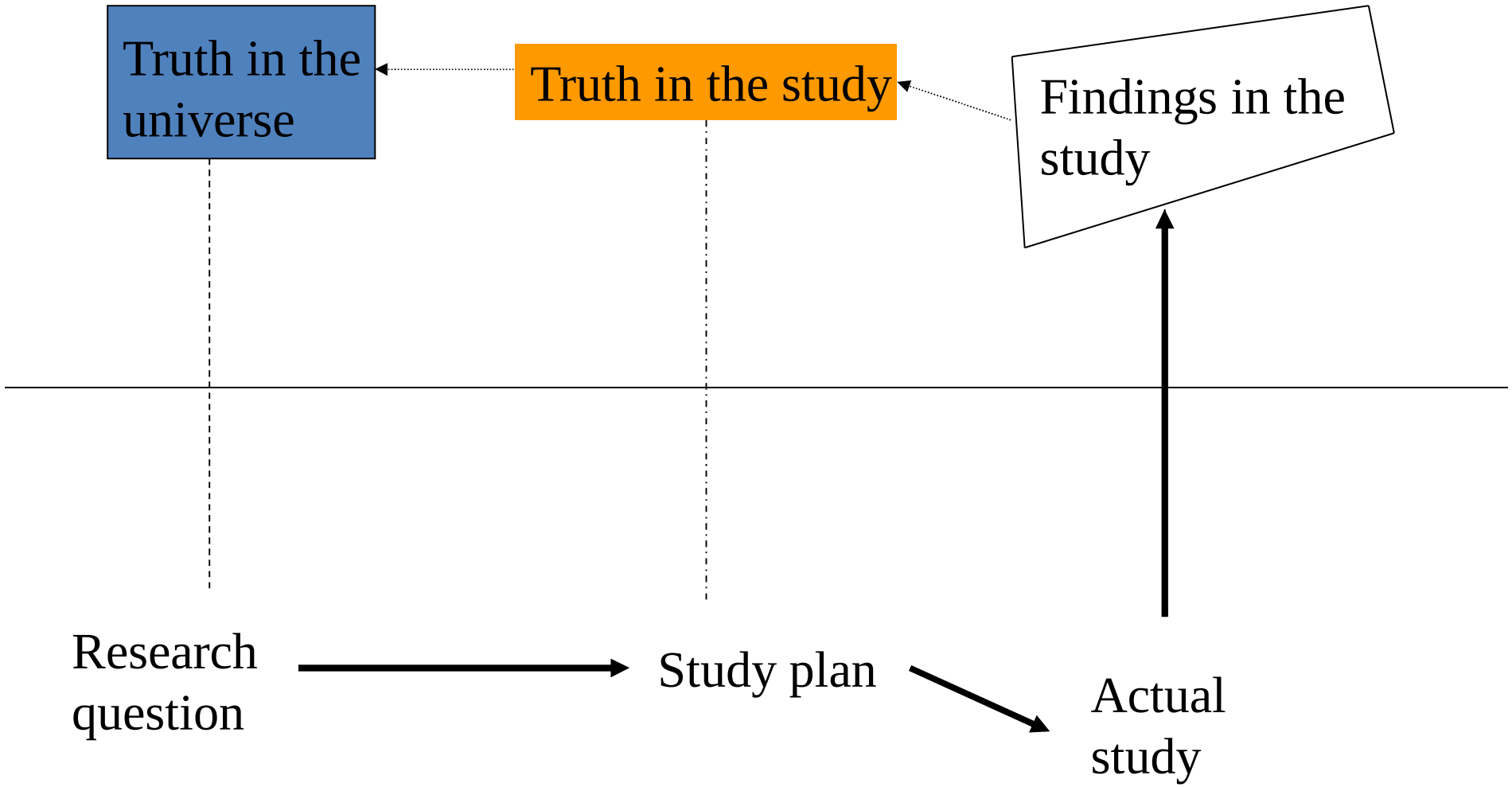


(i) = inference

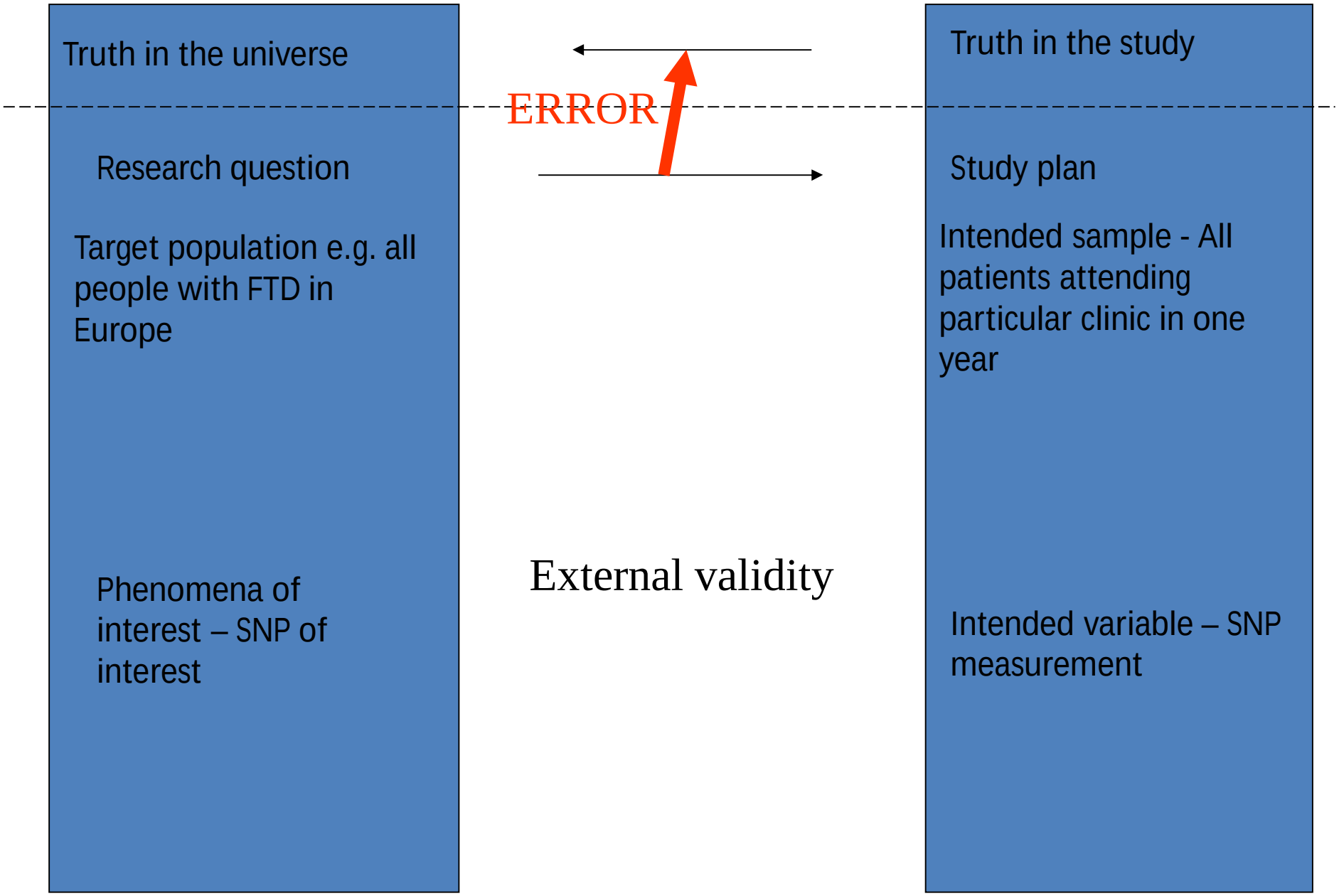
(ii) = inference

