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The importance of pragmatic and platform trials

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Conflicts of interest

No personal conflict of interest to disclose.

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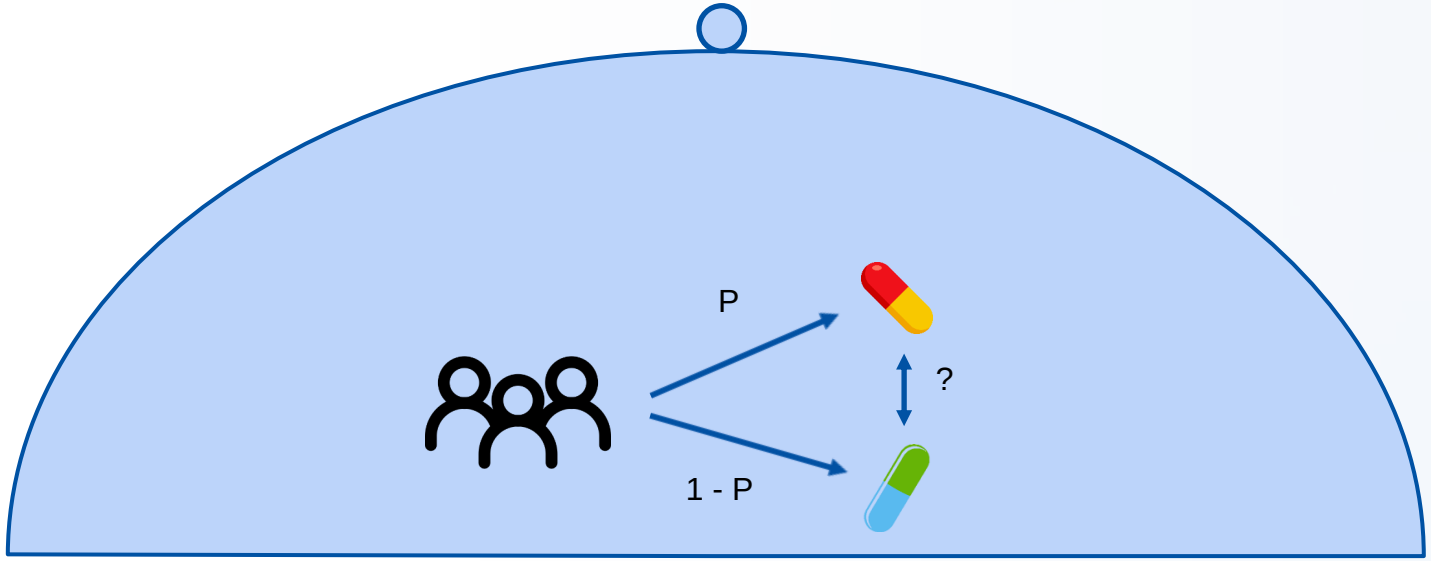
Key characteristics on pragmatic clinical trials

Explanatory trials for knowledge development

Explanatory trials address the question:

Can the treatment work,
if it is applied under ideal circumstances?
→ treatment *efficacy*



Schwartz and Lellouch. *J Chronic Dis* (1967); Roland and Torgerson. *BMJ* (1998); Tunis et al. *JAMA* (2003); Patsopoulos. *Dialogues Clin Neurosci* (2011); Sedgwick. *BMJ* (2014); Ford and Norrie. *N Engl J Med* (2016)

