EORTC
European Organisation for Research and Treatment of Cancer

Developments from the Cancer Medicines Forum and impact across cancer field:

CMF is one year old

CMF gathered 3 times

- 31/03/2022: constitutional meeting, making diagnostics and problem statement, defining a way forward
- 28/06/2022: building the case, identifying the relevant questions to treatment optimisation, involving stakeholders
- 20/12/2022: exploring the EMA for post-authorisation studies, looking into feasibility and methodology of studies (RCT) in the post authorisation setting

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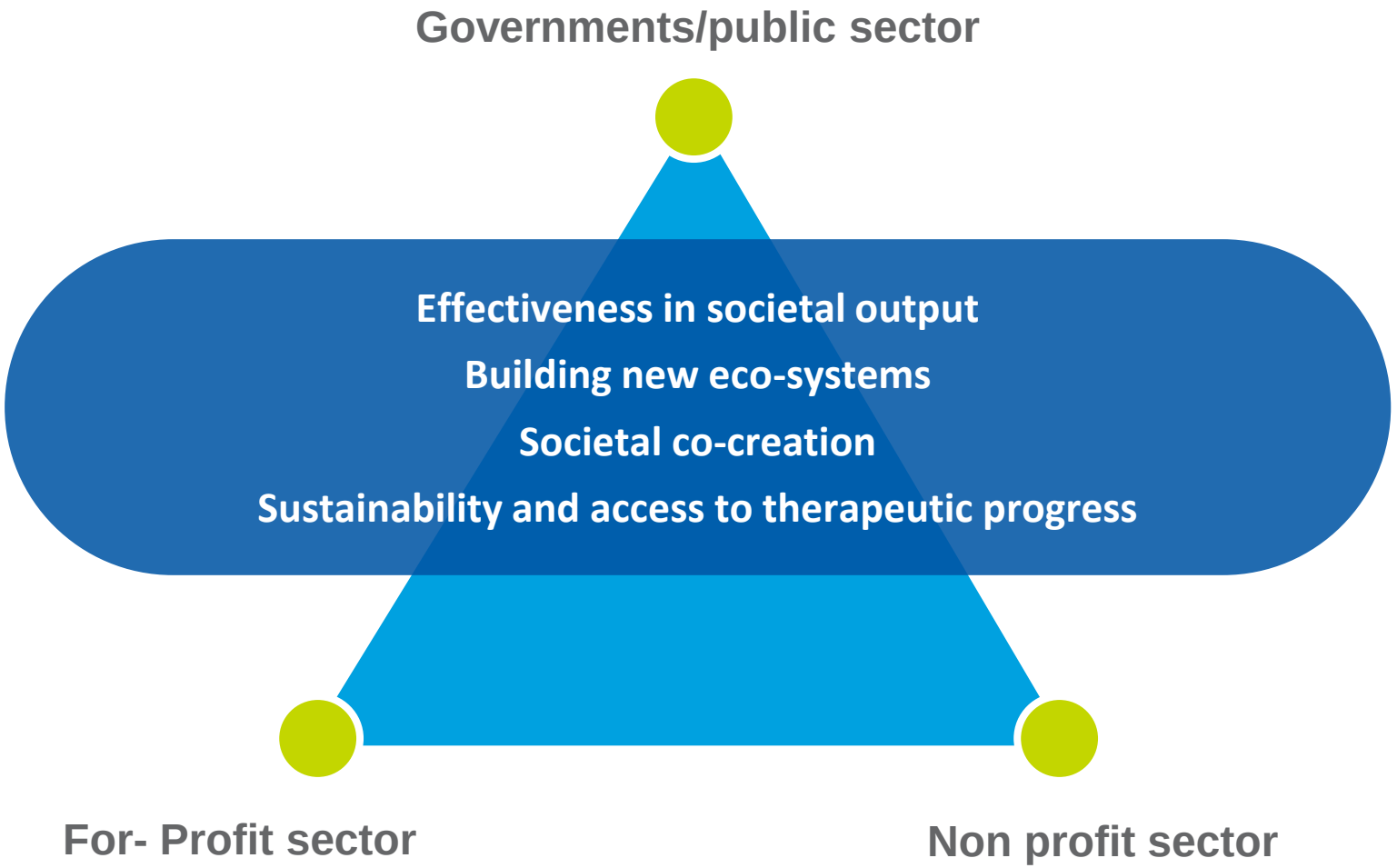
1st meeting

Why EORTC stimulated the CMF?