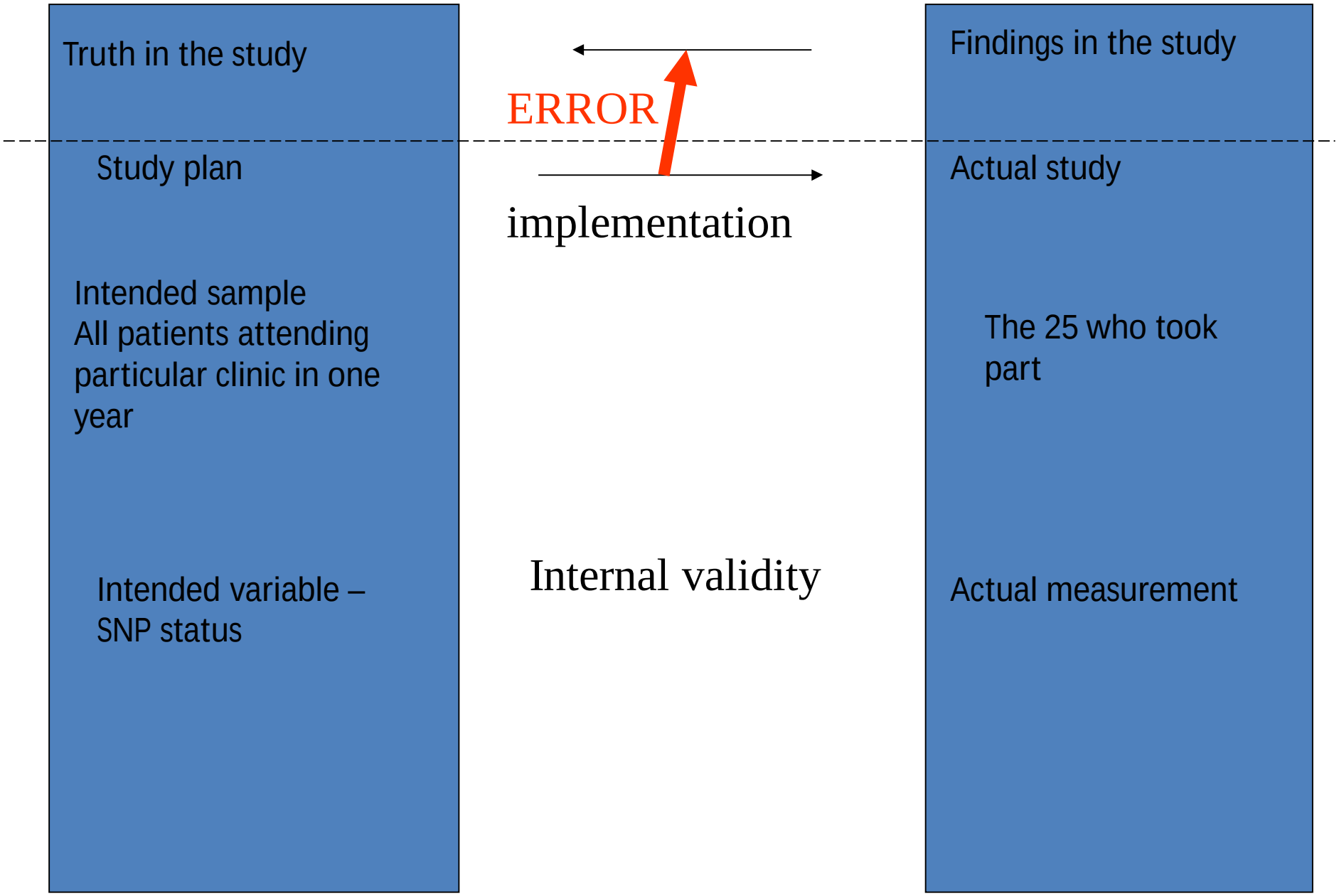

Truth in the universe
Truth in the study
Findings in the study
Research question
Study plan
Actual study