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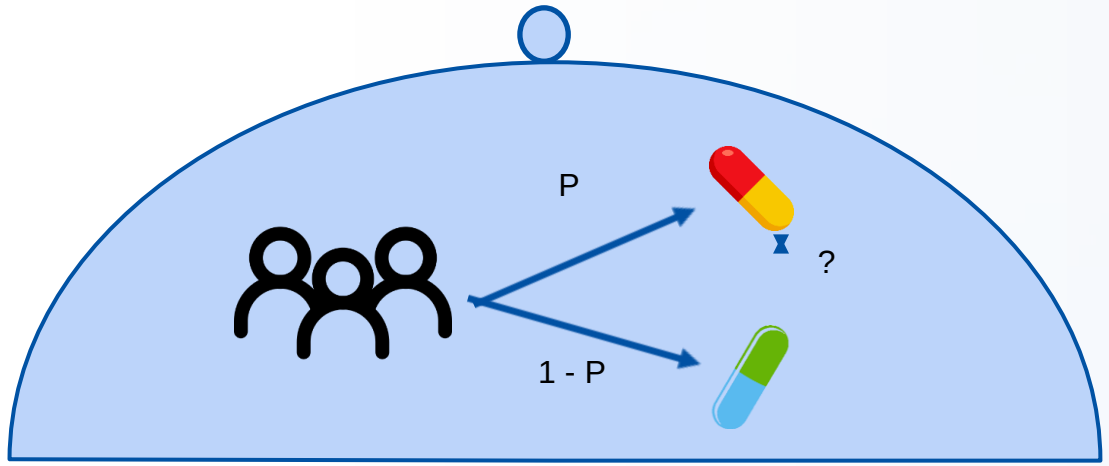
Pragmatic trials for applying knowledge

Pragmatic trials address the question:

Will the treatment work,
if it is applied in real-world clinical practice?
→ treatment *effectiveness*



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The explanatory-pragmatic continuum and key differences

Explanatory Clinical Trials

- **Population:** extensively selected and homogeneous; not necessarily representative of standard practice;
- **Setting:** experimental and controlled conditions; conducted at highly differentiated institutions;
- **Randomization/blinding:** random individual allocation to treatment groups, allocation concealment and double-triple blind set-ups;

Pragmatic Clinical Trials

- **Population:** broadly selected and heterogeneous; representative of the real-world health care setting
- **Setting:** routine clinical practice; conducted extended networks including community hospitals
- **Randomization/blinding:** randomized, at individual or cluster level, or other allocation techniques e.g. patient preferences; open-label

Schwartz and Lellouch. *J Chronic Dis* (1967); Roland and Torgerson. *BMJ* (1998); Tunis et al. *JAMA* (2003); Patsopoulos. *Dialogues Clin Neurosci* (2011); Sedgwick. *BMJ* (2014); Ford and Norrie. *N Engl J Med* (2016)

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The explanatory-pragmatic continuum and key differences

Explanatory Clinical Trials

- **Intervention:** standardized delivery and adherence closely monitored;
- **Comparator:** not necessarily an active comparator/standard of care; controlled via a placebo;
- **Outcomes:** short-term surrogate outcomes, targeting scientific knowledge and biological activity

Pragmatic Clinical Trials

- **Intervention:** flexibility in its delivery and adherence normally monitored
- **Comparator:** usual care, including combination of different treatments/modalities; not-placebo controlled
- **Outcomes:** long-term patient-centric endpoints, targeting the understanding impact on patients' health

Schwartz and Lellouch. *J Chronic Dis* (1967); Roland and Torgerson. *BMJ* (1998); Tunis et al. *JAMA* (2003); Patsopoulos. *Dialogues Clin Neurosci* (2011); Sedgwick. *BMJ* (2014); Ford and Norrie. *N Engl J Med* (2016)

The explanatory-pragmatic continuum and key differences

Explanatory Clinical Trials

- **Informed consent:** extensive and burdensome informed consent processes
- **Procedures:** additional study visits and procedures, requiring additional training
- **Data collection:** collection of highly detailed patient data, resorting to study-specific eCRFs; extensive safety data collection (e.g. treatment-emergent adverse events)

Pragmatic Clinical Trials

- **Informed consent:** simplified informed consent processes; electronic versions preferred
- **Procedures:** study visits and procedures as per usual care; minimal additional training required
- **Data collection:** collection of data as per standard of care, possibly resorting to EHR or hybrid approaches; limited safety data collection (e.g. SAEs)

