The use of PROMs in clinical trials

Professor Caroline Sabin
University College London, UK

BHIVA
British HIV Association

2023 Spring Conference

Mon 24th – Wed 26th April
Gateshead, UK

The use of PROMs in clinical trials

Professor Caroline Sabin
Institute for Global Health, UCL

Conflict of Interest

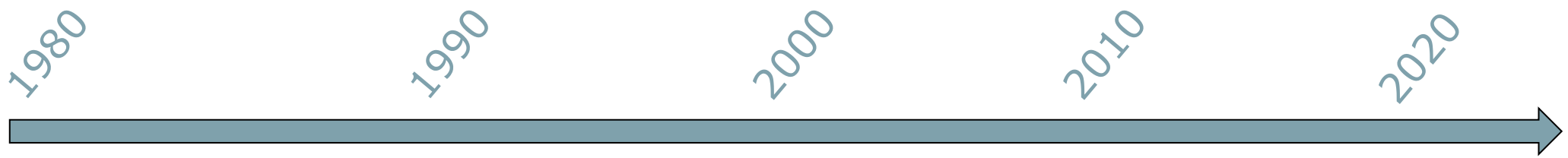
I have received funding for the membership of Data Safety and Monitoring Boards, Advisory Boards and for the preparation of educational materials from:

- Gilead Sciences
- ViiV Healthcare
- Janssen-Cilag
- Merck Sharp & Dohme

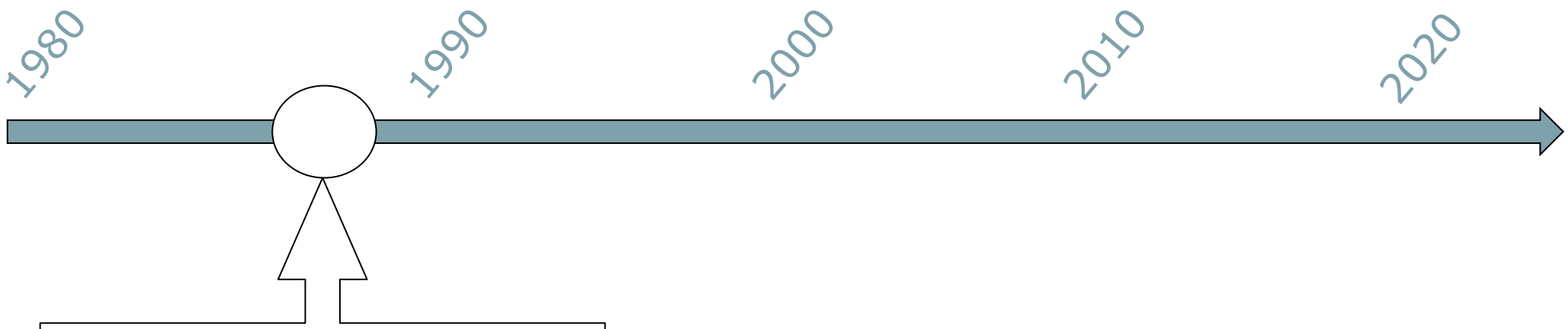
European AIDS Treatment Group (EATG) PROMise Project

- Commissioned in 2020 to analyse the role of PROMs in HIV R&D
- Led by Kevin Moody with involvement of key community, clinical, academic and pharma stakeholders
- PROMise toolbox for community advocates and people living with HIV, but can be used as a resource for anyone interested
- https://www.eatg.org/promise-community-activist-toolbox/