Drawing conclusions



Designing and implementing

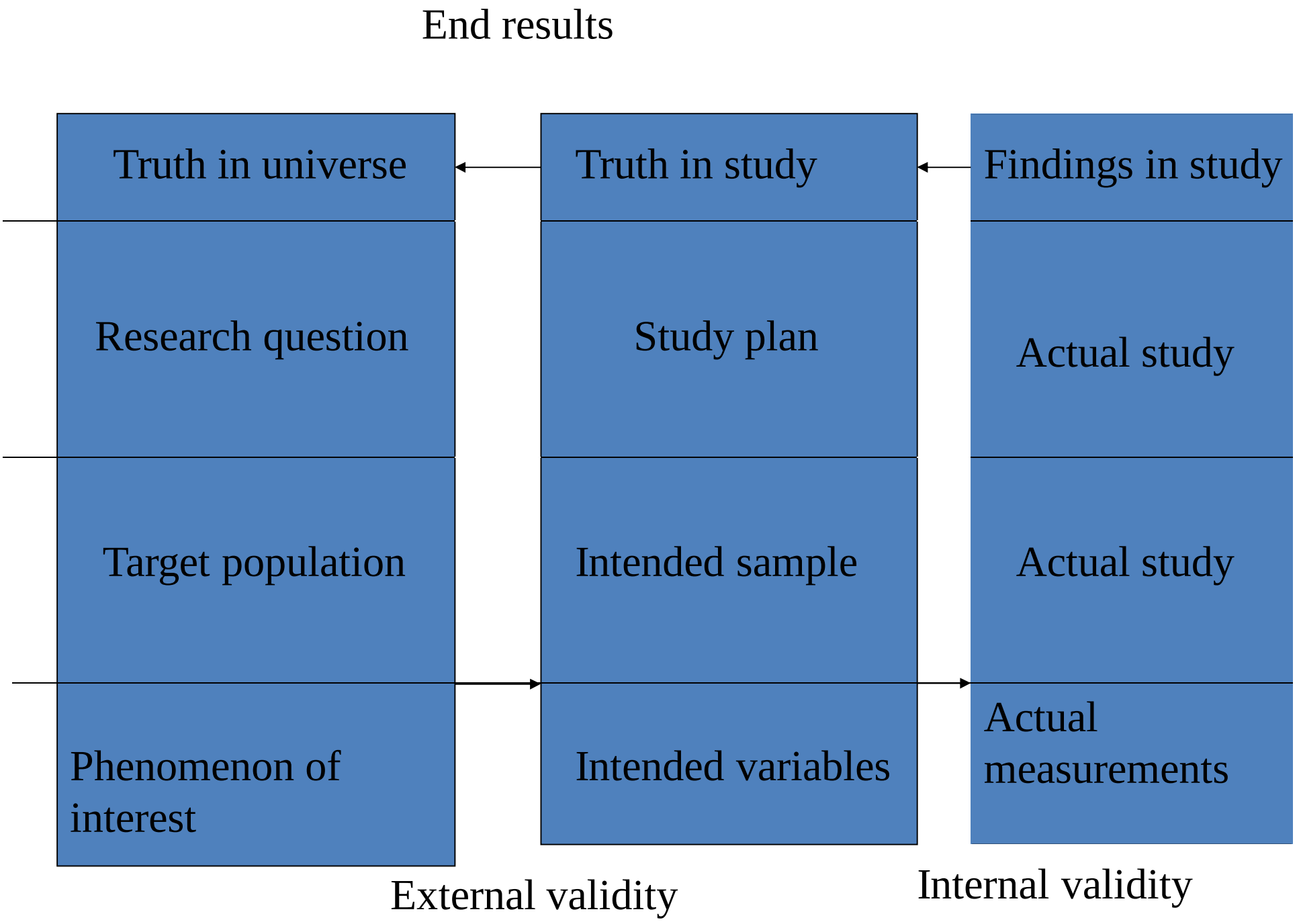

Truth in the universe
Research question
Target population e.g. all people with FTD in Europe
Phenomena of interest – SNP of interest
ERROR
External validity
Truth in the study
Study plan
Intended sample - All patients attending particular clinic in one year
Intended variable – SNP measurement

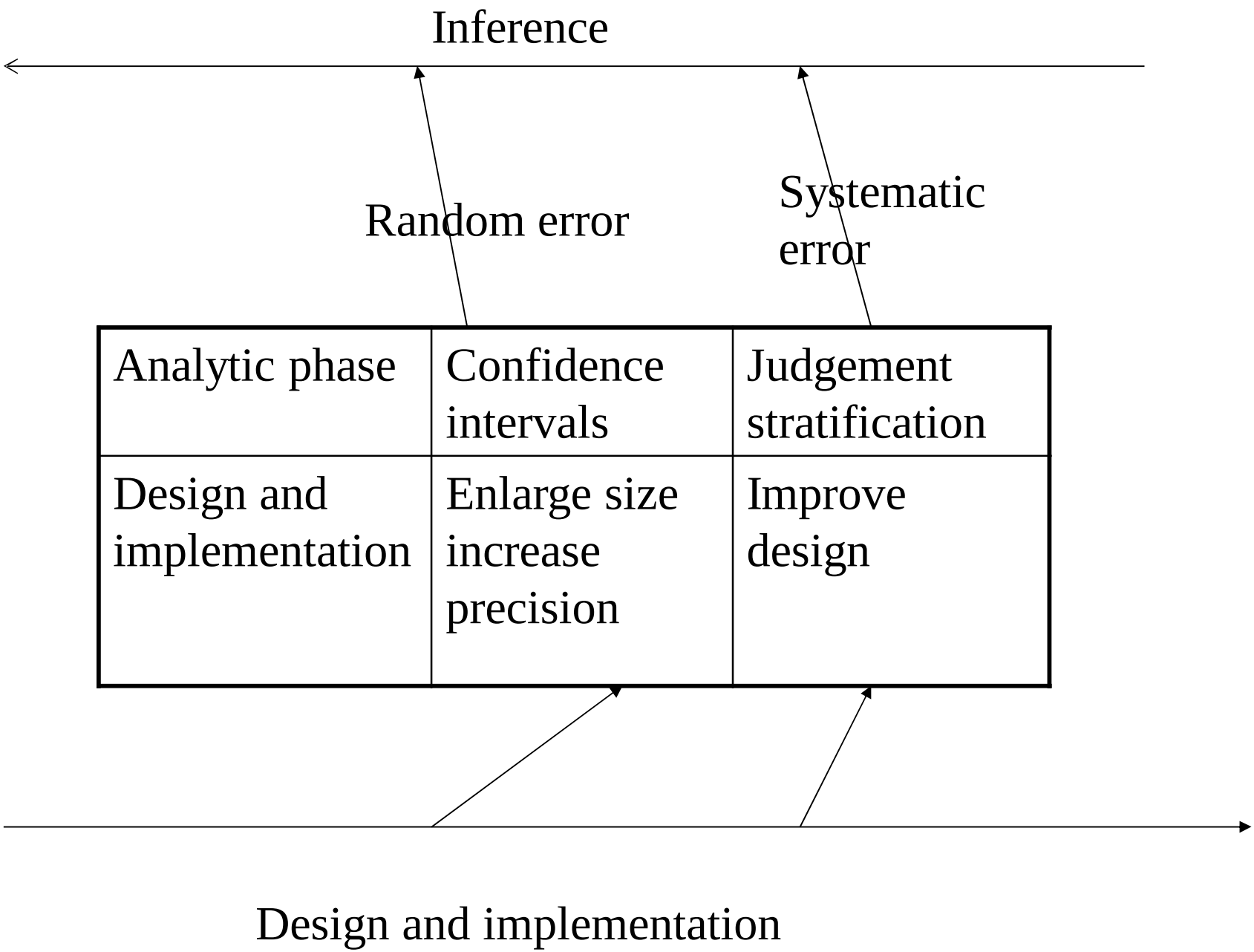

Truth in the study
Study plan
Intended sample
All patients attending particular clinic in one year
Intended variable – SNP status
ERROR
implementation
Internal validity
Findings in the study
Actual study
The 25 who took part
Actual measurement

Validity and reliability – refresher on terms

Validity (accuracy) - degree to which test measures what it should

Reliability (precision) - degree to which measures the same on several occasions


End results
Truth in universe
Truth in study
Findings in study
Research question
Study plan
Actual study
Target population
Intended sample
Actual study
Phenomenon of interest
Intended variables
Actual measurements
External validity
Internal validity


Inference
Random error
Systematic error
Analytic phase
Confidence intervals
Judgement stratification
Design and implementation
Enlarge size increase precision
Improve design
Design and implementation

Types of bias
(systematic deviation from the truth)

- Ascertainment
- Design
- Detection
- Information
- Interviewer
- Lead time
- Length
- Measurement
- Observer
- Recall
- Reporting
- Response
- Sampling
- Selection
- Work up
- Digit preference
- Instrumental error
- Assumption
- Withdrawals
- Autopsy
- Handling outliers
- Presentation of data
- Publication
- Estimators
- Interpretation
- Berkson’s

From Last dictionary of epi

Major focus on neurodegenerative disorders – what are the issues?