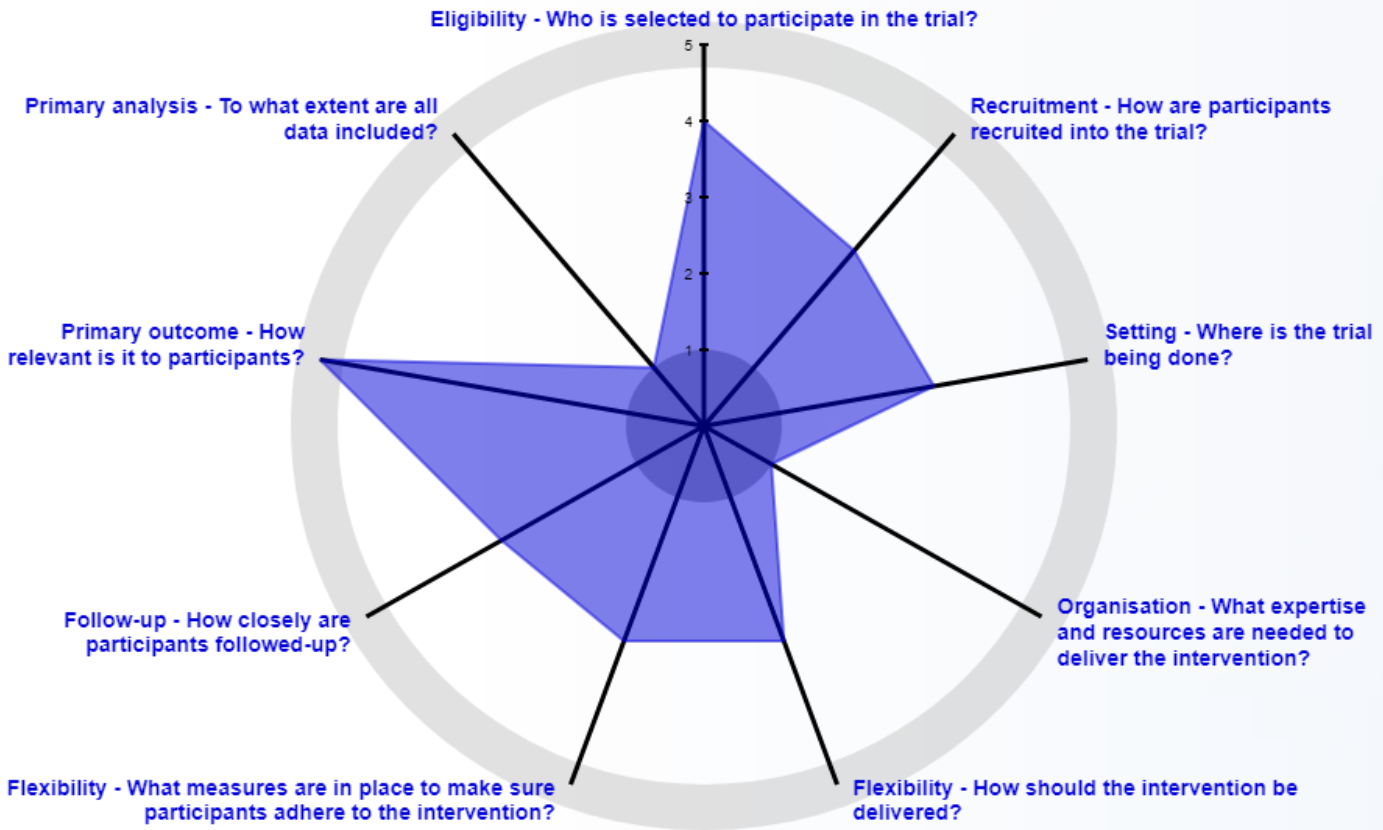
Schwartz and Lellouch. *J Chronic Dis* (1967); Roland and Torgerson. *BMJ* (1998); Tunis et al. *JAMA* (2003); Patsopoulos. *Dialogues Clin Neurosci* (2011); Sedgwick. *BMJ* (2014); Ford and Norrie. *N Engl J Med* (2016)

How can you recognize a pragmatic trial?