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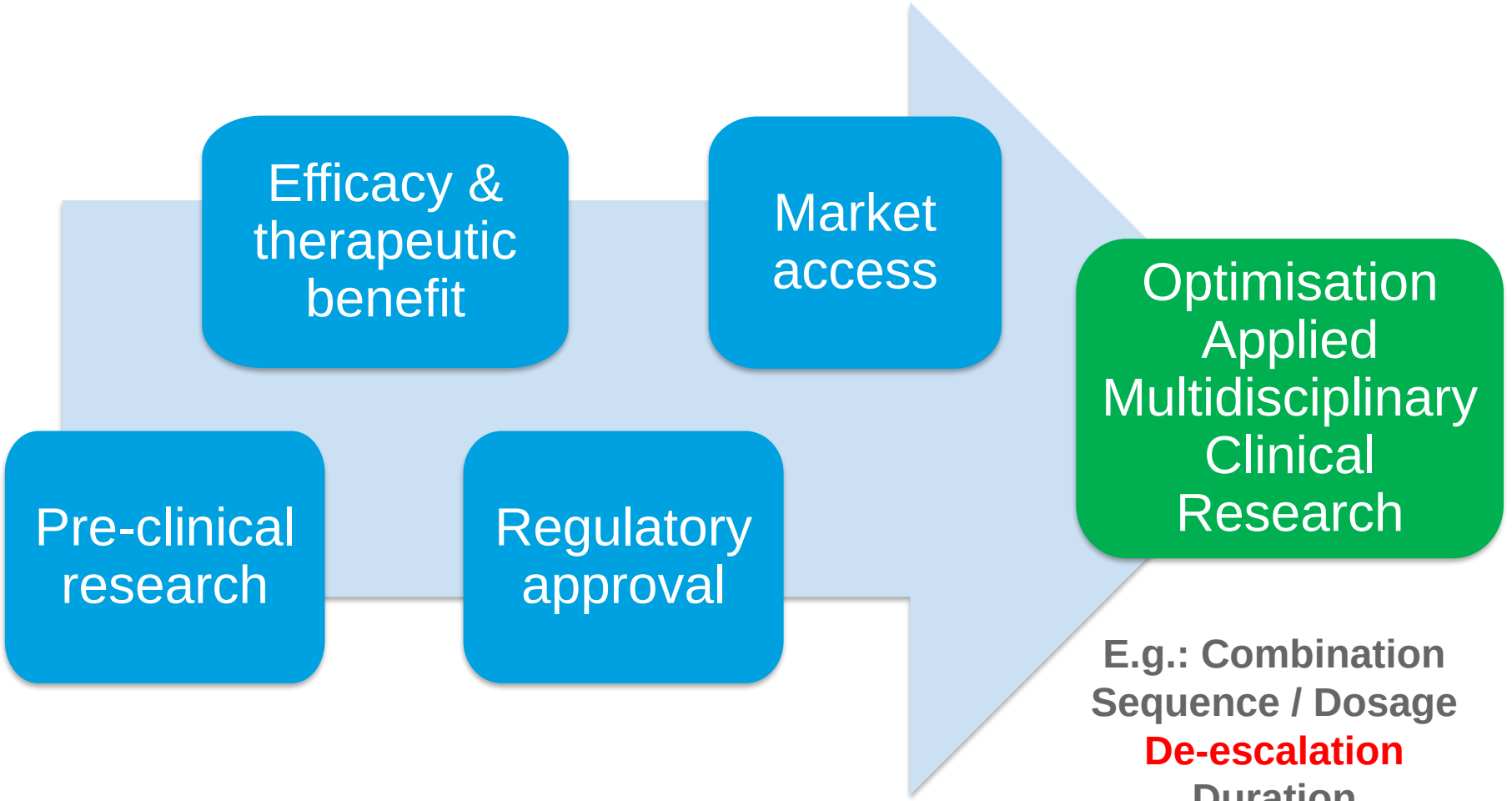
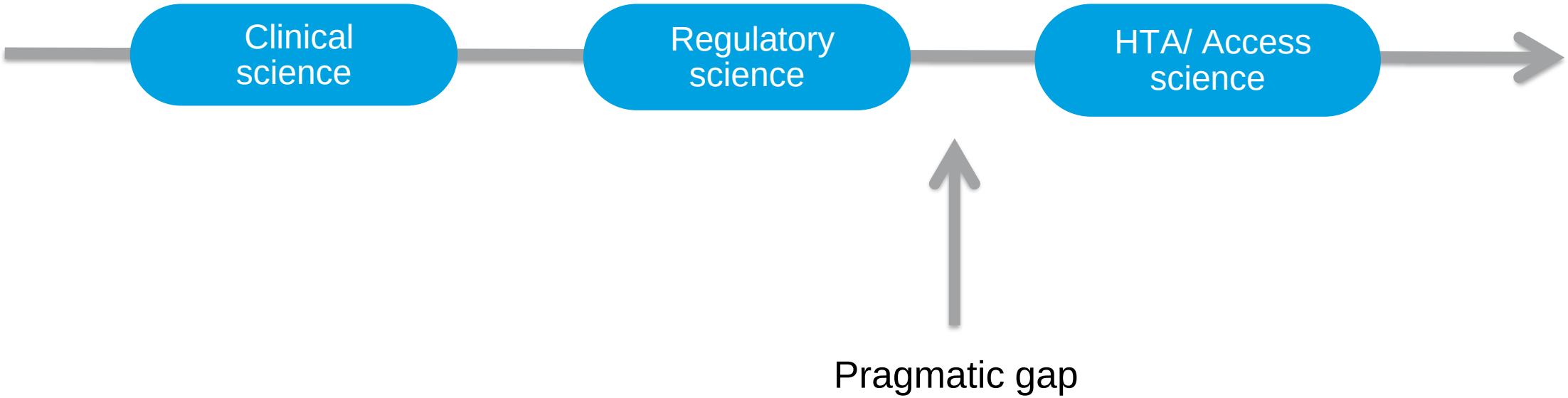
A European Imbalance

The work starts when a technology reaches the market.