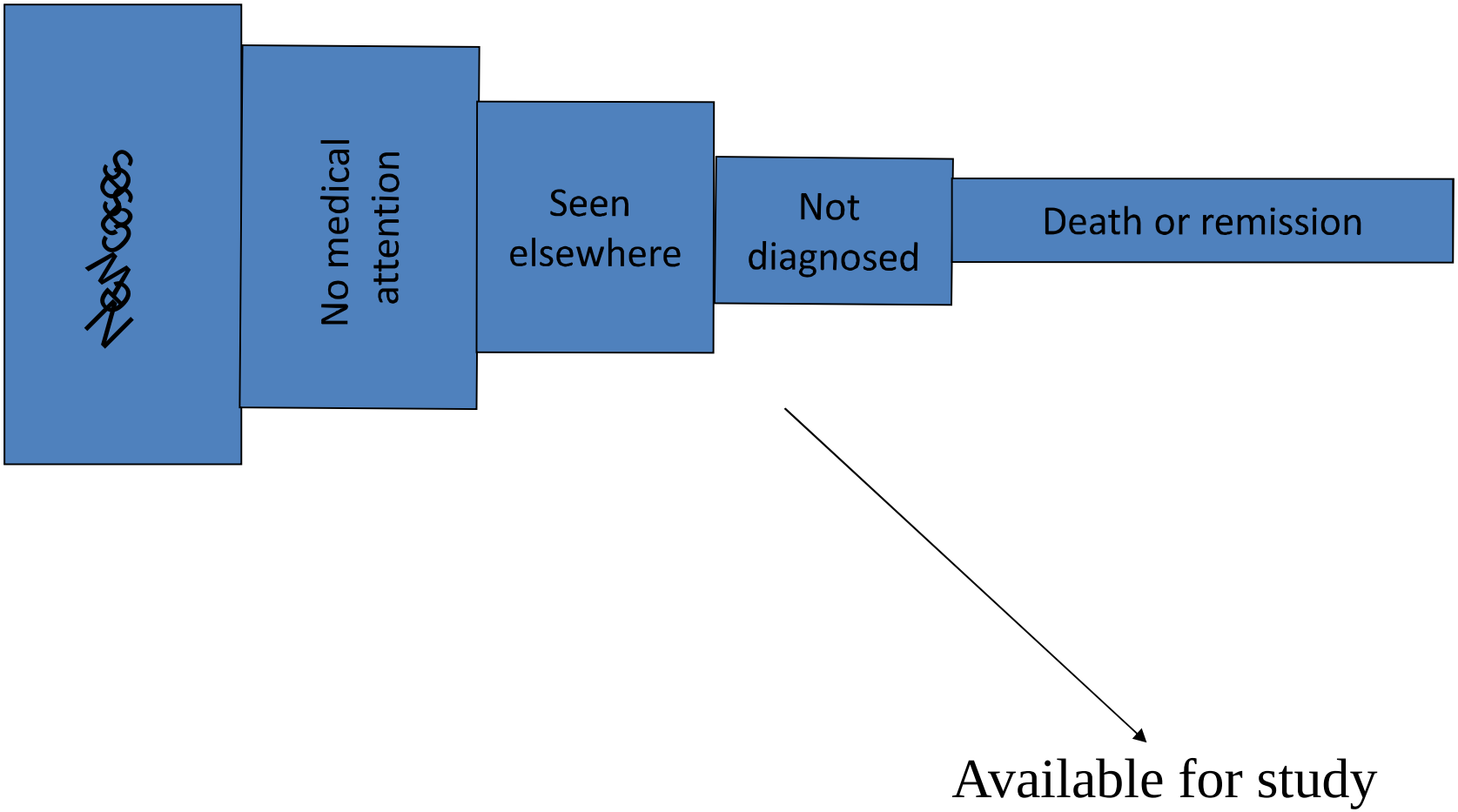
- What exactly are ‘they’?
- How do we measure ‘them’ and in whom?
- What else do we, should we, measure?
- How do we know these pose a big problem now or in the future?
- What do we do with the information?
- Will all the data we collect be used?
- How can we ensure its value?