PRECIS-2 wheel

More pragmatic

More explanatory



Loudon et al. *BMJ* (2015)

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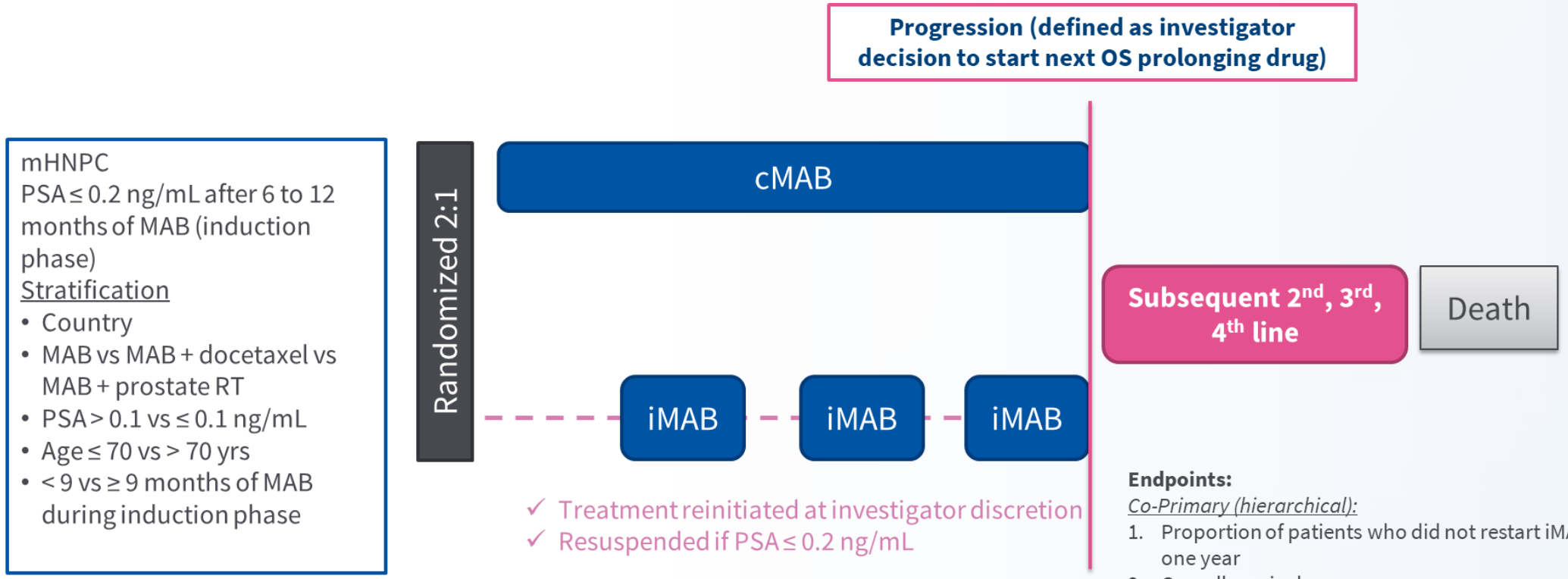
DE-ESCALATE (EORTC-2238-GUCG)

Study schema



mHNPC: metastatic hormone naïve prostate cancer patients
MAB: Maximum androgen blockade = LHRH agonist/antagonist + androgen receptor pathway inhibitor
cMAB / iMAB: continuous MAB / intermittent MAB

Endpoints:

Co-Primary (hierarchical):

1. Proportion of patients who did not restart iMAB treatment at one year
2. Overall survival

Secondary

1. QoL (QLQ-C30; IL249)
2. Time spent on treatment
3. Time to next systemic prostate cancer therapy
4. Toxicity with CTCAE v5