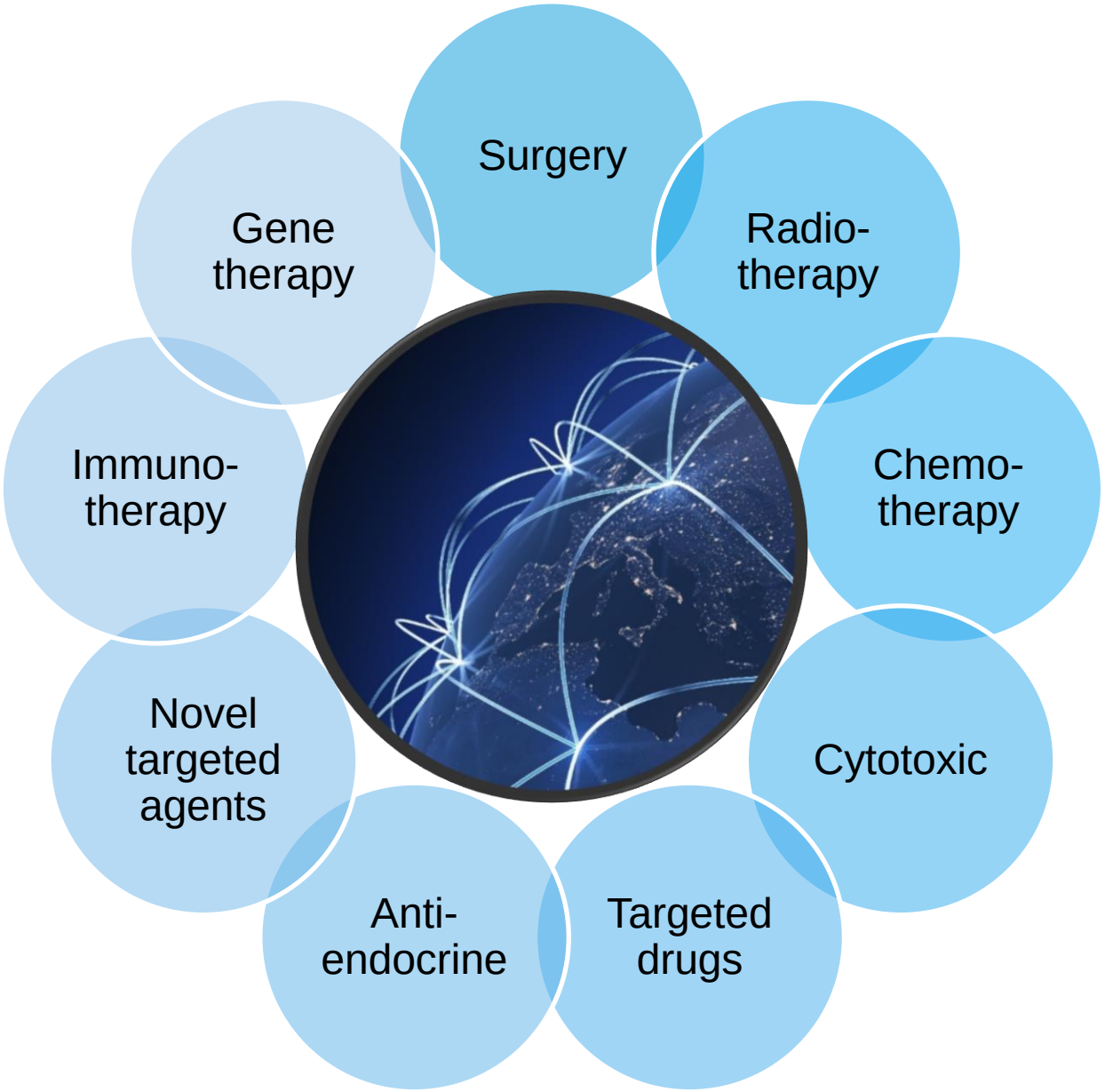
A new continuum to be set up ….Re-engineer….

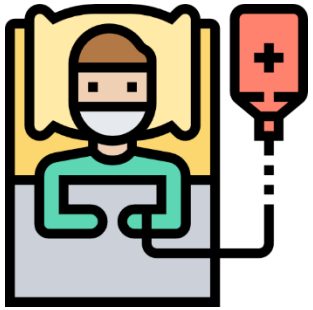


The Future is Combinatorial

Multidimensional data

Authorisation





Access

Optimal access

Objectives of the Cancer Medicines Forum

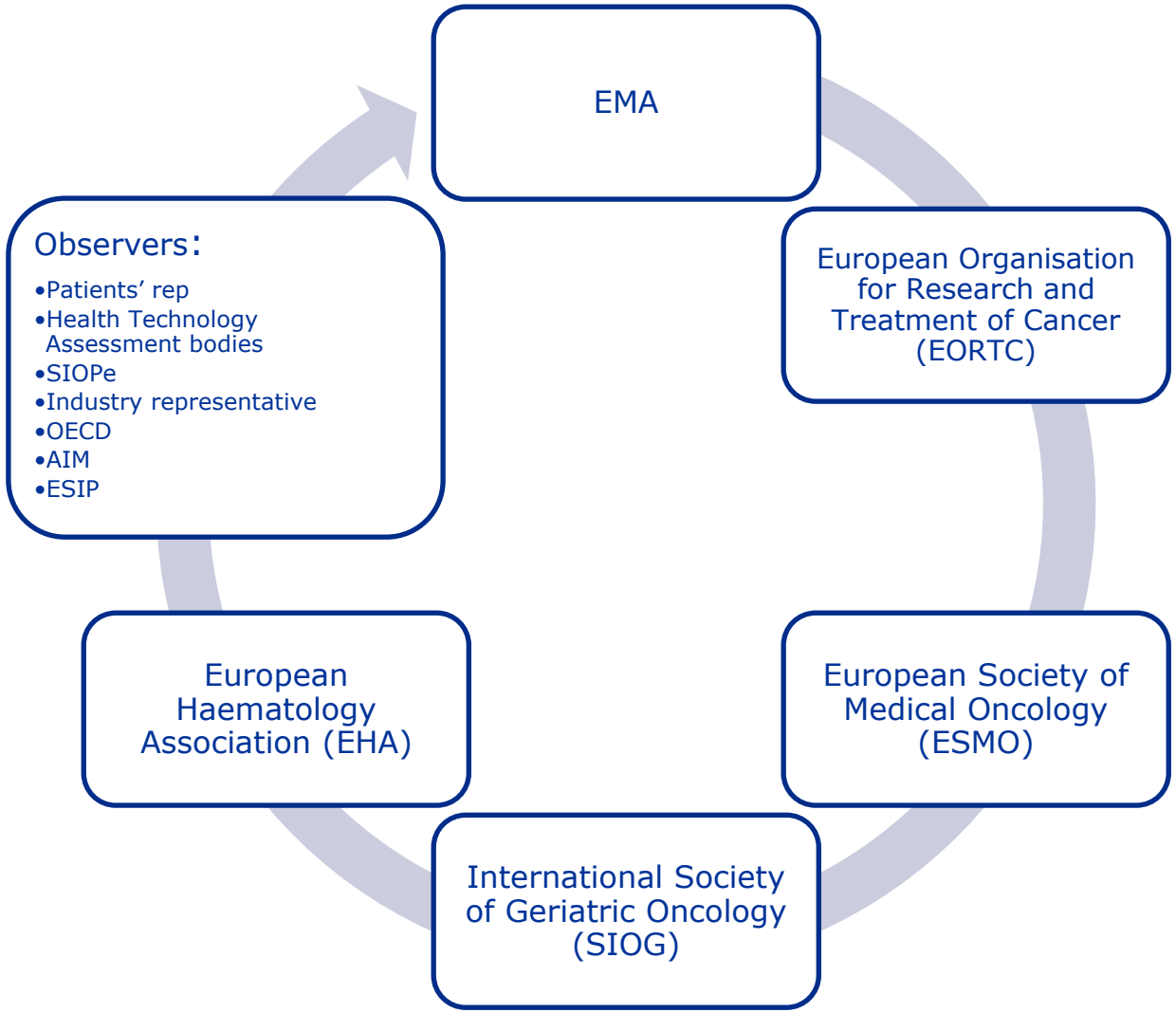
To serve as a direct and official communication channel with the academic community in oncology