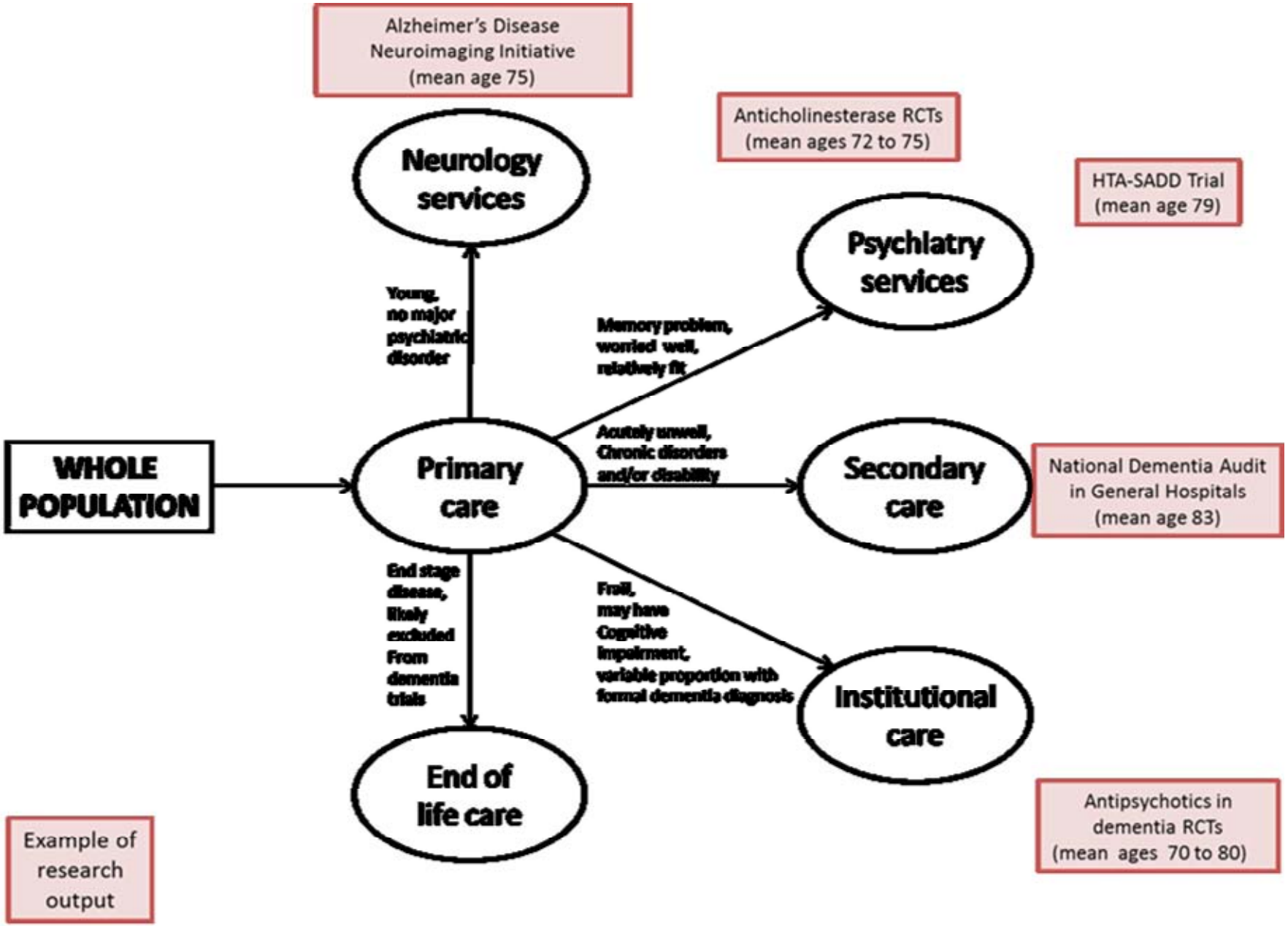
The questions we want to answer determine the nature of the design and challenges we face

- Populations: participation and drop out
- Measurements – clinical, environmental, observational, biological, remote
- Administration – nature of ligand, computerised..
- Way assembled – cutpoints, post hoc analyses, multiple analyses
- Biostatistics and bioinformatics – methods matter
- Blinding
- Uncritical synthesis of results

Types of sample – almost all in ND research come from bottom group

- Entire
- Selective
- Probability
    - simple random
    - stratified random
    - cluster
    - two stage cluster
- Non probability
    - consecutive
    - systematic
    - convenience
    - judgemental


No medical attention
Seen elsewhere
Not diagnosed
Death or remission
Available for study



Brayne and Davis, Lancet 2012

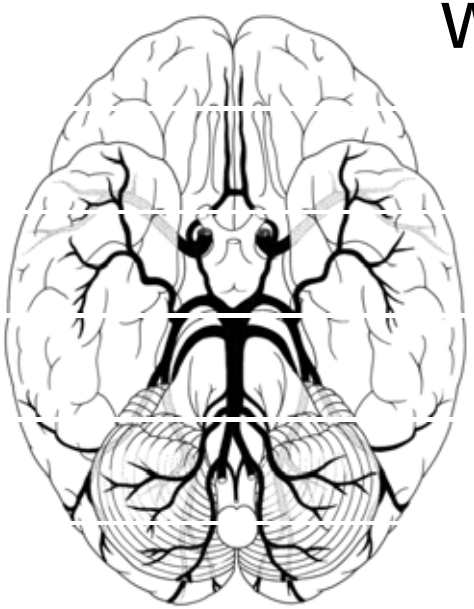
Example from classical literature widely assumed to be generalisable

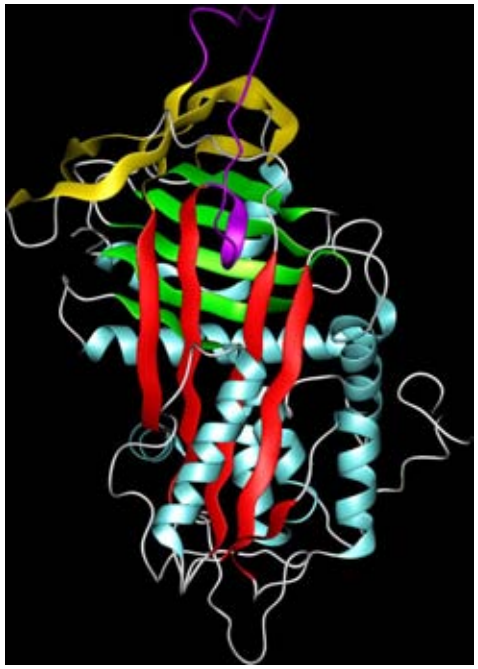
- Framingham cohort study
- Wanted all residents
- Systematic sample of 1 in 2 residents
- 2/3 uptake
- Subsequent resampling
- How generalisable?
- Probably to the intended sample
- Possibly to all Framingham adults
- Less obviously to US adults and
- Even less obviously to other age groups, countries and ethnic groups

Clinical syndromes and underlying biology pose challenges: need to measure both and also interaction with environment

- Syndrome itself: dimensional, cognition, ability to function and exclusion
- Subtypes: Alzheimer's, Vascular (out of fashion, now back), Lewy Body/PD (later), mixed (awkward)…alcohol related
- Multiple re-defining of criteria over years – highly unstable

Whose definition and whose perspective, with which types of measurement?





Neuropsychological/cognitive (crude, detailed, self/interviewer administrated computer and Paper and pencil)