Endpoints in RCTs of antiretroviral treatments



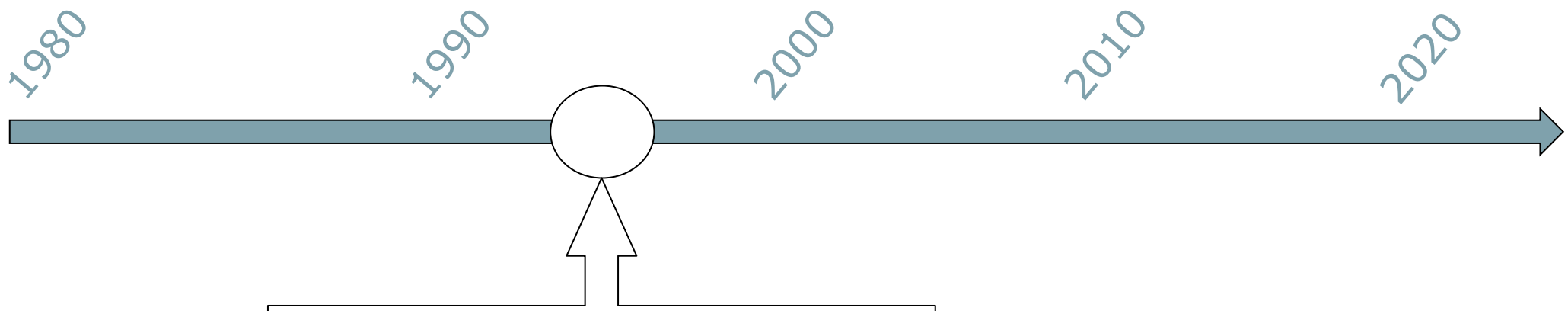
Endpoints in RCTs of antiretroviral treatments



Focus on clinical endpoints:
- new AIDS event
- mortality
- CDC ’B’ events

Use of surrogate markers:
- Change in CD4

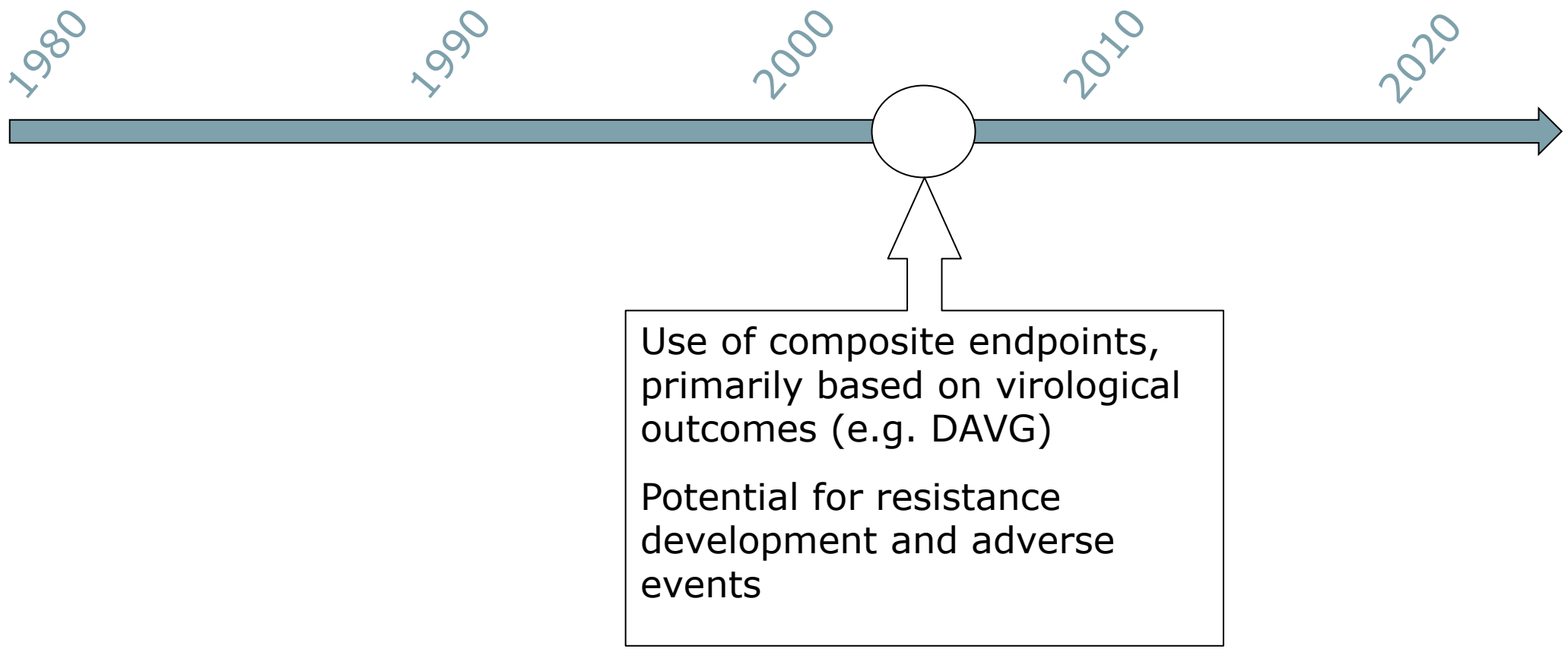
Endpoints in RCTs of antiretroviral treatments