To identify key research questions and best methodological approach to improve the clinical use of cancer medicines

To discuss the uptake of academic work in the wider context of regulatory decision-making in oncology

Treatment optimisation

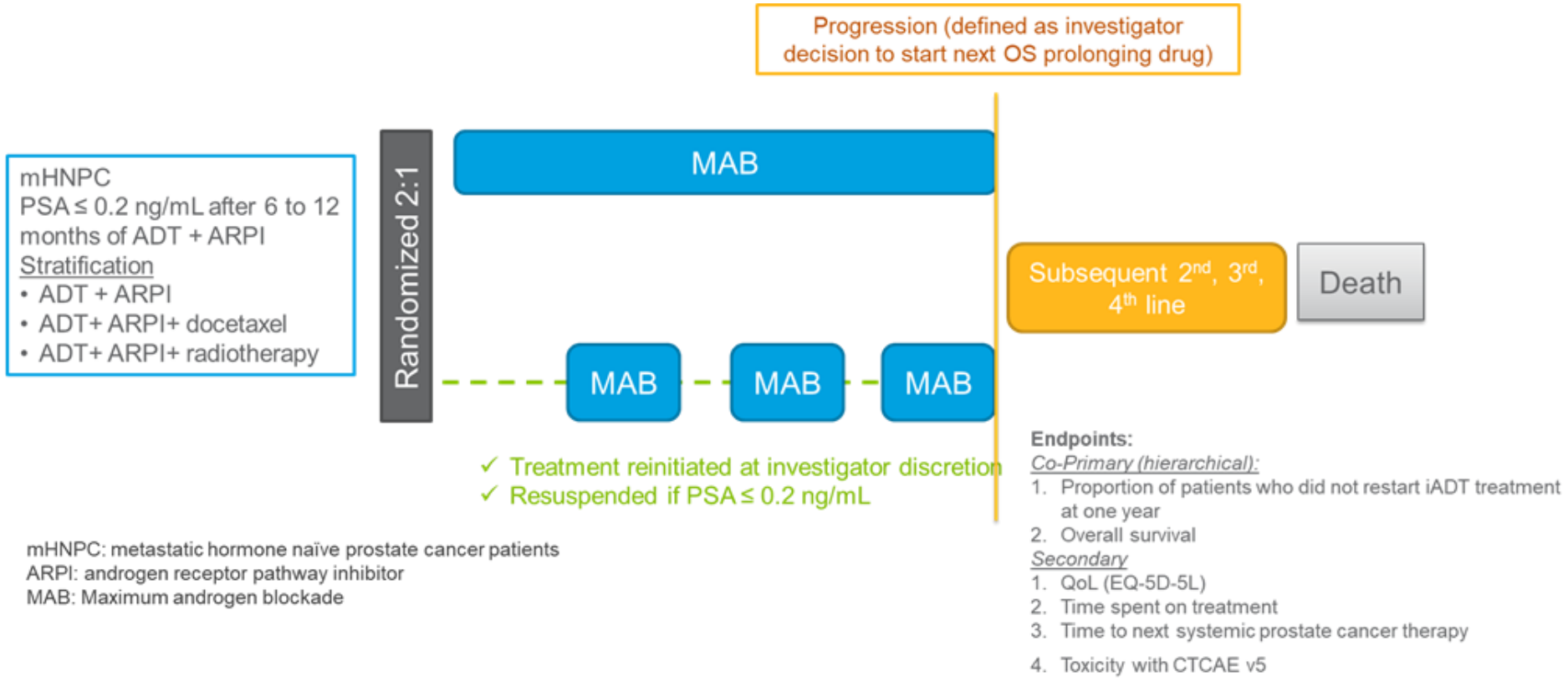
Focus on academia with other stakeholders



Problem statement

- The changing paradigm for cancer drug development and treatment has not taken into account treatment optimisation to confirm and use innovation
- How to improve the process from development into access for patients and society while taking into account the interests and needs of all stakeholders
- Understanding the full EU (and beyond) landscape to explore synergies , avoid duplication i.e. HCPWP, EMA/HTA collaboration, EUnetHTA 21, ACT EU, beating plan and cancer mission….