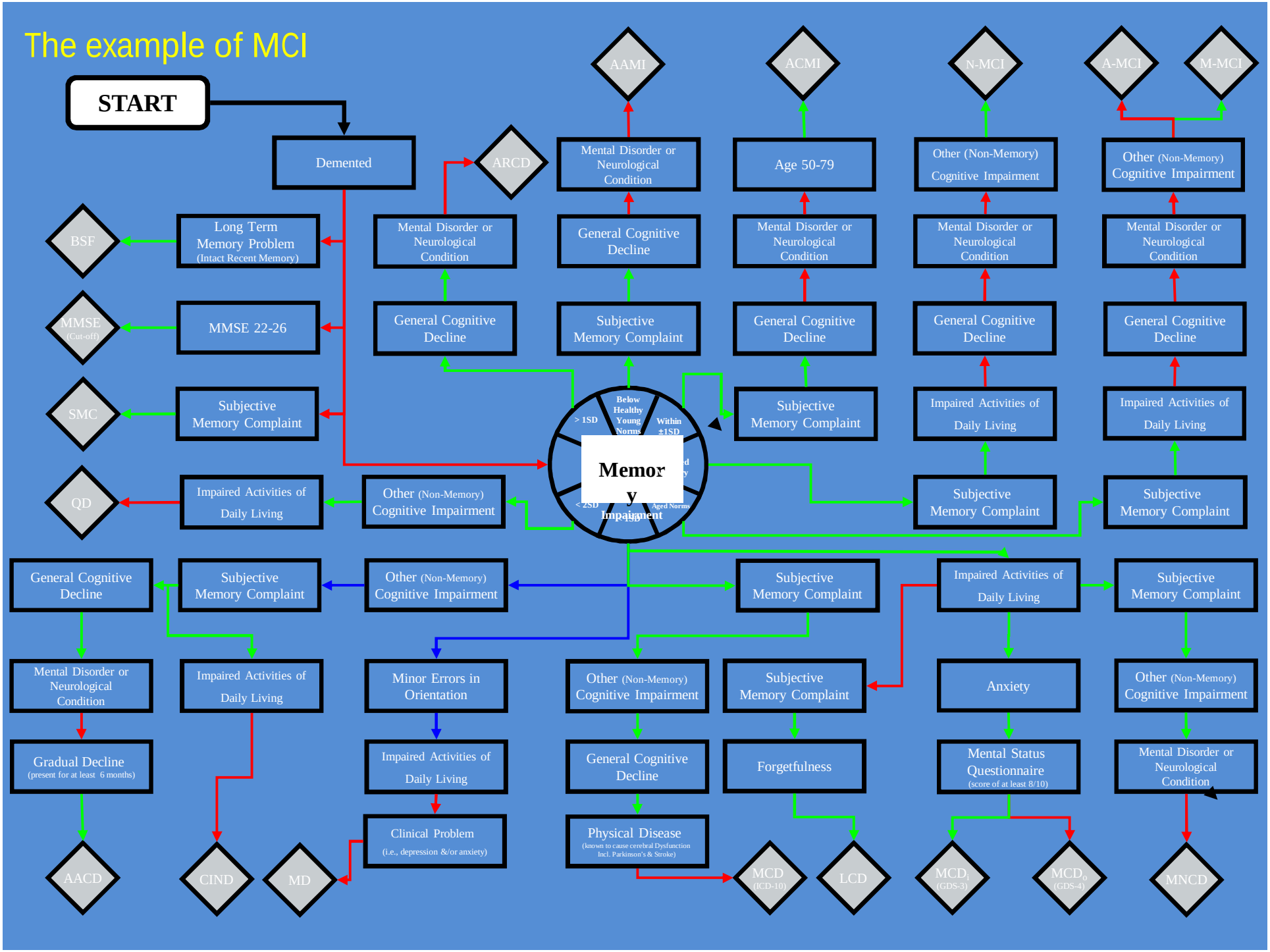
Imaging (structural, functional, ligands)

Clinical (non brain systems and neuropsychiatric/behavioural)

Neuropathological (traditional, novel)

Genetic and –omics

Other molecular (oligomers, dimers, monomers)


The example of MCI
START
Demented
ARCD
AAMI
ACMI
N-MCI
A-MCI
M-MCI
Mental Disorder or Neurological Condition
Age 50-79
Other (Non-Memory) Cognitive Impairment
Other (Non-Memory) Cognitive Impairment
BSF
Long Term Memory Problem (Intact Recent Memory)
Mental Disorder or Neurological Condition
General Cognitive Decline
Mental Disorder or Neurological Condition
Mental Disorder or Neurological Condition
Mental Disorder or Neurological Condition
MMSE (Cut-off)
MMSE 22-26
General Cognitive Decline
Subjective Memory Complaint
General Cognitive Decline
General Cognitive Decline
General Cognitive Decline
SMC
Subjective Memory Complaint
Subjective Memory Complaint
Impaired Activities of Daily Living
Impaired Activities of Daily Living
QD
Impaired Activities of Daily Living
Other (Non-Memory) Cognitive Impairment
Memory Impairment
Subjective Memory Complaint
Subjective Memory Complaint
General Cognitive Decline
Subjective Memory Complaint
Other (Non-Memory) Cognitive Impairment
Subjective Memory Complaint
Impaired Activities of Daily Living
Subjective Memory Complaint
Mental Disorder or Neurological Condition
Impaired Activities of Daily Living
Minor Errors in Orientation
Other (Non-Memory) Cognitive Impairment
Subjective Memory Complaint
Anxiety
Other (Non-Memory) Cognitive Impairment
Gradual Decline (present for at least 6 months)
Impaired Activities of Daily Living
General Cognitive Decline
Forgetfulness
Mental Status Questionnaire (score of at least 8/10)
Mental Disorder or Neurological Condition
Clinical Problem (i.e., depression &/or anxiety)
Physical Disease (known to cause cerebral Dysfunction Incl. Parkinson's & Stroke)
AACD
CIND
MD
MCD (ICD-10)
LCD
MCD (GDS-3)
MCD (GDS-4)
MNCD