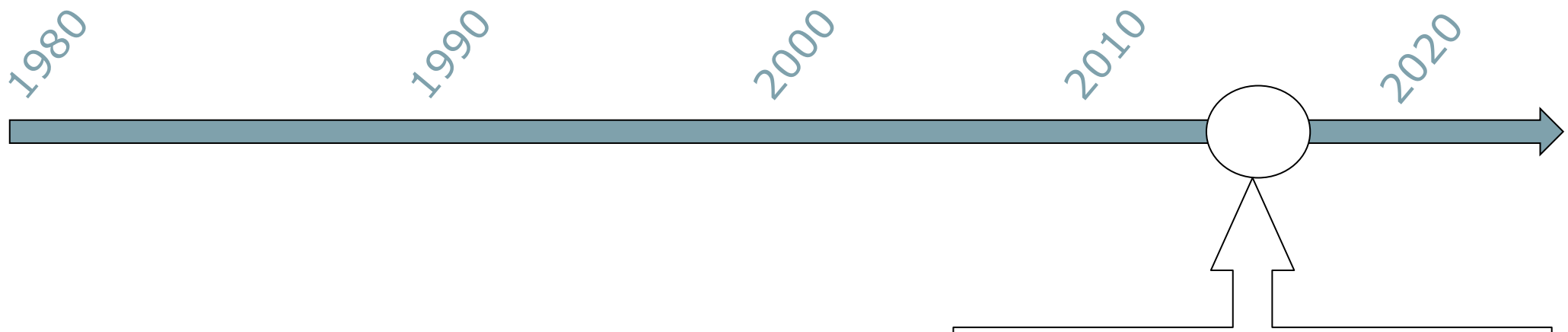
Switch to virological endpoints: undetectable VL @xx weeks, time to VL suppression, time to VL rebound

