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Defining and selecting populations, extrapolation of benefit between populations

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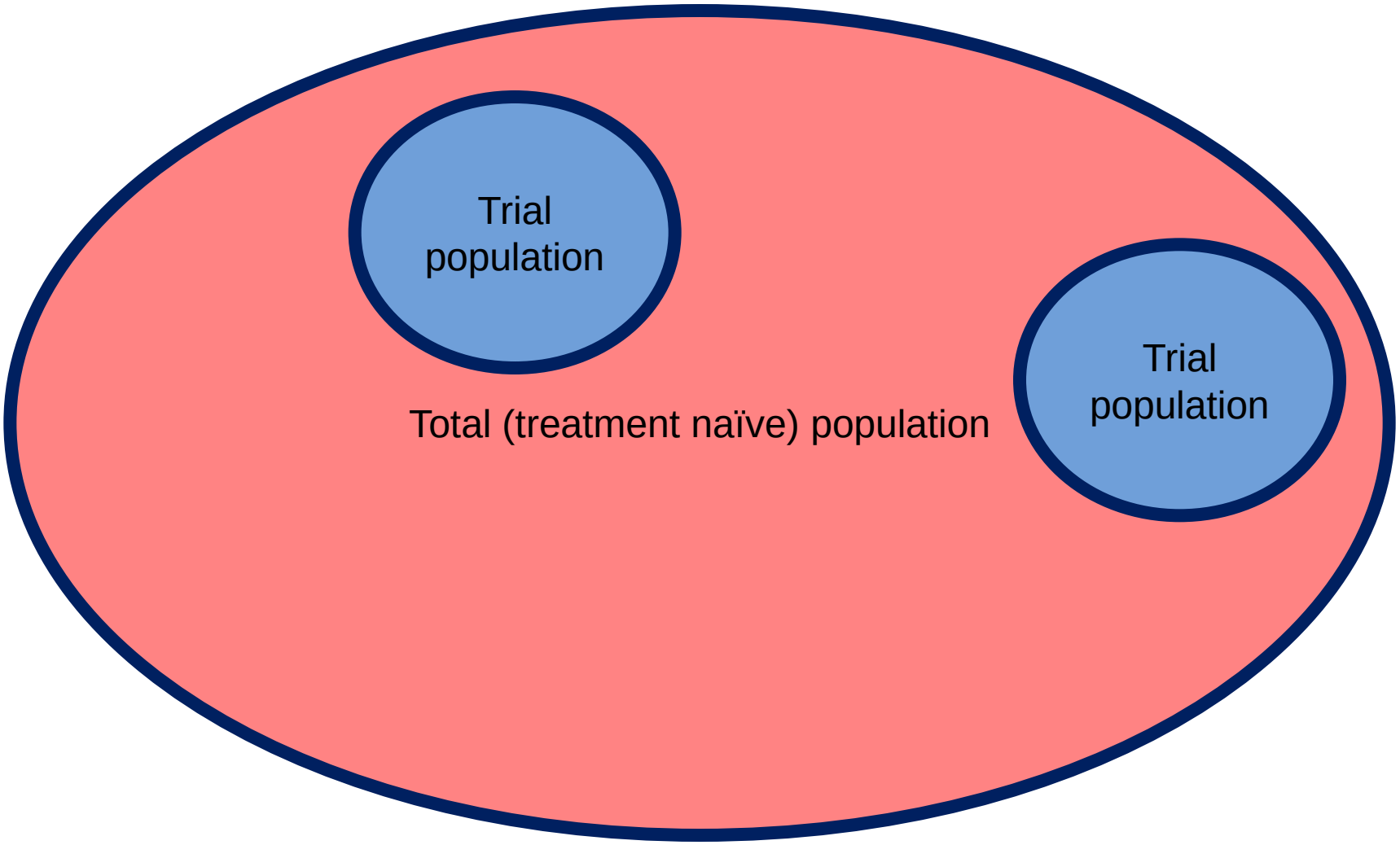