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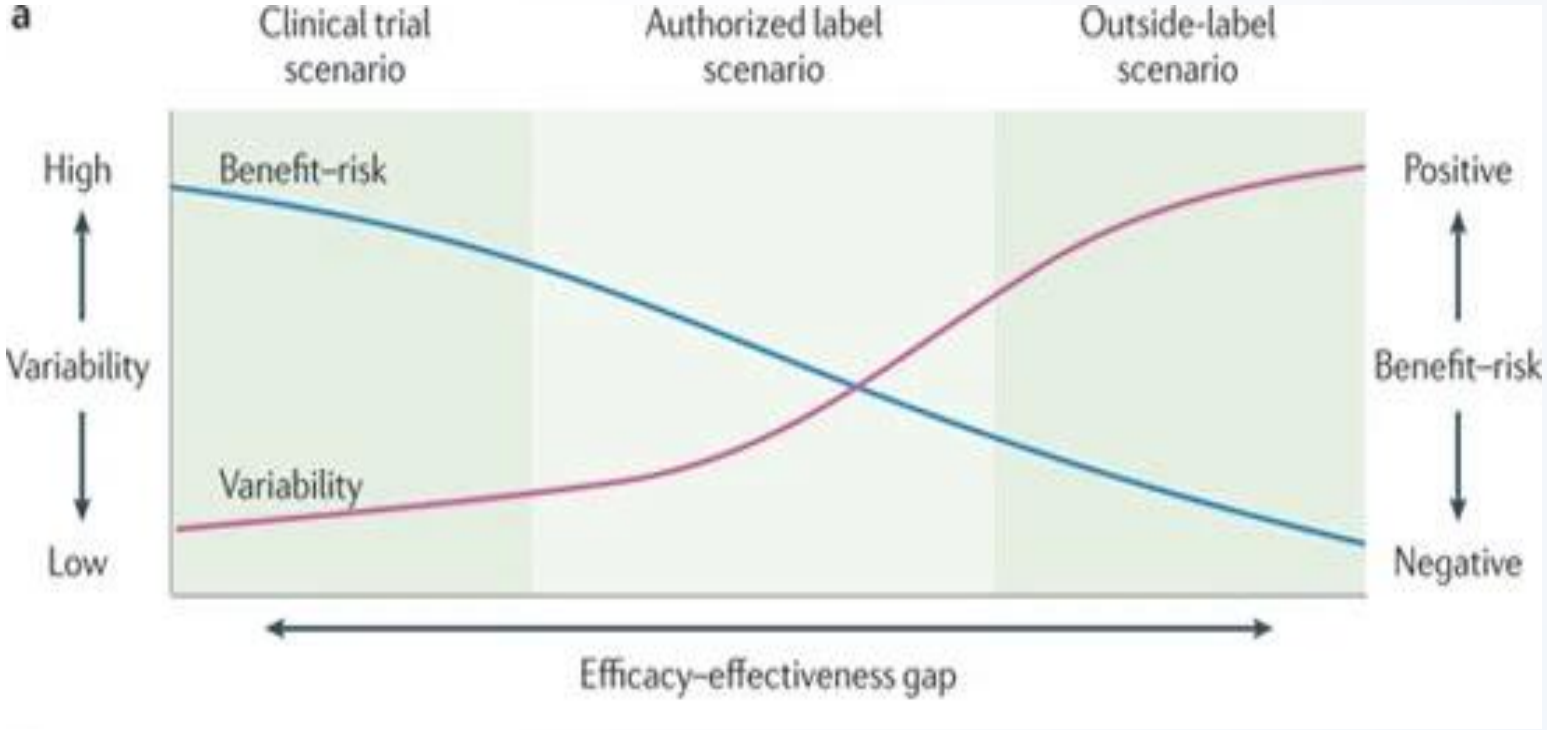
The importance of pragmatic and platform trials and associated challenges

The efficacy-effectiveness gap



Treatment efficacy > Treatment effectiveness

>99% of trials

<1% of trials

Eichler et al. *Nat Rev Drug Discov* (2011)
Chalkidou et al. *Trials* (2012)