Intermittent androgen deprivation therapy in the era of androgen receptor pathway inhibitors in prostate cancer ; a phase 3 pragmatic randomised trial (De-ESCALATE)



Can we identify those patients with high risk TNBC that DO NOT need 1 year of pembrolizumab in high risk early TNBC?

Standard neoadjuvant chemotherapy + pembrolizumab for high-risk TNBC

SYRGERY

R

No adjuvant pembrolizumab

Adjuvant pembrolizumb (27 weeks)

Stratification for pathological complete response at surgery

INSTITUT JULES BORDET INSTITUUT

ULB iris

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Key issues to be addressed by the CMF

Identification and labelling of TO questions	No structural approach to address the key critical questions for integrating a new drug into treatment strategies.	Set up a "mechanism" where field (patient-doctor- access) priorities are identified and agreed upon
Methodology	Which optimal methodology/design for which questions	Bridge the relevant questions and the methodology to apply Early access to innovation while mandating relevant TO agenda of studies Educate stakeholders to accept large simple pragmatic programs (few eligibility criteria)
Who	Currently nobody is in charge for TO resulting in absence of datasets	Analyze what falls in the remit of the commercial sector or not Build on independent solutions and infrastructure for access decisions into the healthcare systems
How	National: reach and impact not large enough International: organisational challenges	Bring evidence to healthcare systems decisional bodies that patient-centric and society-centric research can go together Ensure collegial endorsement for free access to agents which are already available in the health systems
When	Structuring TO questions in the process around marketing application: the earlier, the better	Explore what can be done pre-marketing (i.e. EMA scientific advice) Ensure expedited processes to run TO optimization trials when components of the trials are already available in the healthcare systems. Control efficiently the window of opportunities
Recruitment	Competition with industry-sponsored trials of novel agents if conducted as separate studies Loss of (perceived) equipoise in the post-approval setting	Structure the process of drug development versus TO trials Pragmatic studies with broad inclusion of participants, more attractive to oncologists Educate stakeholders to understand remaining uncertainty and value of additional trials to optimise patient treatment
Regulatory and legal aspects	High regulatory burden due to lack of separate provision for academic trials in Clinical Trials Regulation High regulatory burden due to the IMP status of the investigational drugs if used outside of the label Adherence to multiple different country-level laws and regulations if conducted as an international study	Legislative changes, e.g. separate provision for academic trials, change in definition of IMP Exemptions from existing laws and regulations Granting free access to IMPs which are already in the healthcare system for a given indication (independent of the stage of the disease independent) Cut red tape of undue bureaucracy
Datasets and reporting	Regulatory and access datasets are complementary Access datasets are not delivered efficiently or at all. Reporting to HTA/payers is not systematically in place	Ensure an appropriate continuum of regulatory into access science with complementarity of stakeholders Deliver efficient TO datasets limited to the key variables of relevance Sponsorship by independent, non-commercial parties to ensure public availability and accessibility of the data generated by TO/access studies
Funding	Lack of industry support due to lack of incentives No reimbursement of the investigational drugs since they are used outside of the label Country-level funding sources difficult to combine and coordinate for international studies Wasted resources in the healthcare systems due to lack of information on TO	New partnership with industry to conduct studies in the post-approval setting, as feasible and relevant Access to the investigational drugs through legislative changes or exemptions (doing a de-escalation study by itself cuts costs of the health care systems) Gain-sharing programs to reward countries that provide funding Public funding of TO trials through the savings by de-escalation of treatments.

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2nd meeting

The case by EHA

- Licensing trials for early innovation lead to MA but no real process beyond this to optimise the use of agents
- Importance of late trials for “late innovation”:
  - Guide treatment
  - Address clinical questions
  - Guide future research

Possibility to add here a value proposition for societal use and defining market access to be explored

Example of CLL

- Public trials of chemo-immunotherapy led to define 2 patient populations :
  - Mutated TP53 as a high risk group with poor response
  - Wild type TP 53 standard risk group with good response
- Treatment discontinuation study comparing classical chemo-immunotherapy to combination of biological therapies
  - Limited duration biological therapy is effective for Wild Type TP53
  - 2 drugs as effective as 3
- Echoed the case of the initial need for a randomised discontinuation study for stage IV melanoma for duration of IO
- Support the same concept of de-escalation study (EORTC prostate trial)

Example Chronic Lymphocytic Leukaemia (CLL)

Source: Martin Kaiser

~late 1990:
Public trials
mAb + chemo

~2010:
Exploratory analyses

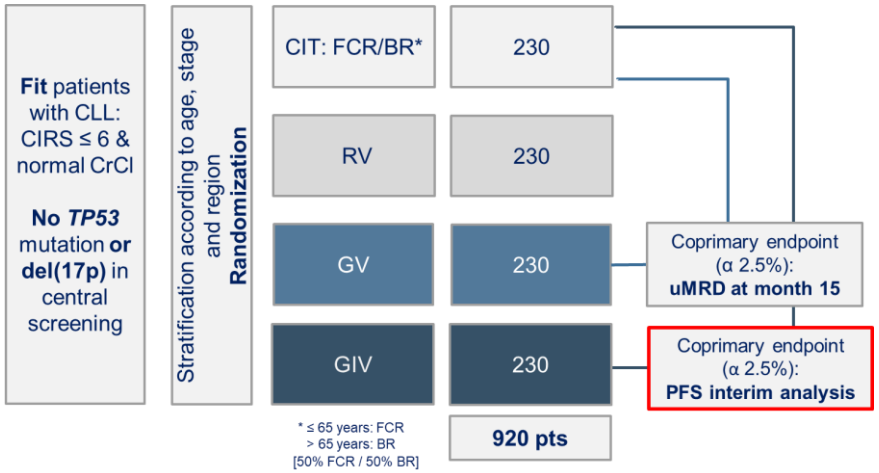
Biology
(TP53mut)

