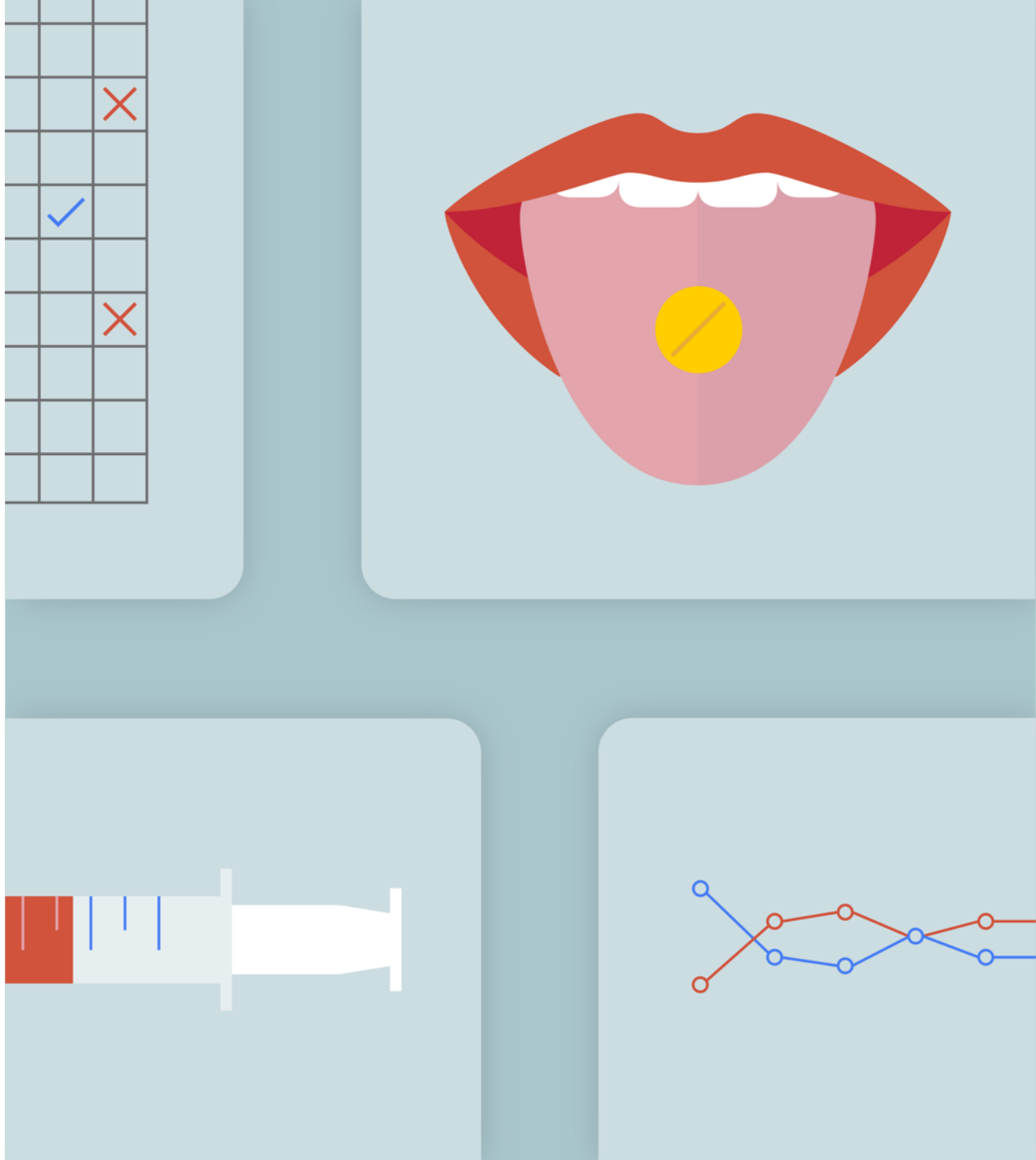
Christine van Hattem (Master student Drug Innovation),
Amos de Jong. MSc (PhD candidate)
Jolien de Groot, MD, PhD (Clinical Assessor, Medicines Evaluation Board)
Lourens Bloem, PharmD, PhD (Assistant Professor Clinical Therapeutics)