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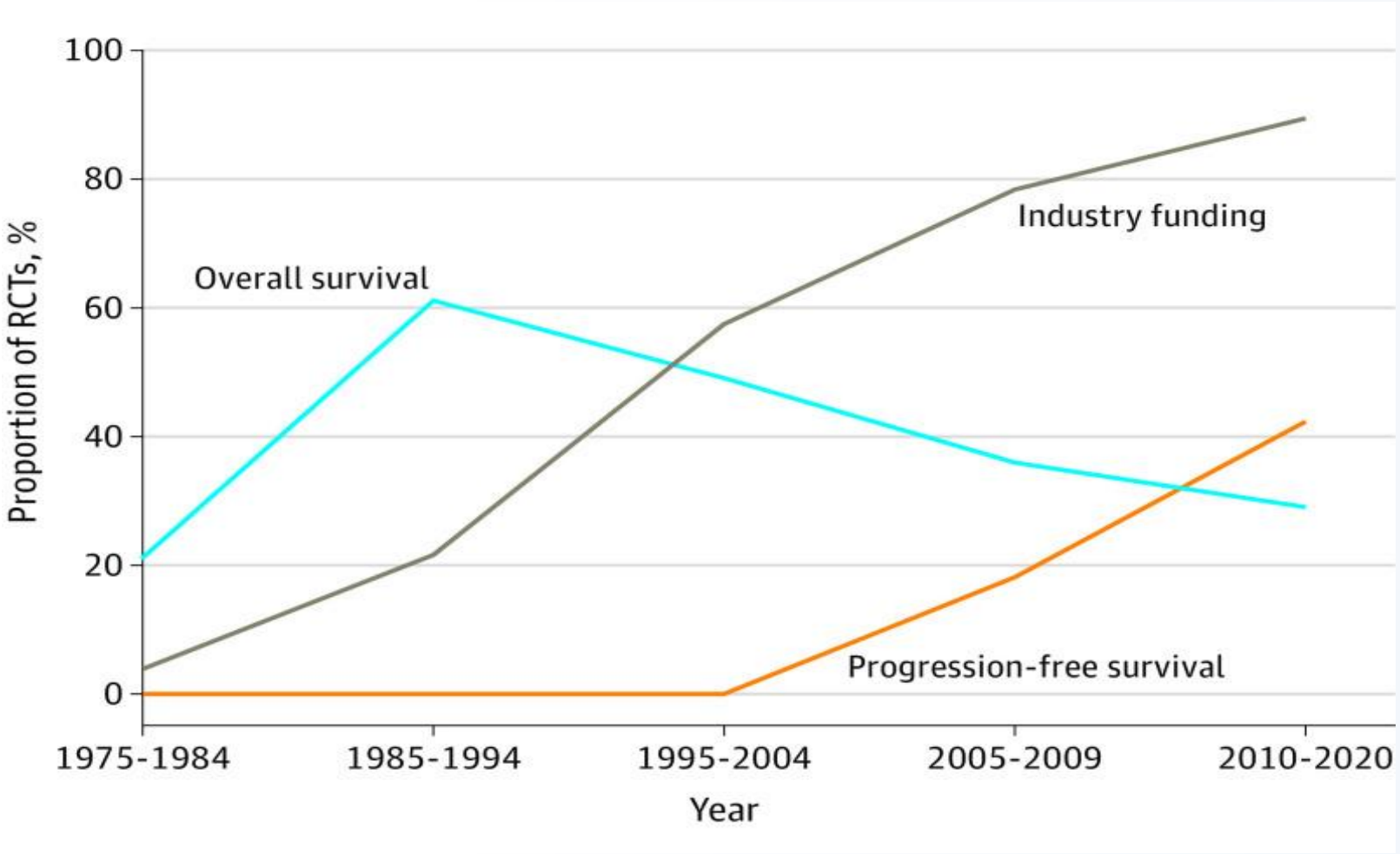
The efficacy-effectiveness gap



Del Paggio et al. *JAMA Oncol* (2021)