MRD

TP53mut
High risk

TP53wt
Standard risk

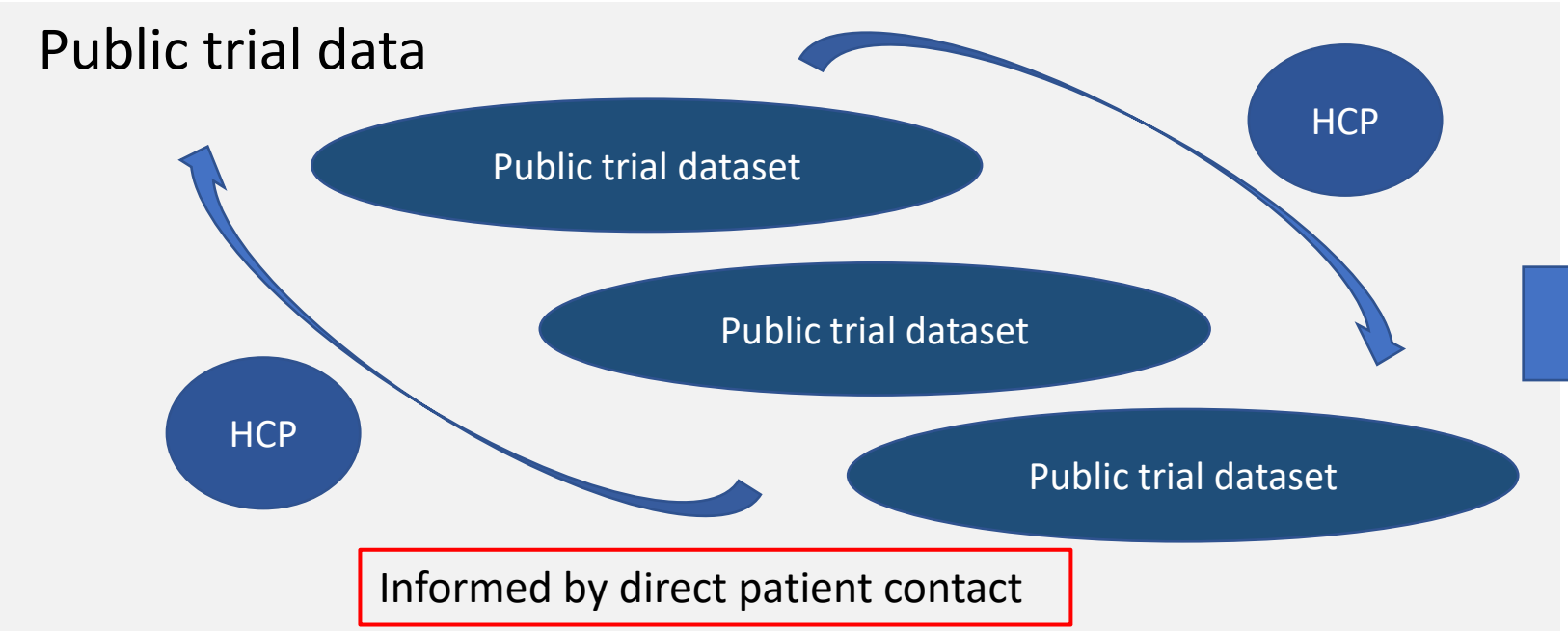
2016:
GAIA/CLL13
Treatment discontinuation trial



NCT02950051

Interconnectedness of public data → added value

Source: Martin Kaiser



Reduce uncertainty

Biological insights

Add value proposition
Patient centricity

Inform future research

Training

Difficult to achieve in commercial setting

Essential for uncommon cancers

Value for multiple stakeholders ‘win-win’

Exemplifying the challenges for public trials

- Funding and sustainability
- Complexity of the designs when addressing public health questions
- Skill shortages across stakeholders to grasp the relevance
- No clear pathway how public trial data can reach the regulator and the HTA bodies

Identification and Labelling of TO questions
1st question on the list of CMF

- No existing structural approach
- Access to commercial data to formulate optimally the questions is improbable and unrealistic
- Questions to be spelled out nevertheless as early as possible in the development process
- Need for a “place to meet” with relevant stakeholders to identify the questions
- A realistic approach:
  - Early stage questions to be handled by the commercial sector
  - Late stage questions to be handled by public trial organisers