Feasibility of post-authorization randomized controlled trials for conditionally authorized anticancer medicines - a multistakeholder perspective



Utrecht University

Pharmacoepidemiology and Clinical Pharmacology

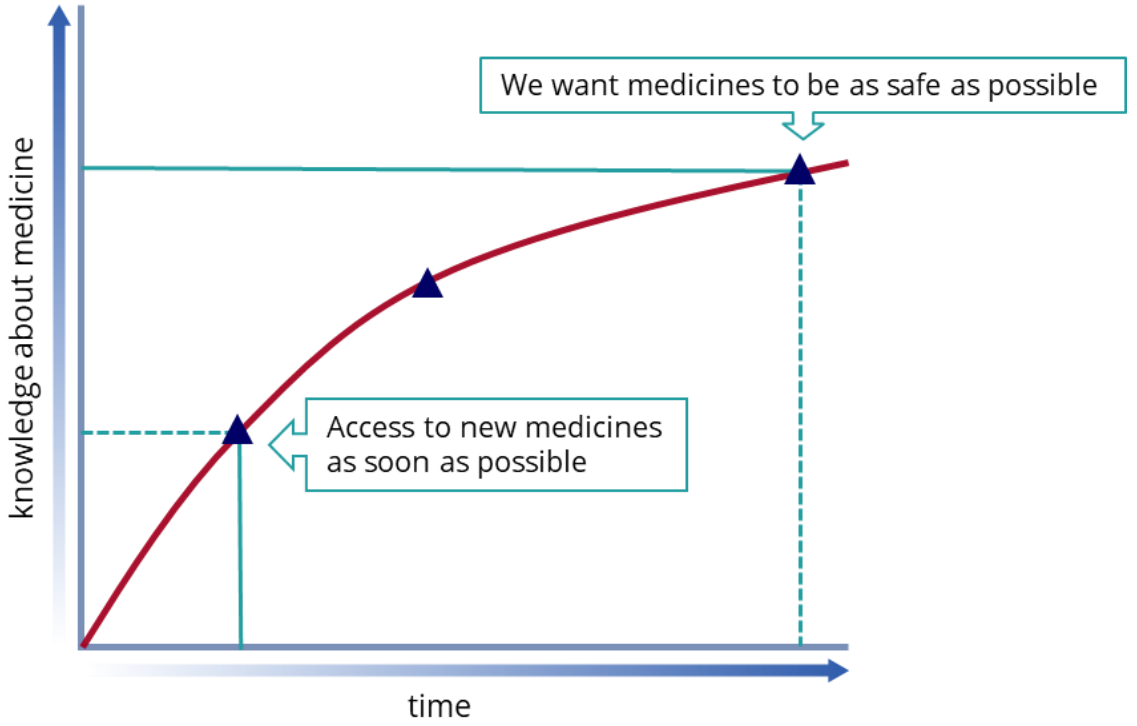
CBG MEB MEDICINES EVALUATION BOARD

Outline

- Background
- Aim
- Study design – qualitative research
- Results
- Discussion & Future approaches

Development of anticancer medicines

- Earlier patient access
- Expedited pathways
- Conditional marketing authorization (CMA)
    - Incomprehensive evidence (e.g., **single arm trial** (SAT))