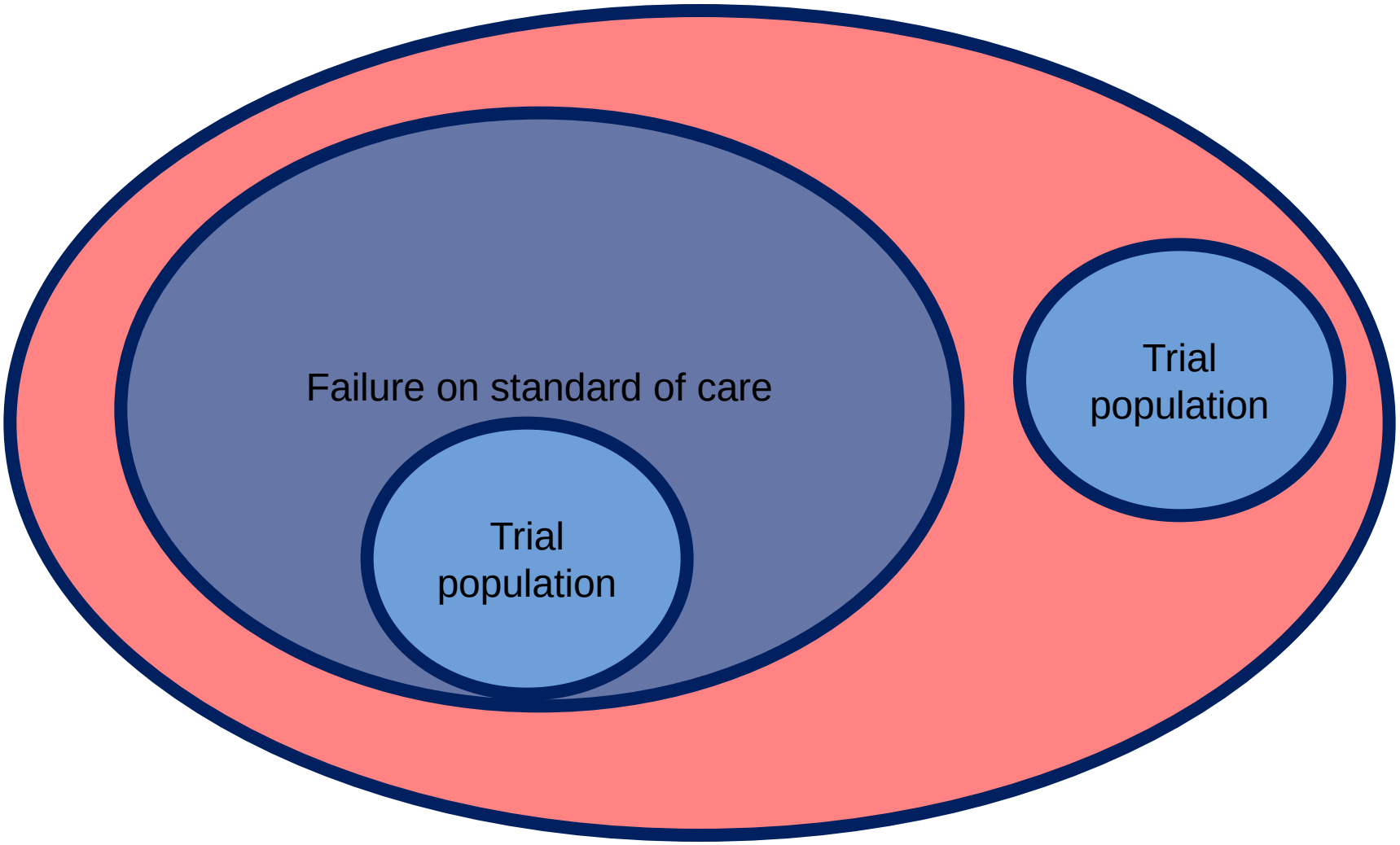
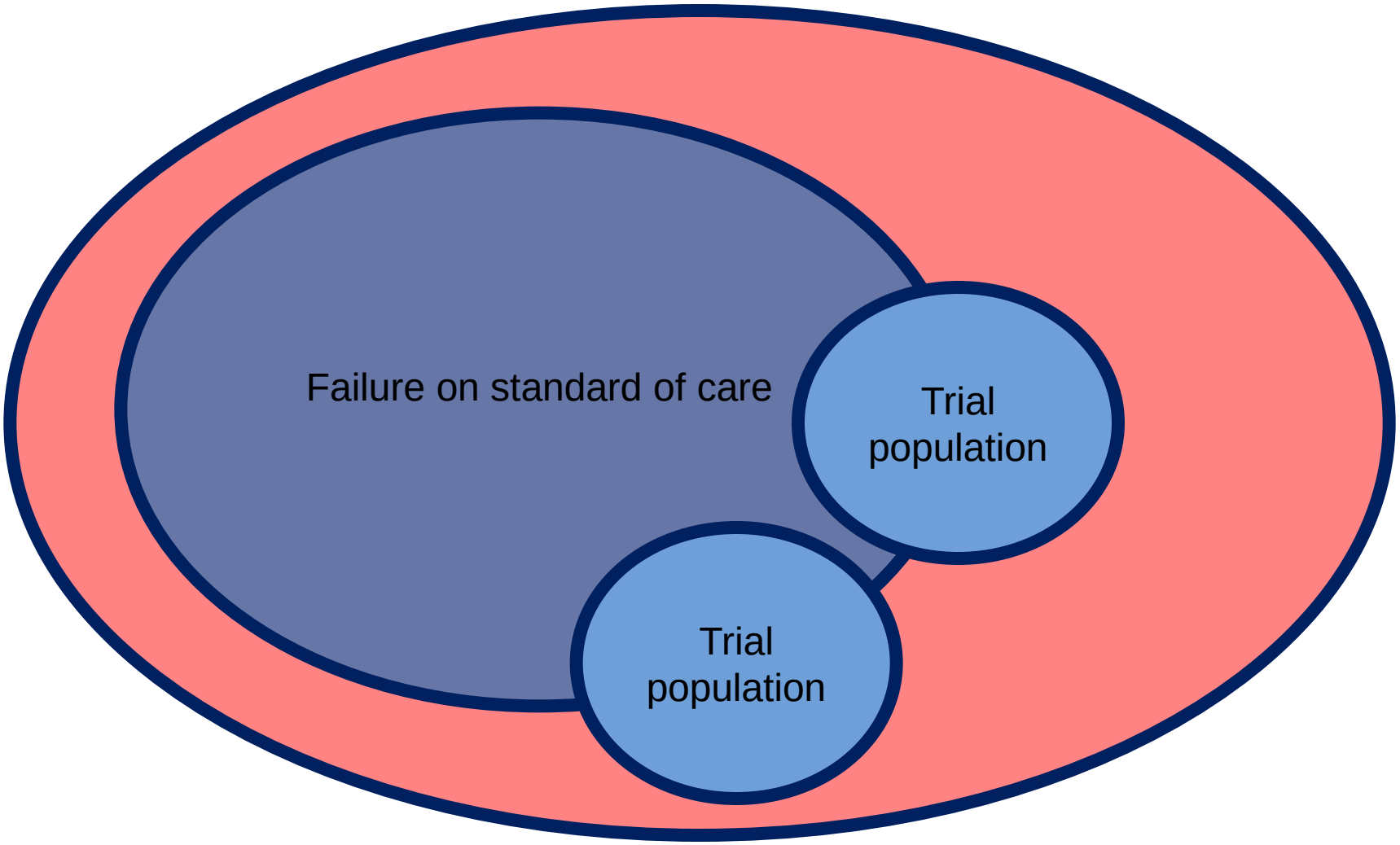
SmPC guideline