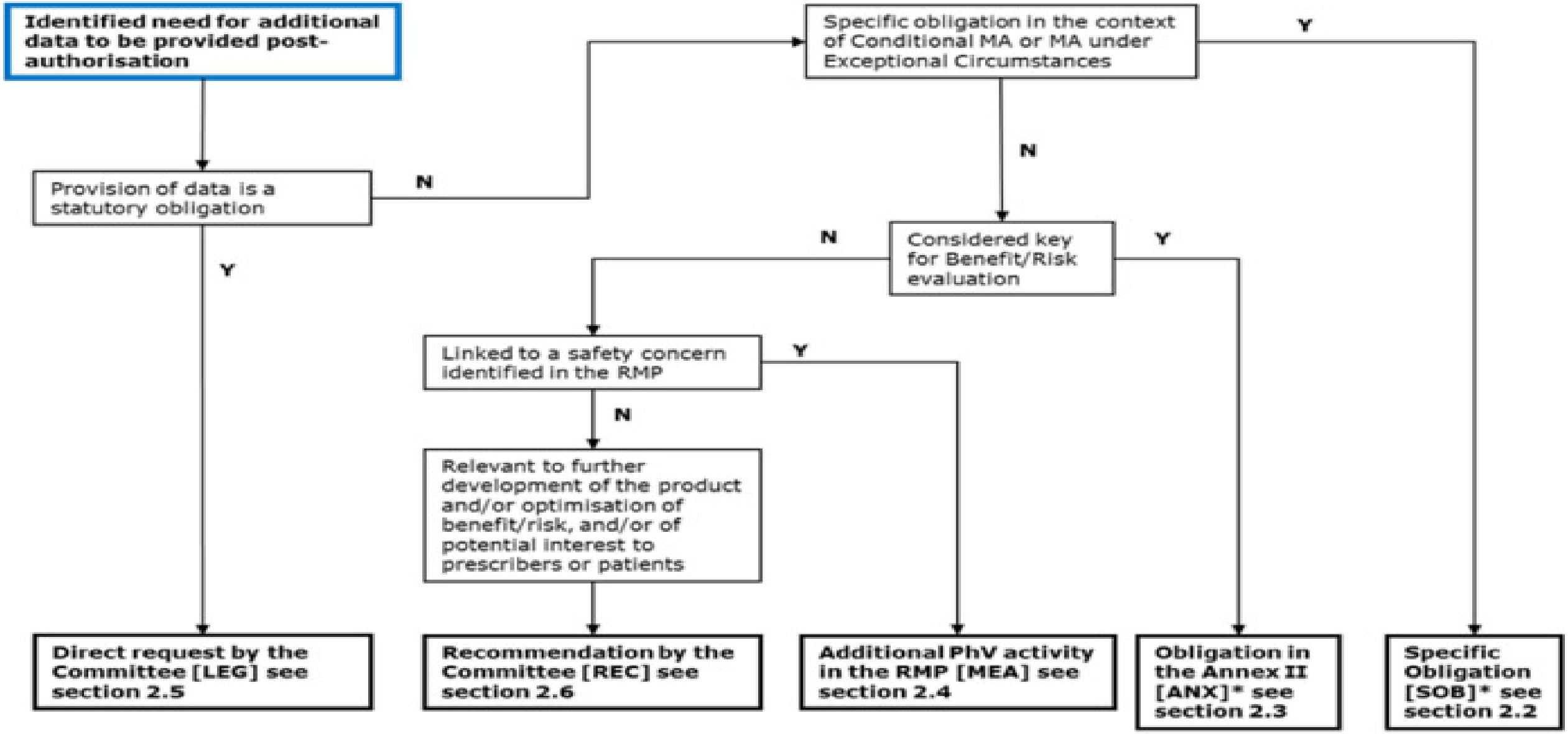
Update on the HTA regulation

- Establishes cooperation between HTA bodies of all EU Member States
- A possible solution to consider treatment optimisation, applicable as of January 2025 for anti-cancer agents
- Prepares healthcare systems for upcoming innovations
- Formalises joint clinical assessment
- Impact for evidence generation:
  - Joint HTA advice (possibly with EMA) to inform companies which data HTA bodies need to deliver to avoid delays
  - Does not cover specificities for the post approval data collection but might include post licensing evidence requirements

3rd meeting

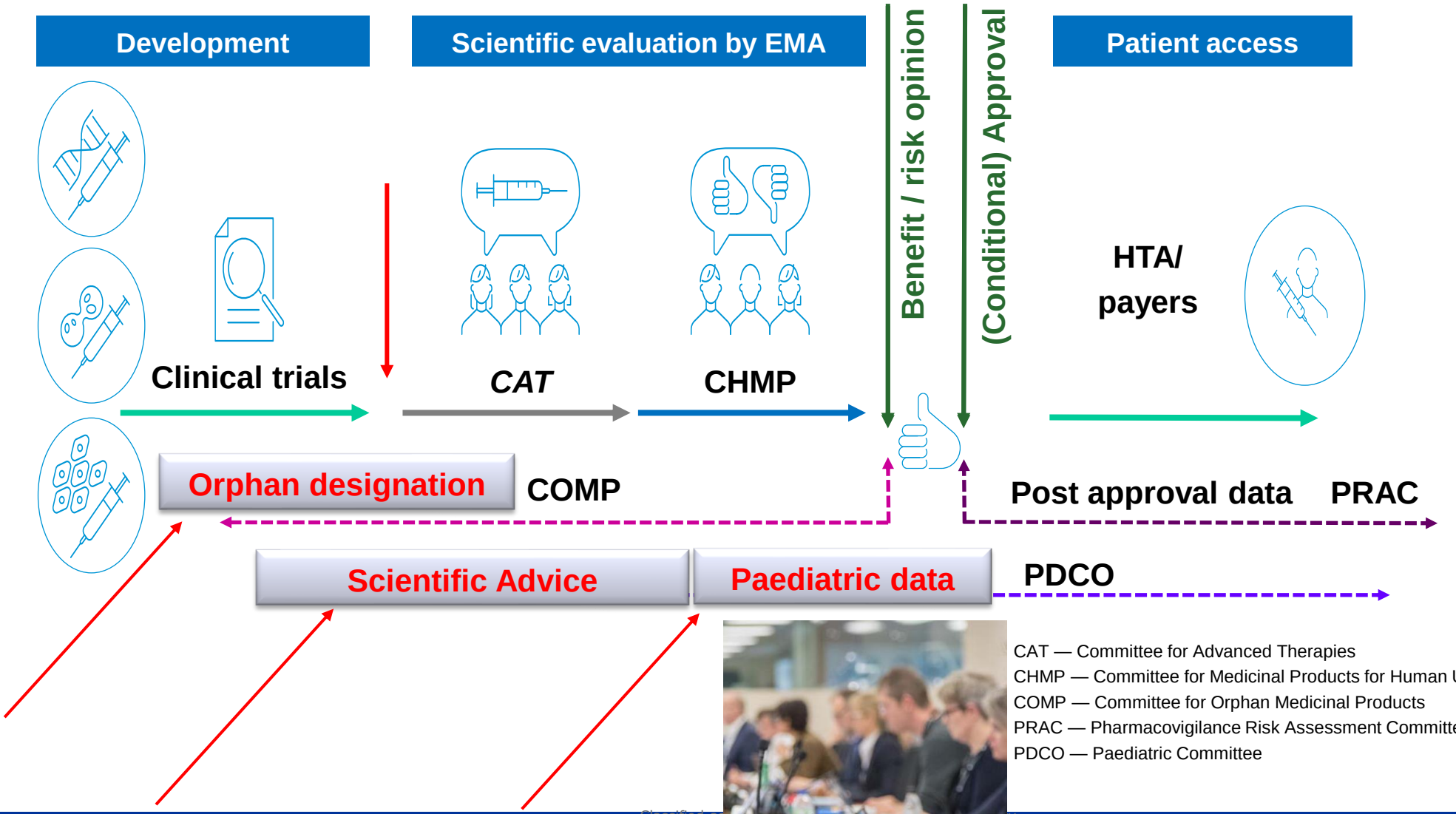
Fig.: Schematic overview of decision tree for the classification of PAMs