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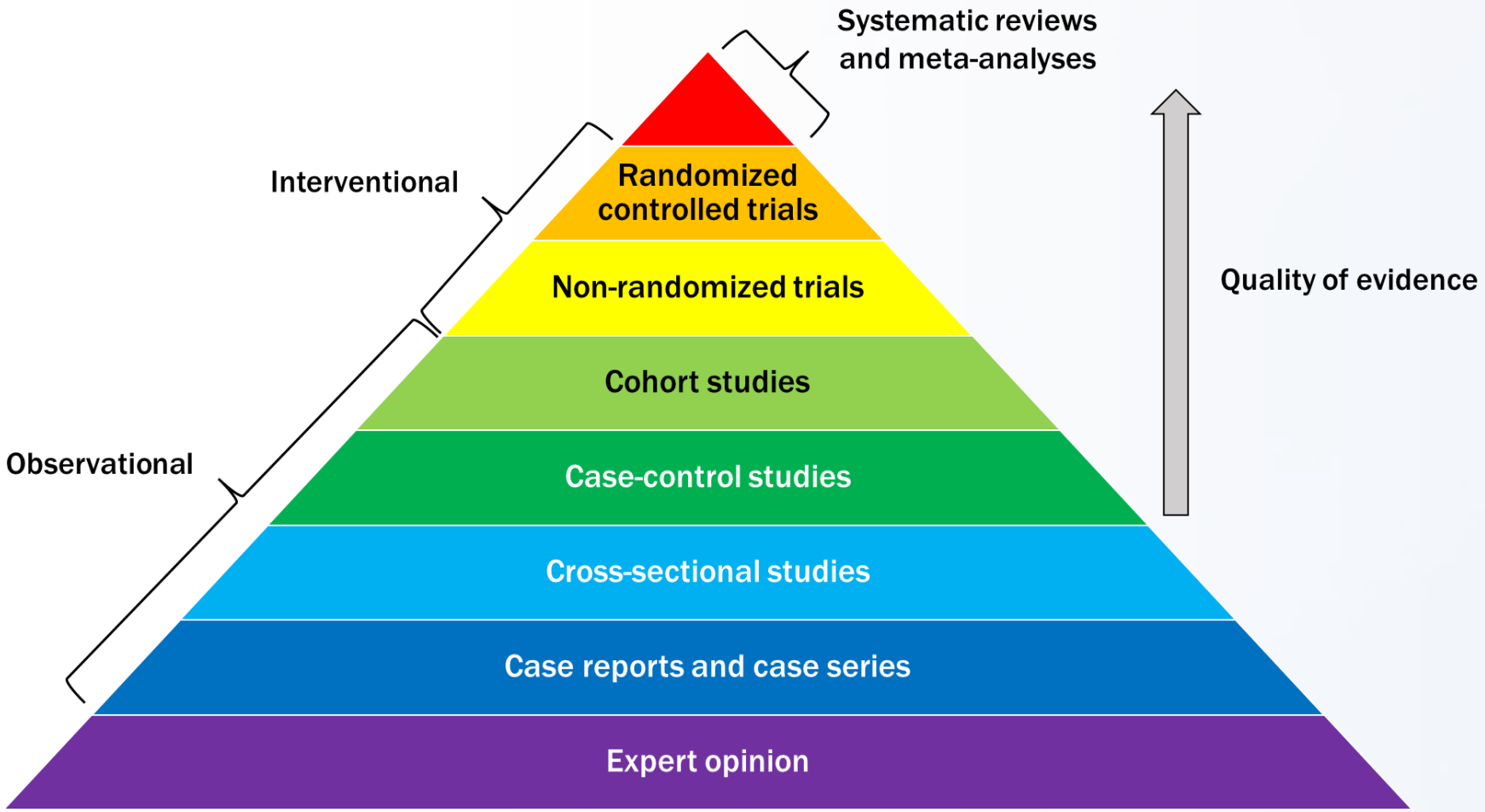
The pyramid of evidence-based medicine



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The value of pragmatic trials

- **Patients**
  - ❑ less burdensome participation
  - ❑ more realistic picture of a treatment's benefits and harms for the average patient
  - ❑ enhances patients' accessibility
- **Clinicians**
  - ❑ offer insights directly applicable to daily decision-making
  - ❑ bring innovative methods, simplified infrastructures and limited data collection

Pragmatic trials combine the methodological strengths of RCTs with the inclusiveness of studies that analyze real-world data

→ Sources of robust and actionable real-world evidence

Simon et al. *N Engl J Med* (2020)
Neyt et al. *J Comp Eff Res* (2016)
Zuidgeest et al. *J Clin Epidemiol* (2017)

Challenges of pragmatic trials

- **Lack of regulatory guidance and specific legal framework**
  - ❑ limited acceptability of reduced regulatory requirements despite their lower risk
- **Ethical concerns**
  - ❑ Distress related to simplified consent procedures and de-escalation trials
- **Feasibility and implementation concerns**
  - ❑ limited attractiveness to patients, investigators and site staff
- **Lack of available funding**
  - ❑ limited attractiveness to pharmaceutical industry, especially in the post-authorisation setting
  - ❑ lack of independent funding options

Ford and Norrie. *NEJM* (2016); Zuidgeest et al. *J Clin Epidemiol* (2017); Steenhuis et al. *Value Health* (2019)
Nicholls et al. *Trials* (2019)

Conclusions

- Pragmatic trials have their role in the current clinical research agenda
- Tools and examples available validate their importance
- Discussions across stakeholders are essential to overcome the current challenges

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