- The indication(s) should be stated clearly and concisely and should define the **target disease or condition** distinguishing between treatment (symptomatic, curative or modifying the evolution or progression of the disease), prevention (primary or secondary) and diagnostic indication. When appropriate it should define the **target population** especially when restrictions to the patient populations apply.


Trial
population
Trial
population
Total (treatment naïve) population


Failure on standard of care
Trial population
Trial population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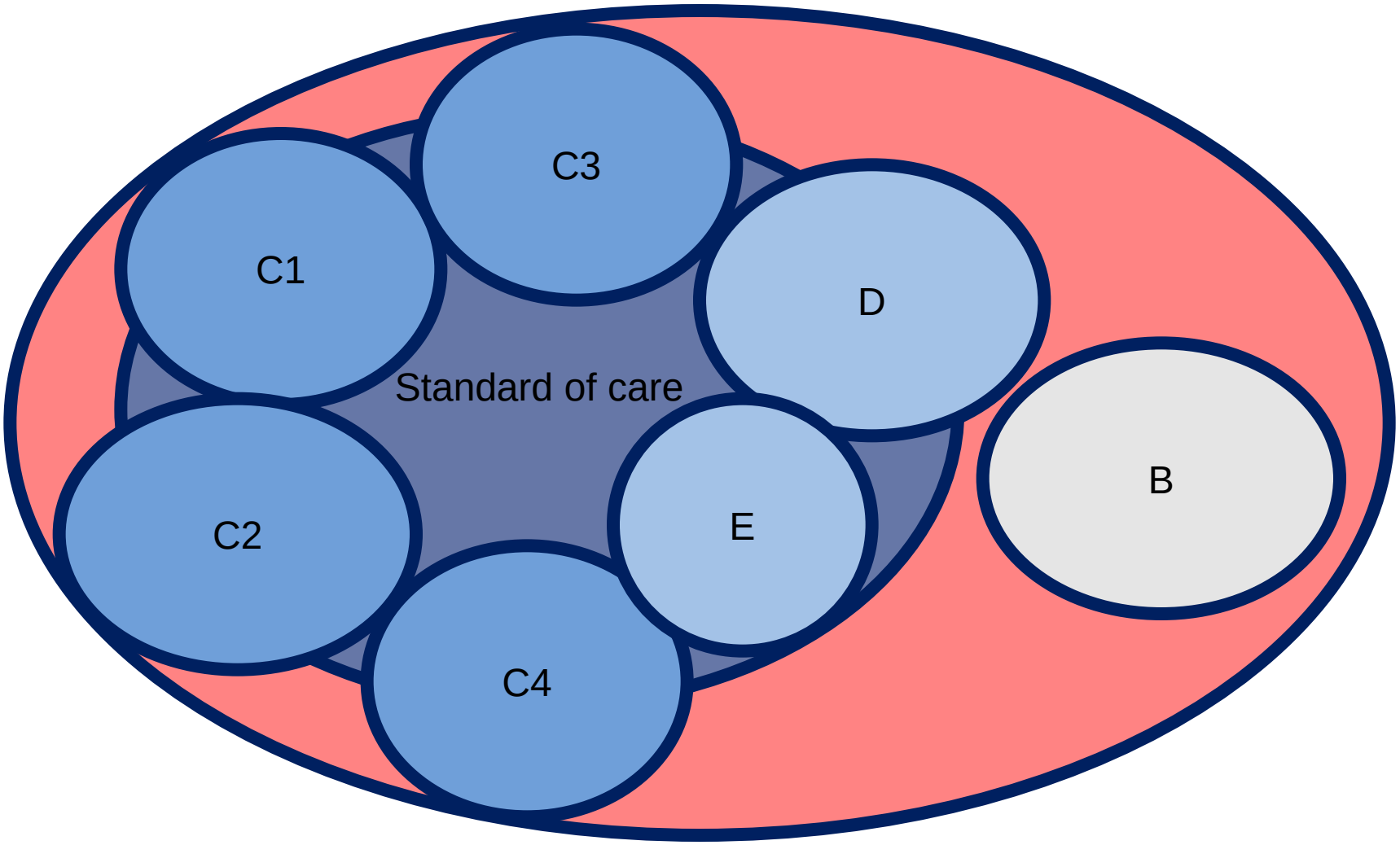
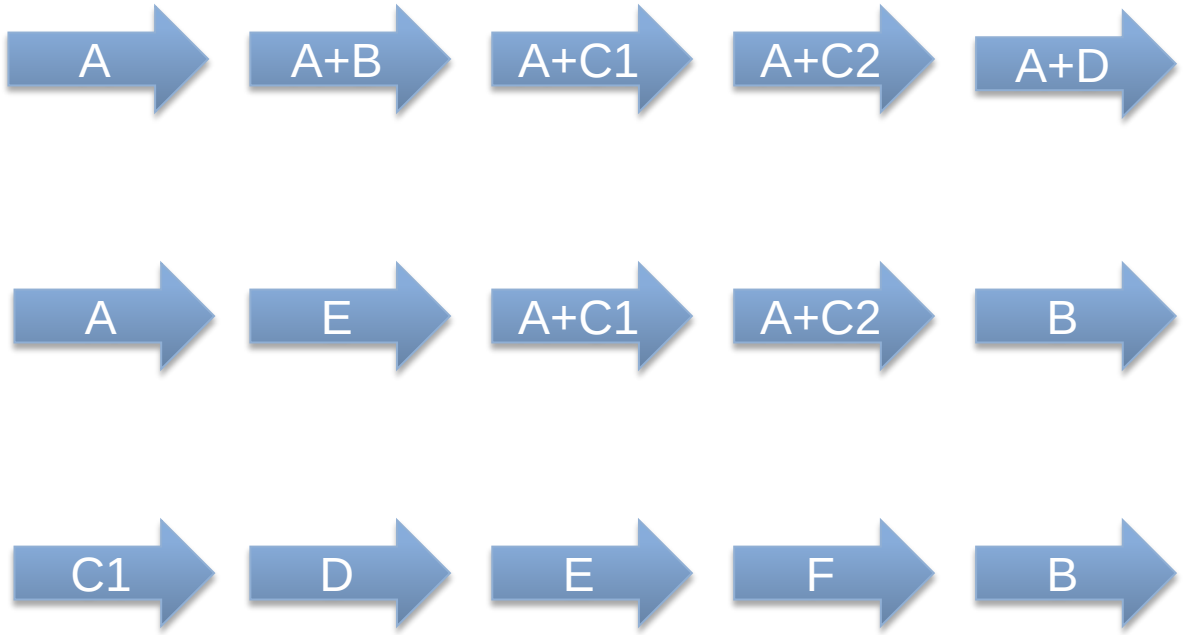