Source: Caroline Voltz



* plus potentially also additional PhV activity in the RMP [MEA] if linked to a safety concern identified in the RMP

Start at the development phase



CAT — Committee for Advanced Therapies
CHMP — Committee for Medicinal Products for Human Use
COMP — Committee for Orphan Medicinal Products
PRAC — Pharmacovigilance Risk Assessment Committee
PDCO — Paediatric Committee

High level conclusions

- De-escalation or integration of new agents in existing treatment modalities are most likely feasible only in the post marketing setting
- Need a solution around possibly the scientific advice but need to re-engineer the process in the post marketing space

Presentation by the Utrecht group

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

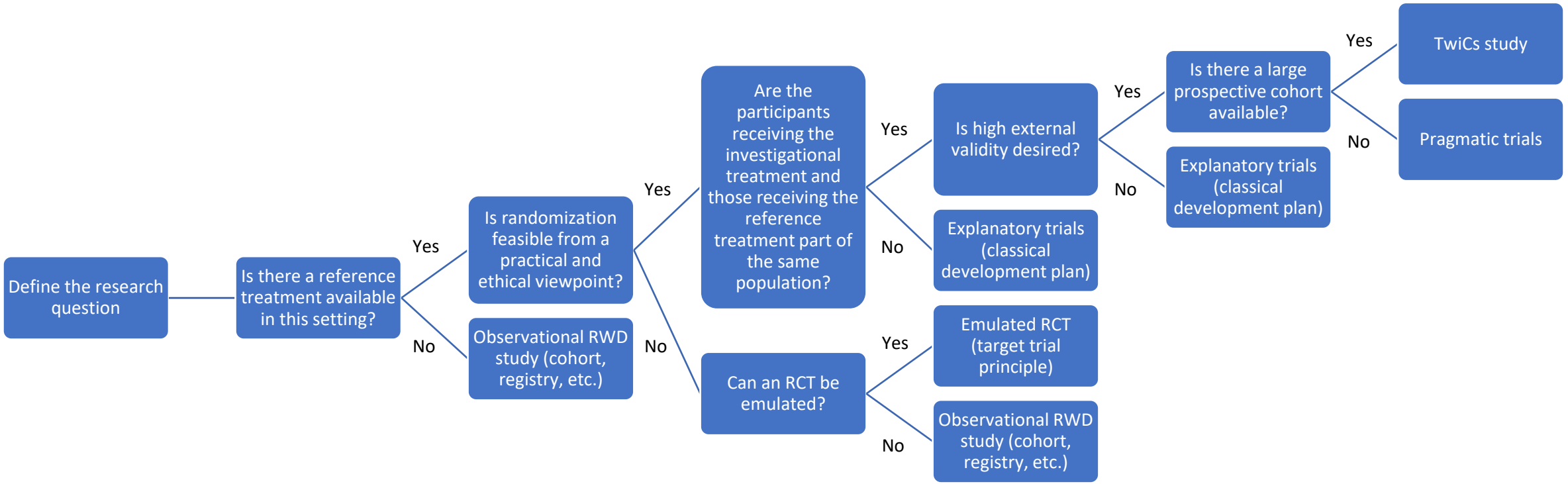
a multistakeholder perspective

- Design: end-points, comparator, randomisation etc..
- Conduct: data collection, HBM
- Motivation: patients, doctors, ethicists, pharma…

Other important elements

- Indication/ tumor type
- Promise of the product / access to the product
- Need for evidence /overall development plan
- Location of the trial

Proposed methodological chart



High level conclusions

- Y1 of the CMF made diagnostics and provided insight in the overall landscape for the concept of treatment optimisation:
  - Vacuum in the post licensing phase for treatment optimisation
  - Public trials not reaching HTA/Payers
  - EMA post approval measures not fulfilling the need today
  - HTA regulation not structuring post licensed evidence generation
  - Dichotomy between early stage and late stage questions

CMF has anticipated what seems to being set up in the US (FDA/NCI)

Future directions

- Let’s now go to the next stage:
  - Set up the basis for deliverables of the CMF
  - Address the very practical aspects to deliver a value proposition
  - Think towards solutions to provide input in the regulatory process
  - Develop roadmap along which treatment optimisation questions can be selected and prioritised
  - Start interacting with relevant bodies (EUnetHTA, EU commission, ..) for acting on the related policy work
  - Develop case studies to illustrate challenges and solutions
  - Assess the role of new methodological approaches for TO questions (pragmatic trials)
  - Educate and communicate about TO all relevant stakeholders

Need for strategic intelligence approaches