Adapted from pharmaphorum.com

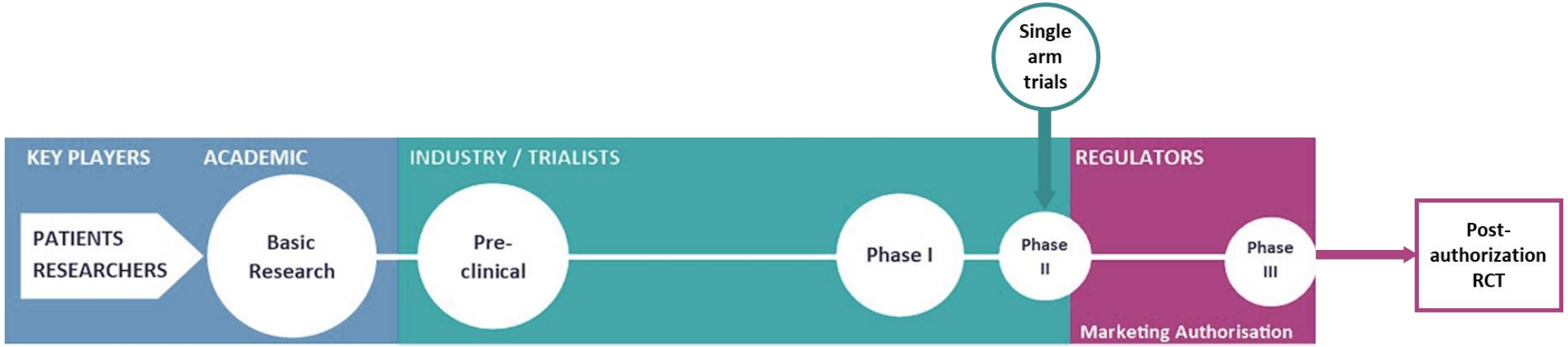
Conditional marketing authorization (CMA)

Requirements:

- Positive benefit-risk balance;
- Medicine fulfills unmet medical need;
- **Comprehensive evidence** will become available in a timely manner while the medicine is marketed;
- Benefits of **timely market access** outweigh risks of **incomprehensive data**

Obligations to the conditional marketing authorization

- Provide comprehensive evidence
  - Post-authorization studies
  - Confirming positive benefit-risk balance
    - ➔ Requested in form of **randomized controlled trials** (RCTs)



Adapted from imi-neuronet.org

Post-authorization RCTs

- **Comprehensive evidence** will become available in a timely manner while the medicine is marketed;
- Benefits of **timely market access** outweigh risks of **incomprehensive data**

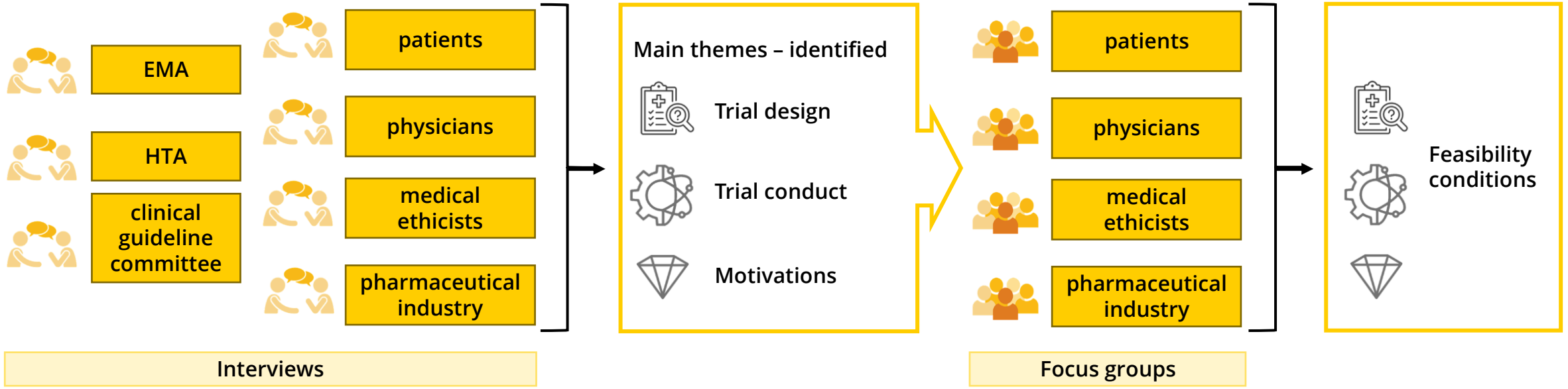
- Meeting these requirements
  - **Delays and incompleteness**