Be careful of

- Inclusion criteria
- Exclusion criteria

- Be clear about reasons for both in relation to the underlying question

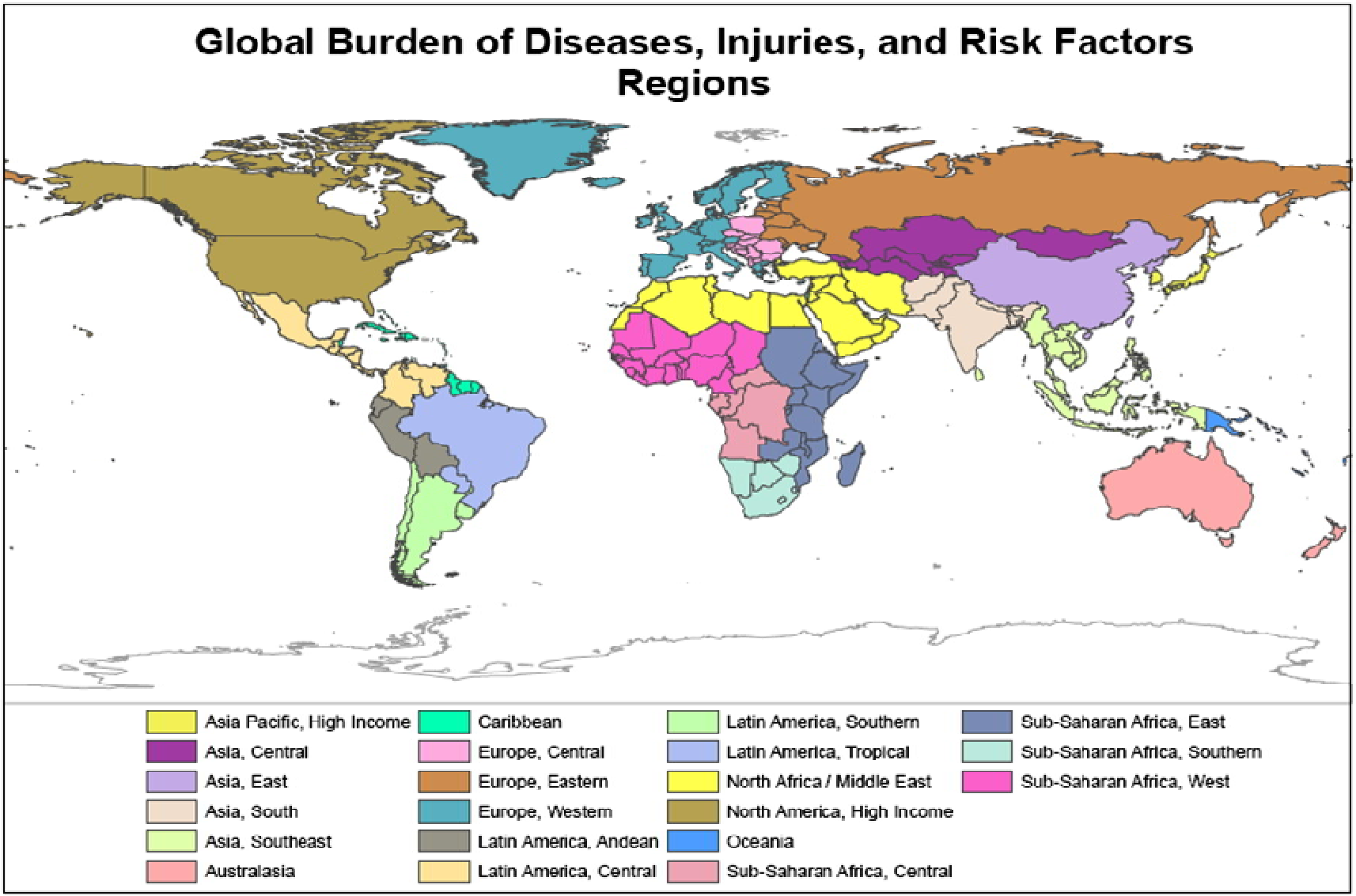
Good measurements

- Standardised procedures
- Operational definitions
- Training interviewers
- Refining instruments
- Automation where possible
- Repetition of measures
- Gold standards for diagnoses and for measurements remain an issue in fast changing environment

...allow for good reporting

- UK and New Zealand based initiative (Bennett, Oxford, Feigin NZ, Brayne UK)

Global Burden of Diseases, Injuries, and Risk Factors
Regions



Background and rationale

- During 1st ICCN conference,in Munich August 2009 approaches to “bridge the gap” between neuroepidemiological research and practice were discussed.

- It emerged that there were issues with the reporting of neurological research and this was a reason for gaps between evidence and practice for both clinicians and health policy decision makers.

Background and rationale

- Many reporting guidelines exist for different types of study design or different disease areas
- They have two main purposes:
  - they help researchers design and undertake robust studies;
  - they help reviewers and potential users of research outputs assess validity, reliability, and generalisability.
- Examples include:
  - CONSORT for randomised controlled trials; AGREE for clinical guidelines; STROBE for observational epidemiological studies

Background and rationale

- However, based on an examination of the STROBE explanation and elaboration statement there is a need for a new guideline pertaining to the conduct of descriptive health policy research in neurological disorders.
- This project aims to:
  - devise some guidance based initially on stroke
  - produce a set of quality criteria and comparable reporting guidance specifically for common neurological disorders.

Objectives

- Collate and summarise the existing literature on the principles of reporting both clinical and methodological aspects of incidence and prevalence studies of stroke ;
- Produce a draft set of items and principles that exemplify the reporting of incidence and prevalence studies;
- Identify:
  - the extent to which these principles have been followed by published incidence and prevalence studies of stroke
  - how rigour may be lost and how existing reporting could be improved;

Methods

- Identified reporting guidelines for incidence and prevalence studies in general.
- Identified reporting guidelines that are specific to stroke.
- Identified consensus reports, published reporting guidelines using PubMed and Medline (from inception to August 2012).

Methods

- Cochrane Methodology Register, Enhancing the Quality and Transparency of Health Research (EQUATOR) Network website and The US National Guideline Clearing House (up to August 2012).

- Reference lists and bibliographies of published systematic reviews of guidelines or checklists for incidence and/or prevalence studies.

Methods

- Information from the systematic review was used to identify the key pieces of information that:
  - must be included in order to assess potential sources of bias.
  - could be reported as it would be useful for policymakers.
- Created an initial checklist of these key items.

