

Innovative trial designs: the EU HTA prespective

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Innovation and Access in Rare Cancers

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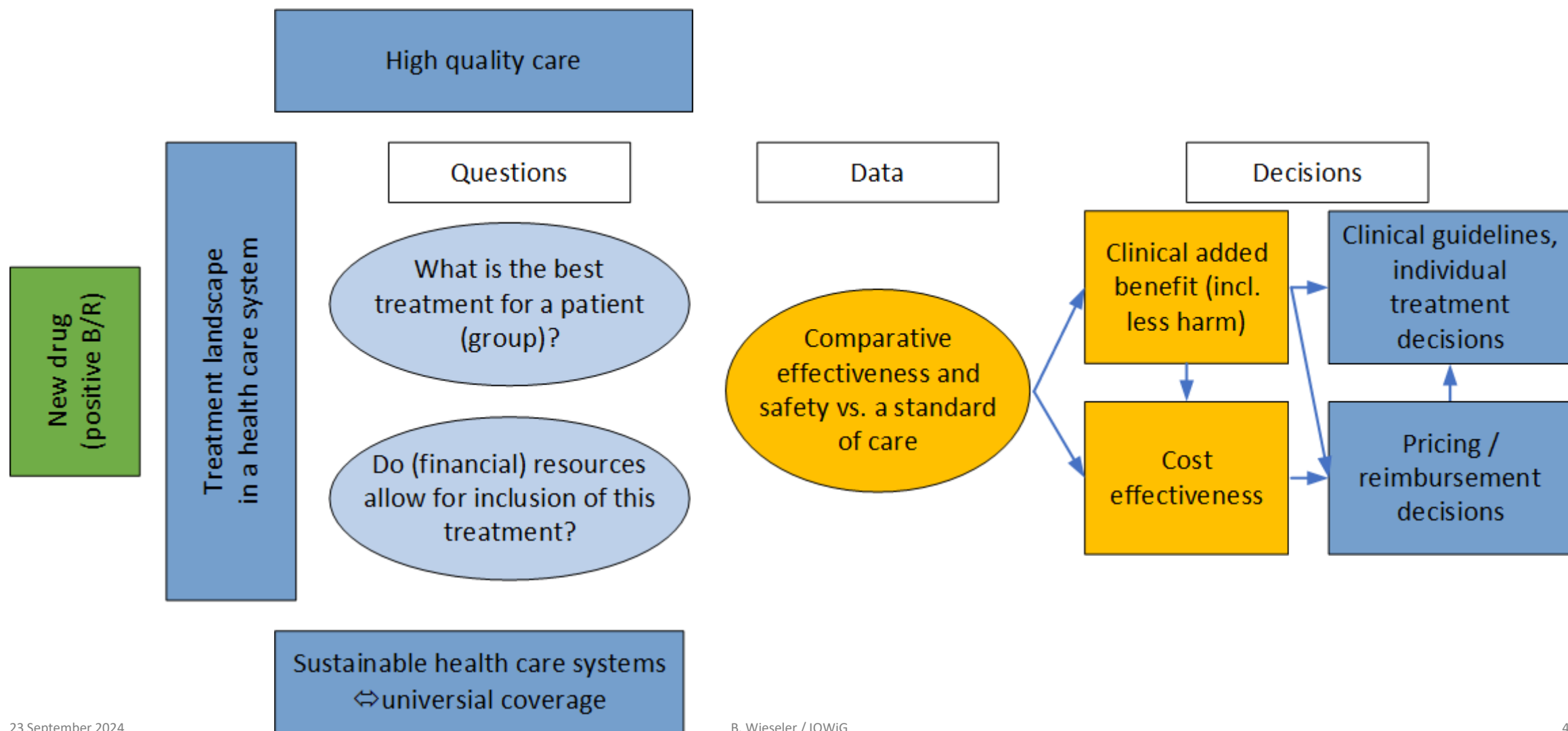
Conflict of interest statement