Clinical endpoints and surrogate markers as secondary endpoints

Endpoints in RCTs of antiretroviral treatments



Endpoints in RCTs of antiretroviral treatments

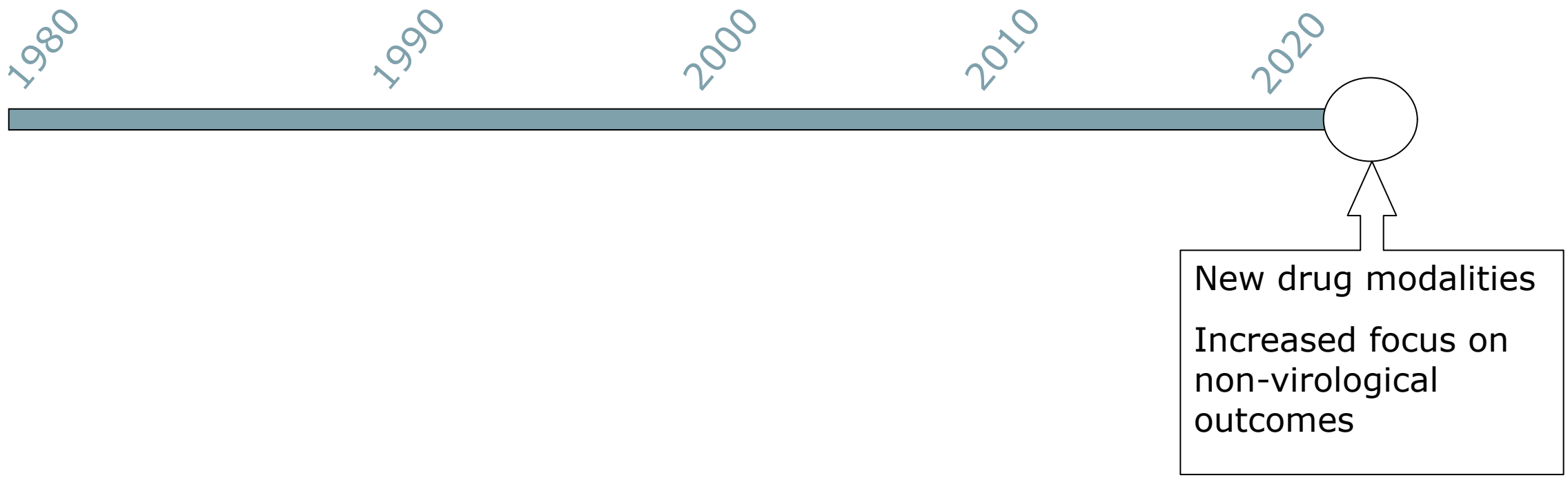


FDA ‘snapshot’ analysis – primarily virological but also capturing ability to remain on regimen

Switch from superiority to non-inferiority designs

Blinded trials are rare

Endpoints in RCTs of antiretroviral treatments



Desirable features of a new drug

- Potent antiviral efficacy – ability to suppress viral load quickly and maintain this over time
- Minimal potential for development of resistance
- Rapid increase in CD4+ T-cell count
- Minimal potential for drug-drug interactions
- Few/minor toxicities
- Positive or minimal negative impact on quality-of-life
- Convenience/easy to take
- No other negative impacts on daily life

Desirable features of a trial endpoint

Desirable features of a trial endpoint

- Responsive to treatment
  (at 12, 24, 48, 96 weeks….)

Desirable features of a trial endpoint

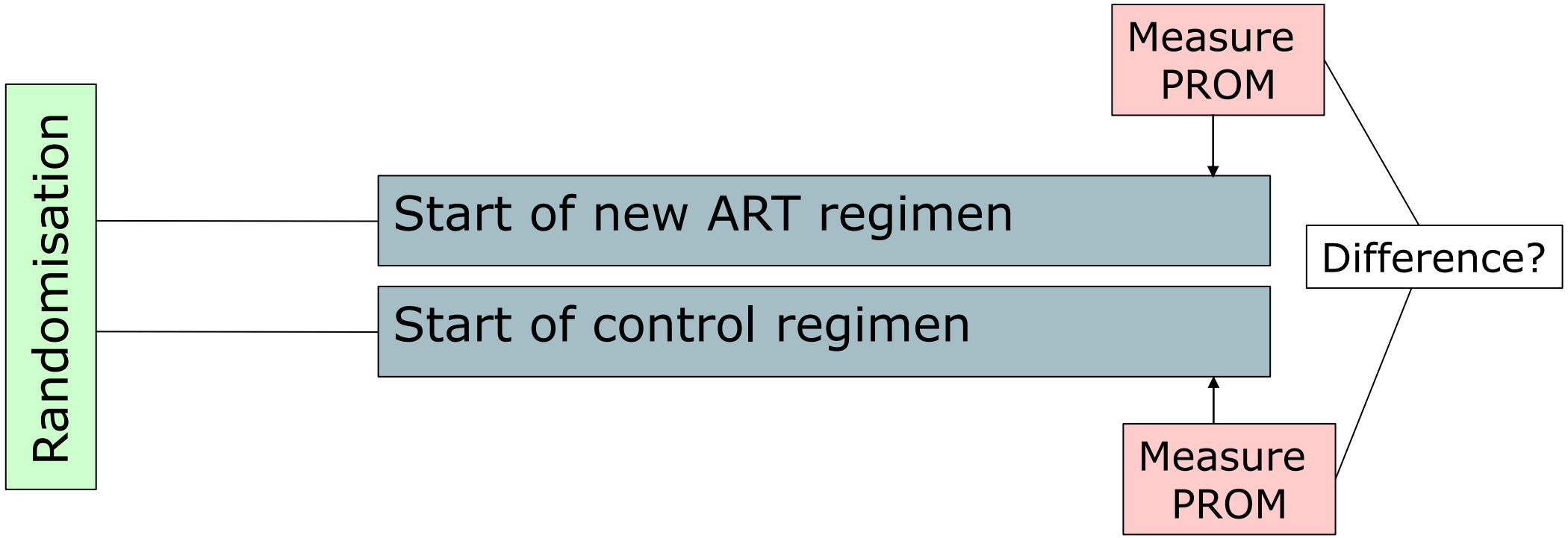
- Responsive to treatment
  (at 12, 24, 48, 96 weeks….)
- Able to discriminate between treatment arms