- How feasible are PA-RCTs

Aim

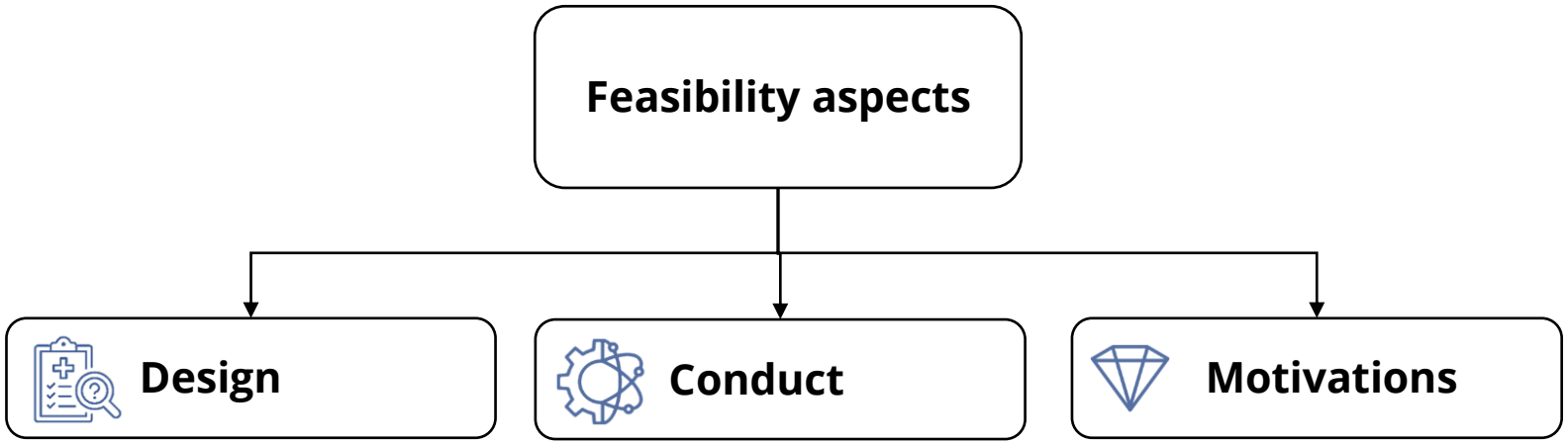
Explore & identify conditions that enable or disable the conduct of a PA-RCT for anticancer medicines with CMA – from a multistakeholder perspective