- I have no conflicts of interest to declare

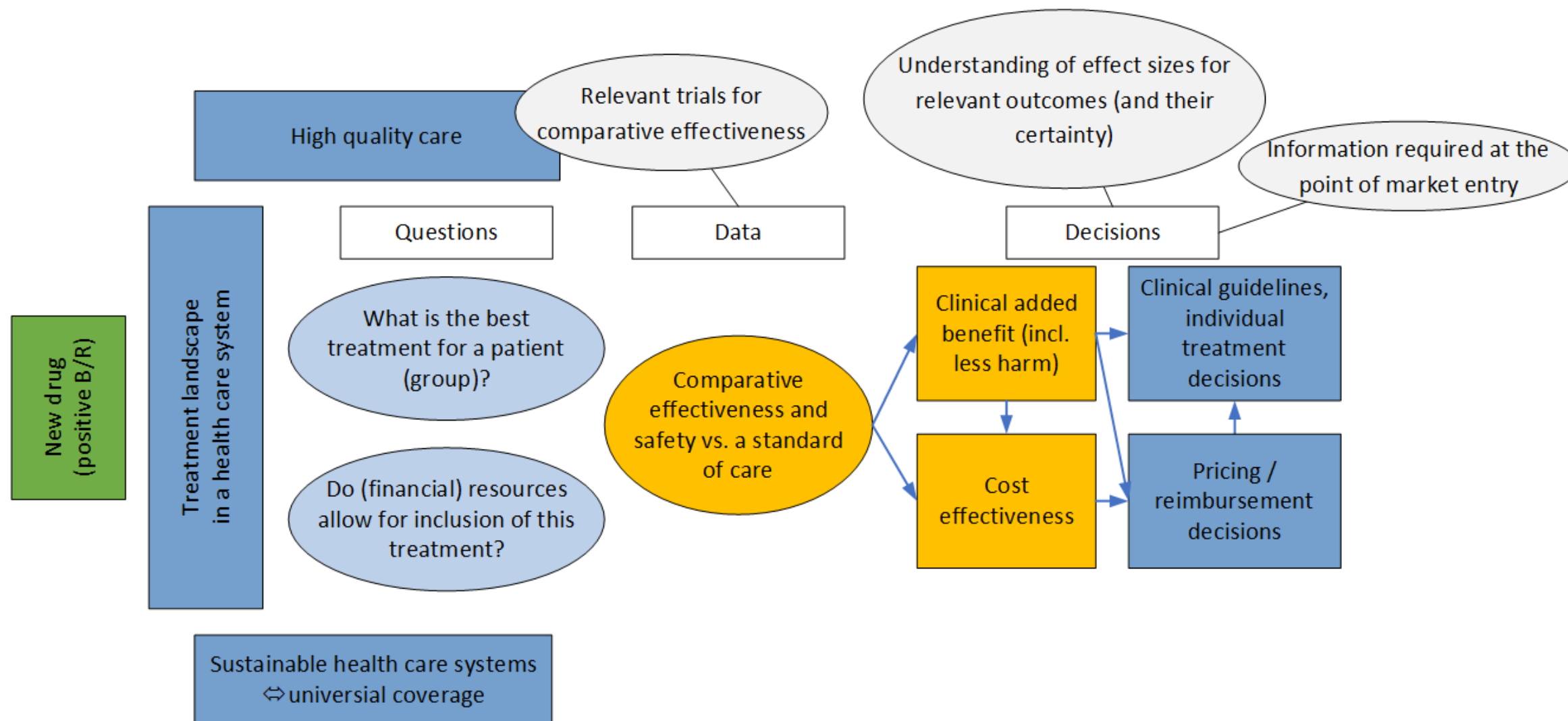
Agenda

- HTA decision making and corresponding research questions
- European HTA incl. methodological recommendations
- Experience with available evidence
- Suggestions to improve the situation

HTA decision making



Evidence needs of HTA



Regulation (EU) 2021/2282 on HTA

- Article 9 (1) A joint clinical assessment shall result in a joint clinical assessment report that shall be accompanied by a summary report. Those reports shall not contain any value judgement or conclusions on the overall clinical added value of the assessed health technology and shall be limited to a description of the scientific analysis:
 - (a) of the **relative effects of the health technology** as assessed on the health outcomes against the chosen parameters which are based on the **assessment scope** as set out pursuant to Article 8(6);
 - (b) of the **degree of certainty of the relative effects**, taking into account the strengths and limitations of the available evidence.