C3
C1
D
Standard of care
B
C2
E
C4

Treatment paths of individuals



What is the goal?

- Provide good evidence for safety and efficacy in patients with RA
- Come to conclusions for a population as broad as possible
  - Provide options for patients
  - Not unnecessarily restrict prescribers
- Minimise unnessary exposure of patients in clinical trials
  - Placebo controls

What are the challenges?

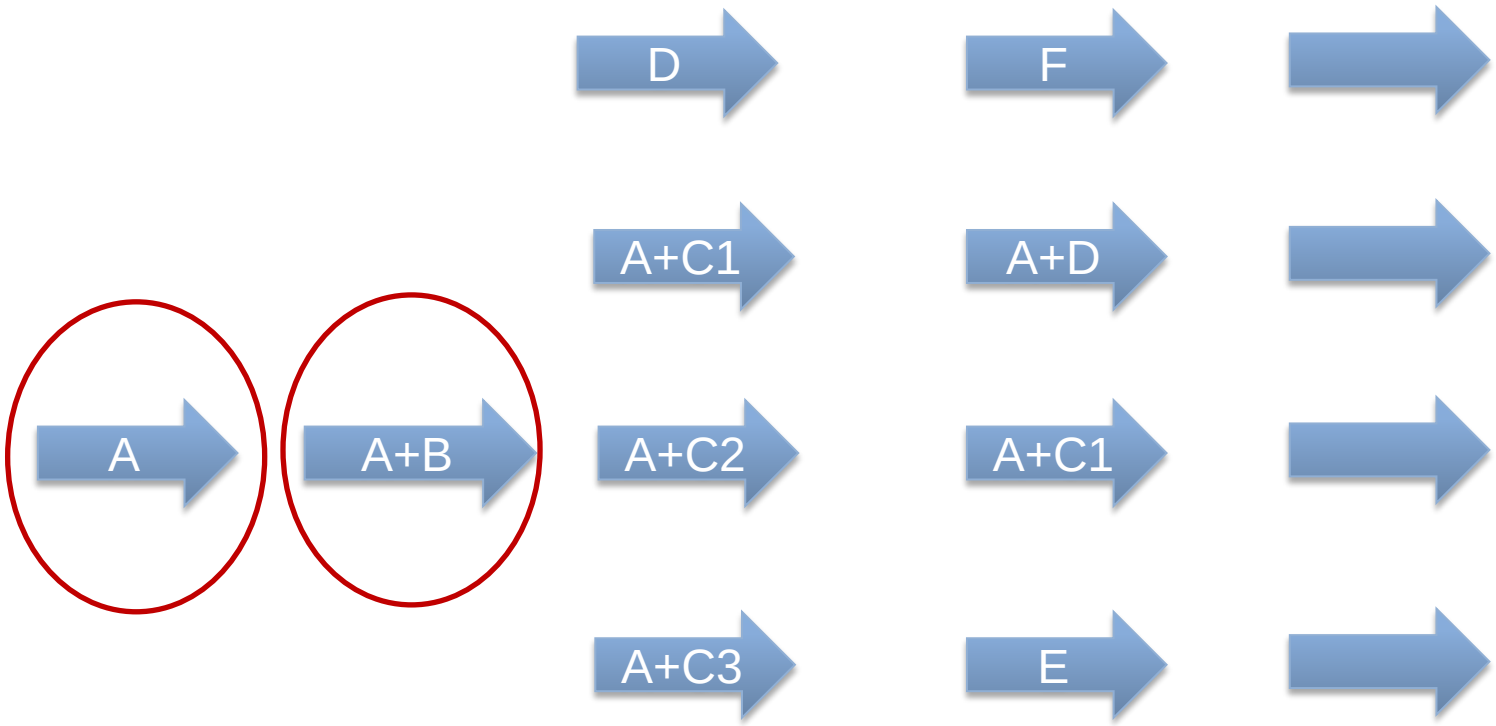
- Disease is heterogenous per se
- Individual patients are being treated based on prognostic risk factors and clinical response with different drugs in different sequences
- The availability of several pharmacological treatment options make it more difficult to define „treatment lines“ now
- Response of patients to treatment varies
  - Structural progression despite clinical response is possible
- To what degree do we need to differentiate subpopulations especially based on prior therapy?
- To what degree can we extrapolate between populations