Study design – qualitative research



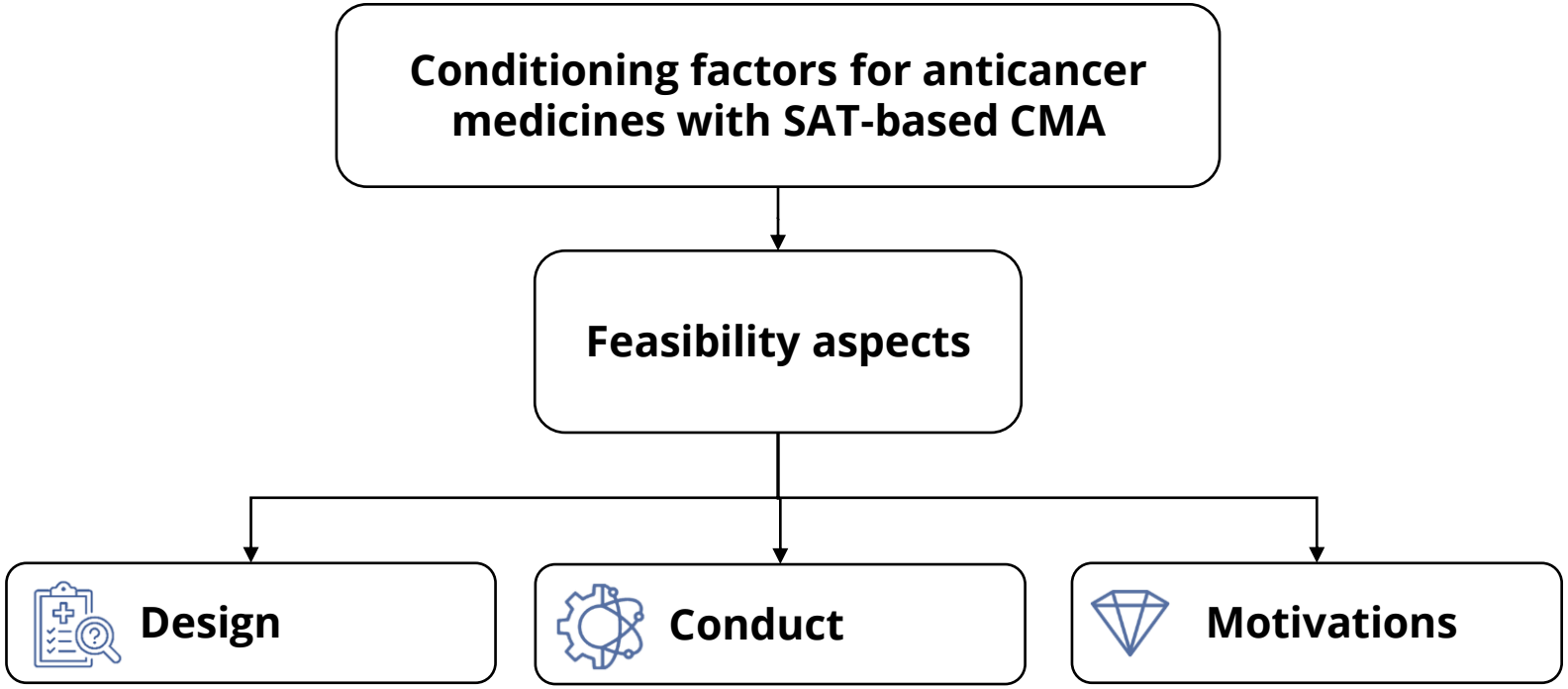
Results

Feasibility aspects



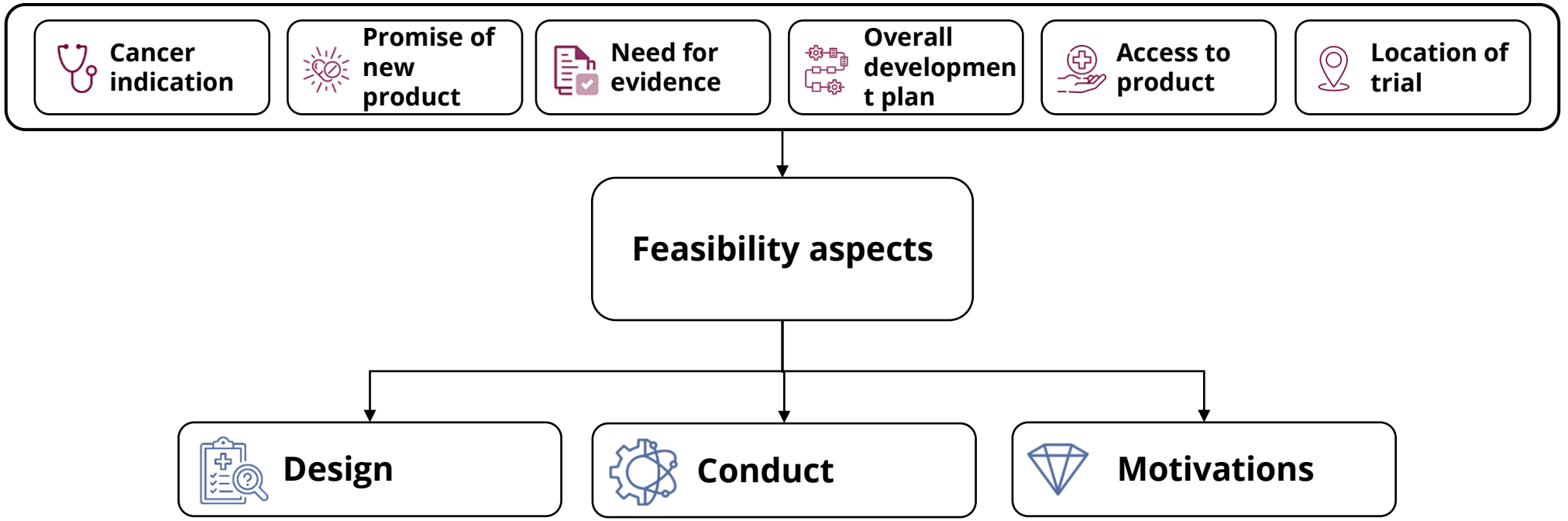
Results

Feasibility aspects & conditioning factors



Results

Conditioning factors



Conditioning factor – promise of new product

- Highly versus not promising
  - “If is **very promising** and it is already available outside the trial, then forget it, yes, and if it is a **little promising with a lot of tox**, then no one will participate.” – physician

Conditioning factor – overall development plan

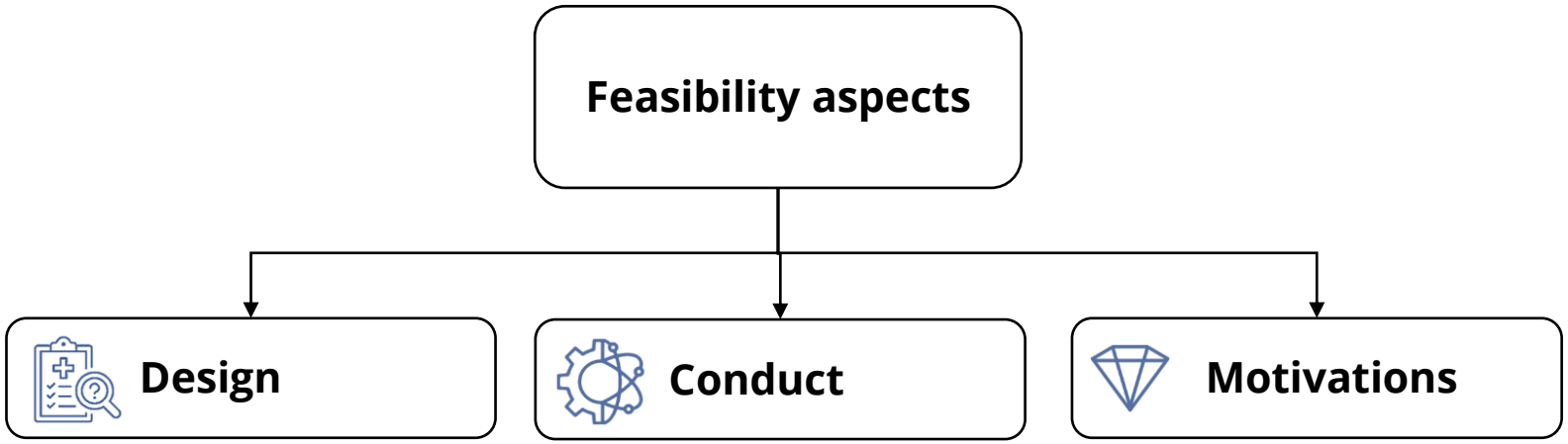
- Anticipation of CMA
- Timing of PA-RCT initiation

Conditioning factor – access to product

- Enabling access
- Differences between countries
  - “sometimes access may take quite a while. So, before patients have access, you have a longer time. You can also provide, or get some more patients in those **countries where access might be delayed**.” – industry

Results

Main themes



Trial design – trial aim

- Trial aim
  - Endpoints
  - **Comparator, randomization**
  - Cross-over
  - Trial patient population & line of therapy

Trial aim – comparator, randomization

- Type of comparator therapy
  - “I think that it is important that you test them randomized against the **best comparator,** and not **placebo-controlled**, that that is not meaningful anymore in that setting.” – physician