Assessment of relevance of this checklist

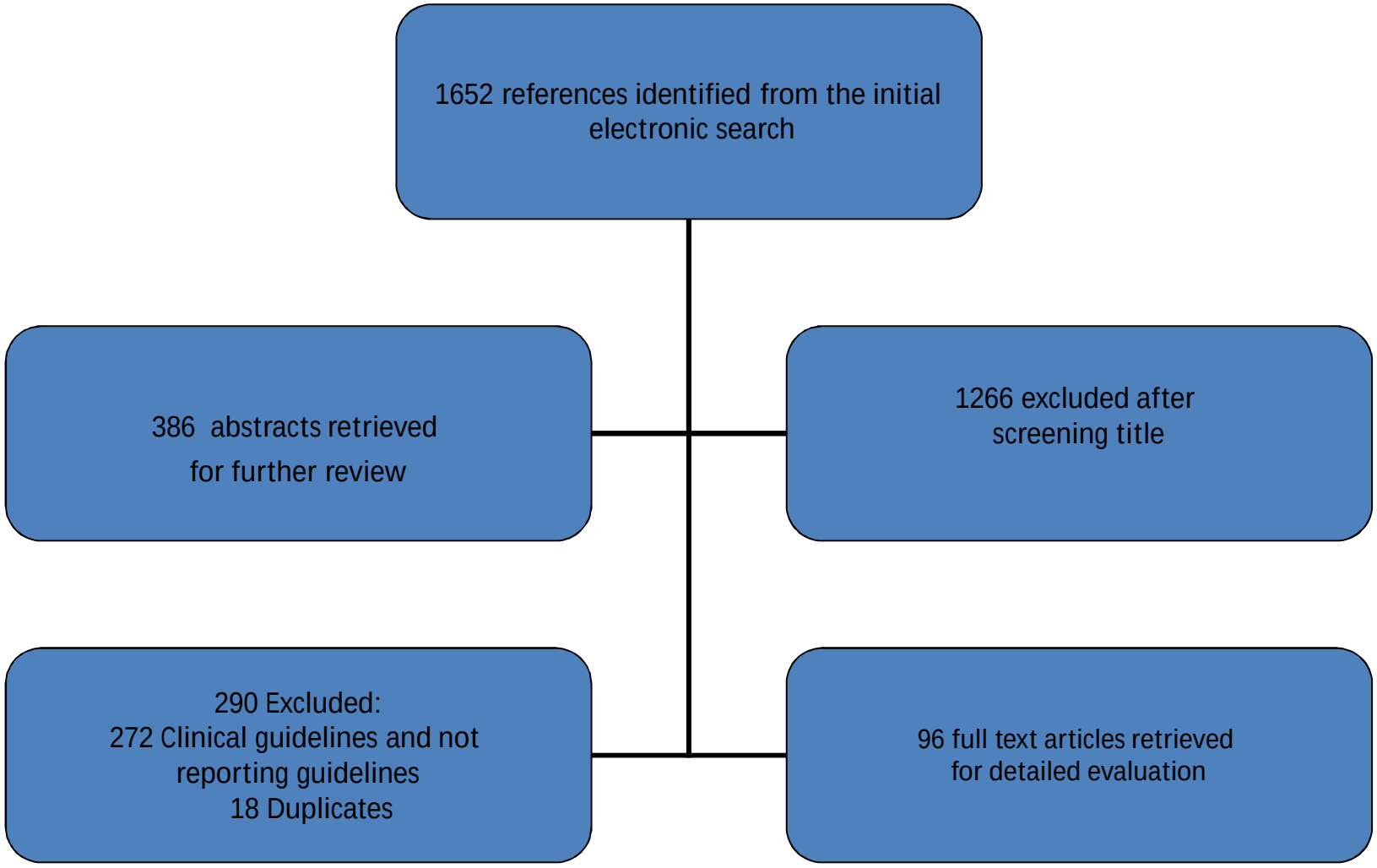
- Reviewed of a random sample of ~30 incidence or prevalence studies of stroke published between 2005 and the end of 2010 identified by the Global Burden of Disease and Injuries (GBD) Stroke 2010 project for inclusion.

- These studies used as a preliminary starting point in order to assess what is actually reported and the quality of reporting of these types of study.

- The aim of this process is to identify areas of deficiencies in reporting using contemporary sample of stroke incidence and prevalence studies.

Results

Results of search strategy



Summary of checklists and scales retrieved

Characteristics of tool	Checklist	Checklist and scale	Scale
Developed	12	0	5
Modified	18	0	27
No information about development of the tool	20	1	13
Can be applied to incidence/prevalence studies	8	0	14
Unlikely to be used for incidence prevalence studies	40	1	27
Created for incidence / prevalence studies	4	0	3
Validated	2	0	8
Reliability reported	4	0	17
Conflict of interest included	3	0	1
Levels of evidence	14	0	7
Grading	18	1	15
Total	*50*	*1*	*45*

Checklist items identified: clinical issues

- *Case-finding and sample size*
  - Evaluate all eligible members of the population using multiple overlapping case-finding procedures (hospitals, outpatient clinics, death certificates).
  - Assessment of completeness of case-ascertainment described.
  - Assessment of whether completeness of case-ascertainment is adequate.
  - What is the rate of admission in the particular population.

Checklist items identified: clinical issues

- *Case definition*
  - Cases of first ever in a lifetime event reported for incidence studies.
  - Clearly defined and consistent with globally accepted criteria.
  - If the disease under consideration is heterogeneous (as stroke is) then it should be reported how pathological subtypes are distinguished.
  - Prevalence should be defined as the number of cases existing in a specific time point.

Checklist items identified: clinical issues

- *Source of diagnosis*
  - Fully validated source or “gold-standard” criteria applied.
  - Define and justify severity.
- *Functional outcomes*
  - Measures of disability reported (such as modified Rankin scale for stroke).
  - Quality of life reported using a recognised measure.
- *Organization of healthcare*
  - Details of the health care system in country.
  - Description of how a person with stroke gets referred (with the filters).

Checklist items identified: methodological issues

- *Time-frame and population*
  - Data should refer to some specified time period (usually whole years).
  - Population should be clearly defined (usually, but not always, on a geographic basis) and stable, with limited in- and out-migration.
  - Details of the sampling method (is the population representative).
  - Well-defined denominator.
  - Prospective study design for incidence studies.
  - Sources of data (e.g. administrative database, medical records).
  - Response rate/ Exclusion rate.

Checklist items identified: methodological issues

- *Statistical considerations*
  - Raw numbers should be reported in sufficient detail to calculate the appropriate rates (by age, gender, ethnicity).
  - Rates should be given for all pathological stroke subtypes separately and combined.
  - Any assumptions made in calculations should be described.
  - Explain how missing data was addressed.
  - Any sensitivity analyses should be reported.
  - Reliability of the estimates.

Random sample of ~30 GBD 2010 stroke studies

- The studies covered diverse regions of the world
  - included low- and middle-income countries as well as high-income countries.
- Studies were published in a range of journals:
  - E.g. *Lancet Neurology, Stroke, Neuroepidemiology*
  - Mixture of open access journals and subscription based journals.
  - All published between 2006 and 2009.

Summary of results

- All studies described the time-period of the study, sampling method and details of how cases were obtained via multiple overlapping sources.

- All studies reported case-definition, diagnostic criteria and verification of stroke sub-types extremely well.
- Many studies outlined details of how they arrived at the number of cases included in their study and discussing exclusions (e.g. outside the study period, or not a first-ever in a lifetime stroke for incidence studies).

Summary of results

- Actual details of completeness of case-ascertainment not explicitly reported (does not mean that it wasn't assessed!).
- None of the studies explicitly reported whether the number of cases ascertained was adequate as assessed by some specific criteria.
- Very few studies reported details of the healthcare system and how patients were referred (only 4 and 3 studies respectively).
- All studies reported age- and sex-specific results with appropriate confidence intervals.

Conclusion

- Our review (and that of others), have found that many tools did not:
  - provide a clear description of their design.
  - describe development or the empirical basis for item inclusion.
  - describe how they evaluated of the tool's validity and reliability.
- We are in the middle of Delphi study with consultation on what should be included within reporting guidelines (led by Bennett from Oxford).

If you are interested let us know

- Carol.brayne@medschl.cam.ac.uk
- Reporting guidelines

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Conclusions

- Neuroepidemiology has much to contribute and more if research well conducted and recorded
- When writing up studies ensure good reporting using basic principles, and available guidelines
- Big Data should not blind us to need for rigorous and detailed explanatory research
- Need to integrate methods and work across many disciplines including quantitative and qualitative
- Need to be aware of the motivation for our research – not always simple