General approaches

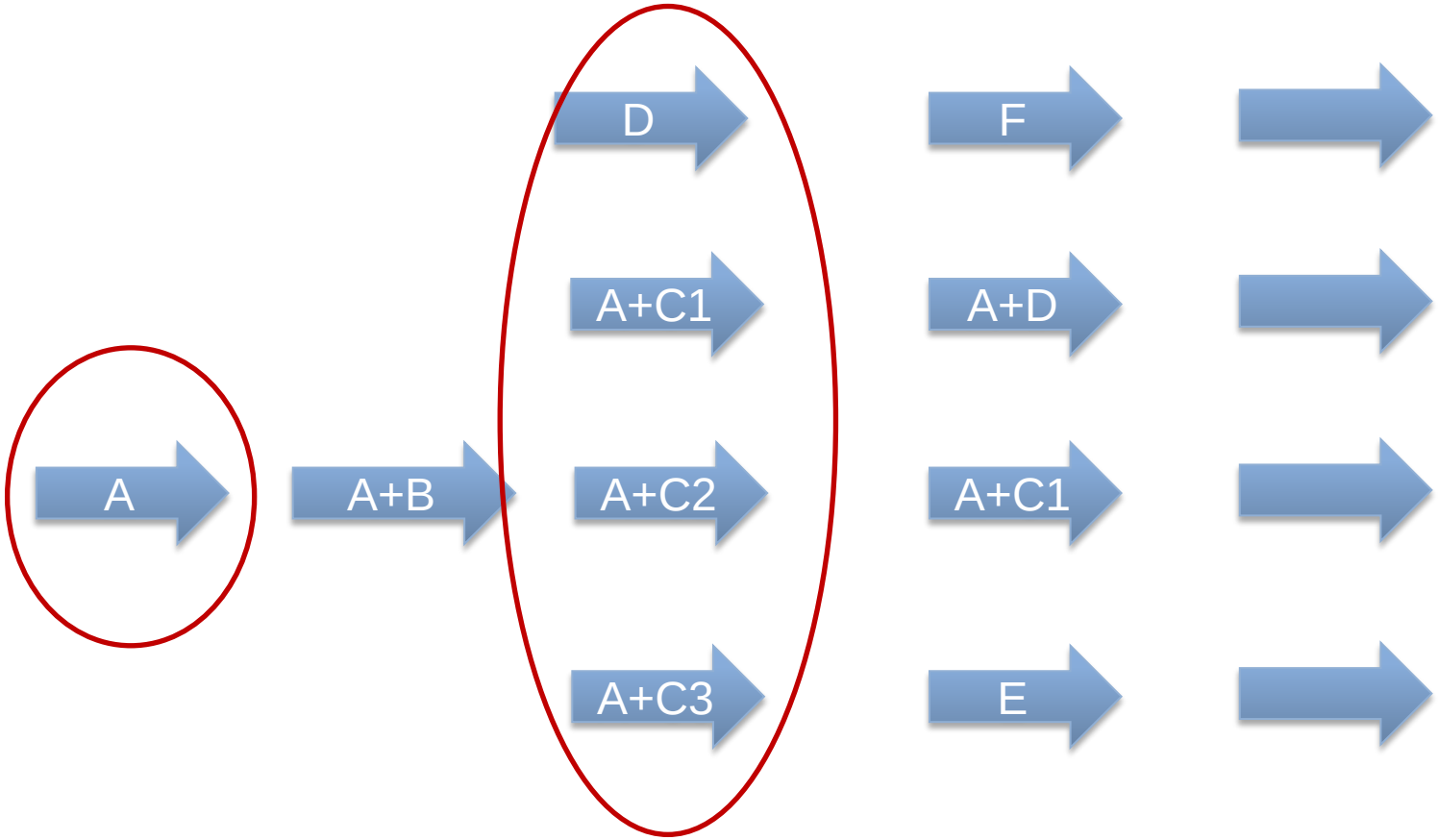
- Recruit „all comers“ i.e. heterogenous population
  - How to handle inconsistent results in subpopulations?
  - Power in relevant subpopulations reduced

- Recruit „subpopulations“ in different trials
  - Which are the relevant subpopulations?
  - How many subpopulations are required?