- Fair comparator
  - “Because, if it really is a promising medication and the **comparator** is, well, **inferior** in the views of many people, then, then it will be, I think, very difficult to find people for such a trial.” – physician

Trial design – complexity

- Trial complexity
  - **Data collection**
    - Type of data
    - Amount of data
    - Part of clinical practice
  - Burden (for patients & physicians)
  - Involved stakeholders
  - Multipurpose trial designs

Main theme – Trial conduct

- Data collection
  - Burden
  - Biomarkers and biobanking
  - **Resources & expertise**
- Competition

Trial conduct – data collection

- Resources & expertise:
  - “I mean, well, we in the <academic medical centre> crumble too under all the trials. We really have to **select** more critically and assess what, yes, what fits us? Where is our **strength**? And that will not always be, yes, well this kind of post-authorization studies.” – physician

Main theme – Motivations

- Patients
- Physicians
- Medical ethicists
- Pharmaceutical industry

Motivations – patients

- Altruism
- Available new treatments and trials

- Burden
  - “So it should not be a real burden for a patient, because then why should they participate? So, **not too many extra visits to the hospital**, extra, […], bone marrow things, etc. Don’t […] do it too often.” – patient

- Awareness
  - “How aware would a patient be that **if there are no more data, that you could lose this drug**? (…) If they **understand** that, they may be motivated to participate even more.” – patient

Motivations – physicians

- Meaningful aim
- Scientific interest
  - "And, just because the key investigators […] are interested in, you know, **new things** […] which are going heading for approval and […] not necessarily something which is a post-approval marketing study." – industry
- Professional obligation for patient care

Motivations – medical ethicists

- Paternalism
- Therapeutic misconception
  - “But for me, I guess always the main concern with this kind of study is therapeutic misconception. […]. And to just do whatever is **necessary to try to ward that off**.” – medical ethicist

Motivations – medical ethicists

- Clinical equipoise
  - “but I think that that for a randomized controlled trial after conditional authorization, the concept of **equipoise** is **essential**. […], and I also agree that it's very very **difficult to assess**. An ethicist cannot do that on his her own. You really need a multidisciplinary company of the research ethics committee. And then, there is also, in this concept, a certain kind of **arbitrariness**.” – medical ethicist

Motivations – pharmaceutical industry

- Obligation
  - “the motivation is clear, right? […] You **have no choice** to do. Whether it's an RCT or any post-approval activity, you have to do it to finally get your product **fully approved**.” – industry
- Accountability
- Extra indication
  - “especially if we do it in a different line of treatment, it also may give us **another indication**.” – industry

Conditioning factors for anticancer medicines with SAT-based CMA

Cancer indication

Promise of new product

Need for evidence

Overall development plan

Access to product

Location of trial

PA-RCT

Feasibility aspects for PA-RCTs

Design

- **Trial aim**
  - Endpoints
  - Comparator
  - Cross-over
  - Trial patient population & line of therapy
- **Trial complexity**
  - Data collection
  - Burden (for patients & physicians)
  - Involved stakeholders
  - Multipurpose trial designs

Conduct

- **Data collection**
  - Burden
  - Biomarkers & biobanking
  - Resources & Expertise
- **Competition**

Motivations

- **Patients**
  - Altruism
  - New treatments and trials
  - Burden
  - Awareness
- **Physicians**
  - Meaningful aim
  - Scientific interest
  - Professional obligation
- **Medical ethicists**
  - Paternalism
  - Therapeutic misconception
  - Clinical equipoise
- **Pharmaceutical industry**
  - Obligation
  - Accountability
  - Extra indication

Unpublished results, please keep confidential

Discussion & Future approaches

- Prospective exploration
- Patient recruitment depends on various factors
- Generalizability in PA-setting
- Differences with pre-authorization

- Validation
- Recommendations to advance feasibility assessments

Questions?

Contact:

Christine van Hattem (c.c.vanhattem@students.uu.nl)
Amos de Jong (a.j.dejong@uu.nl)

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