Desirable features of a trial endpoint

- Responsive to treatment
  (at 12, 24, 48, 96 weeks….)
- Able to discriminate between treatment arms

Desirable features of a trial endpoint

- Responsive to treatment
  (at 12, 24, 48, 96 weeks….)
- Able to discriminate between treatment arms



Desirable features of a trial endpoint

- Responsive to treatment
  (at 12, 24, 48, 96 weeks….)
- Able to discriminate between treatment arms
- Reliable, repeatable, valid…
  (in the context of non-blinded trials)

Desirable features of a trial endpoint

- Responsive to treatment
  (at 12, 24, 48, 96 weeks….)
- Able to discriminate between treatment arms
- Reliable, repeatable, valid…
  (in the context of non-blinded trials)
- Support adequately powered trials

Desirable features of a trial endpoint

- Responsive to treatment
  (at 12, 24, 48, 96 weeks….)
- Able to discriminate between treatment arms
- Reliable, repeatable, valid…
  (in the context of non-blinded trials)
- Support adequately powered trials
- Concise and clinically relevant

Desirable features of a trial endpoint

- Responsive to treatment
  (at 12, 24, 48, 96 weeks….)
- Able to discriminate between treatment arms
- Reliable, repeatable, valid…
  (in the context of non-blinded trials)
- Support adequately powered trials
- Concise and clinically relevant
- Acceptable to regulators/funders/treatment guideline groups

Why is the choice important for funders?

- Funders need to be able to weigh up the benefits associated with a new ART drug against the additional costs incurred
- Need a ‘standard currency’ for assessment of QoL
- **Quality-adjusted life years (QALYs)** – generic measure that combines quality and quantity of life lived
- Can then compare ‘costs per QALY’ in a Cost-Utility Analysis across different interventions
- **EuroQol EQ-5D** – measure of HRQoL that measures 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression – can be easily converted to QALYs

Current use of PROMs – FLAIR Trial

- Change in Perception of Injection Questionnaire (PIN) scores
- % with ‘extremely’ or ‘very acceptable’ Pain and Local Reaction Acceptability Score on PIN
- Change in Life Satisfaction, HIV Medication and Disclosure Worry Using HIV/AIDs-targeted Quality of Life (HATQoL) Questionnaire
- Change in SF-12
- Change in Total Treatment Satisfaction (HIVTSQs) and item scores
- Change in Treatment Acceptance using "General Acceptance" Dimension of the Chronic Treatment Acceptance (ACCEPT) Questionnaire
- Change in tolerability of Injection at Weeks 5, 40 and 41

Source: Clinicaltrials.gov

Is there a PROM that is suitable?

Is there a PROM that is suitable?

- No – unfortunately not at this stage
- Most RCTs currently incorporate at least one PROM as a secondary endpoint, but choice of PROM is up to the investigators
  - Can lead to ‘game-playing’
- Some limited guidance from regulators
- PROMise Project – next steps
  - Review currently available PROMs to identify key domains that are included
  - Map domains against likely needs of RCTs for new ART drugs
  - DELPHI exercise to agree consensus on domains to be included