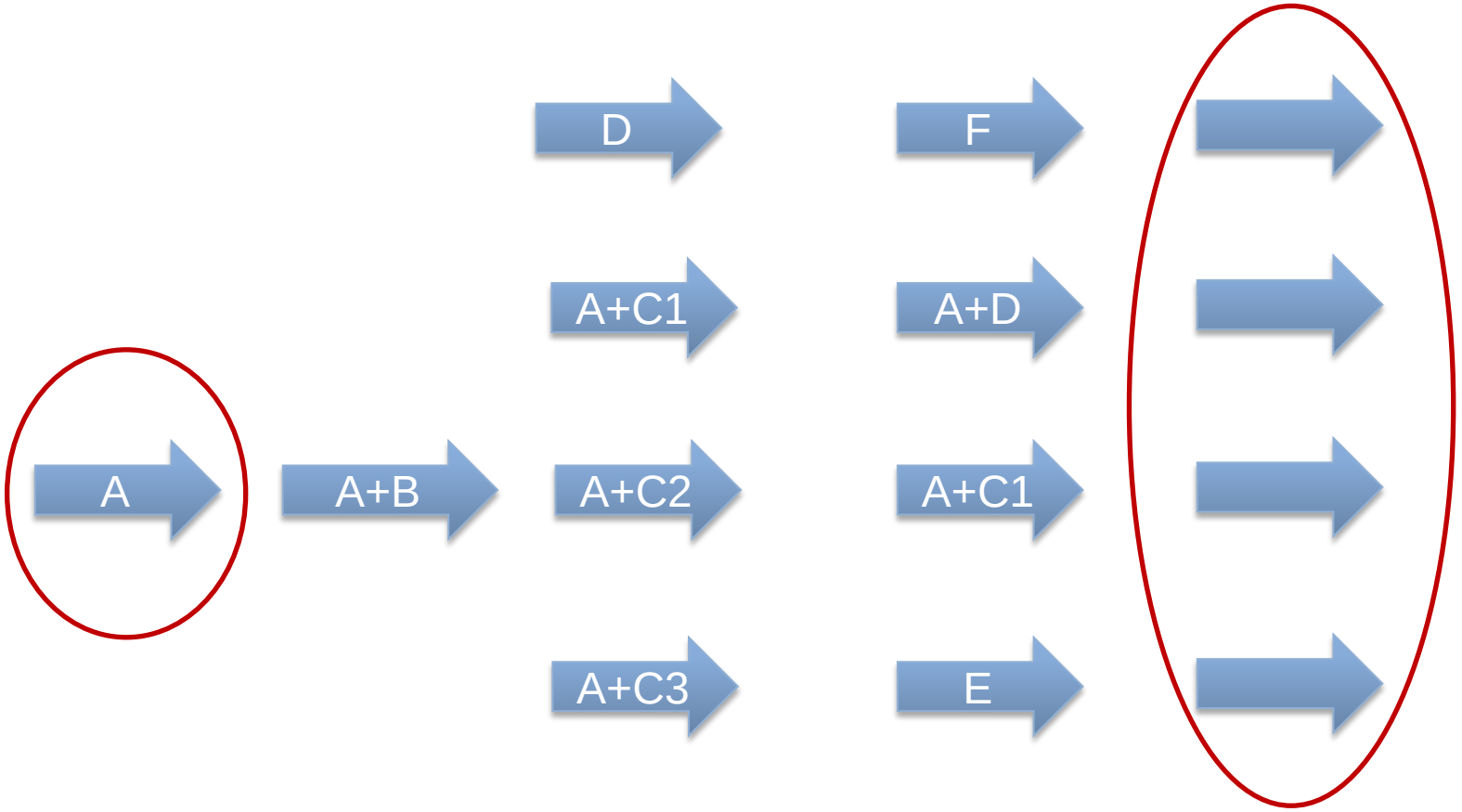
Approaches



Approaches



Approaches



Extrapolation

- External validity = „To whom do these results apply?“
  - There is no objective methodology to determine and establish external validity
- Ultimately it is the perceived benefit/risk balance for the population that is described in section 4.1
  - Available data are presented in section 5.1 of the SmPC
  - Discussion on the extrapolation should be part of the EPAR
- There is no „one-size fits all“ approach

Questions

- Are there distinct subpopulations in RA?
- Which important (sub)populations should be included in a development program?
- To what extent is extrapolation possible? Is there a specific „direction“ of extrapolation?
- What data are required to be confident in extrapolation?