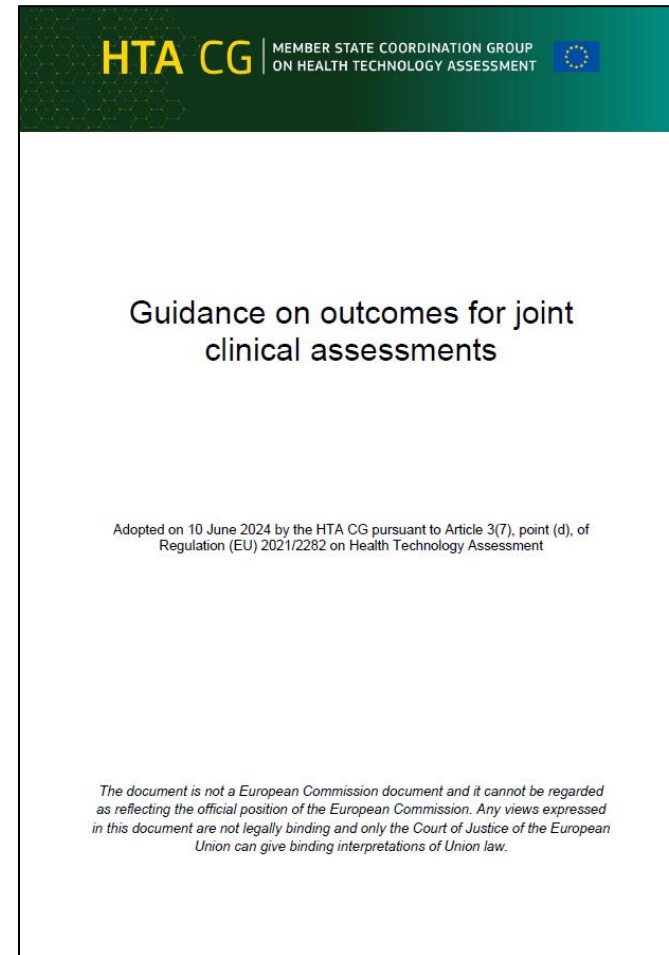
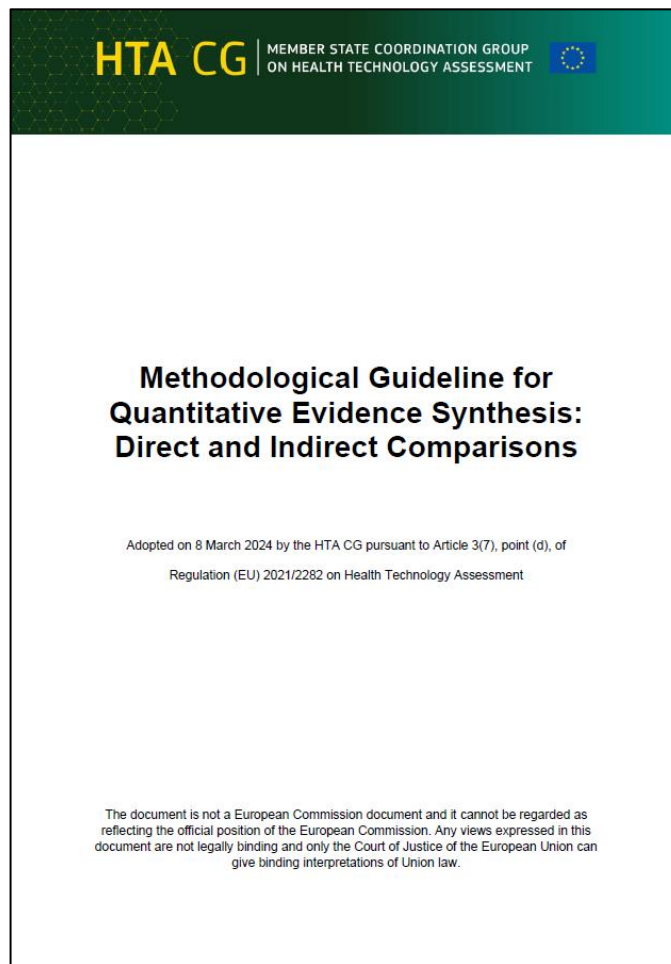
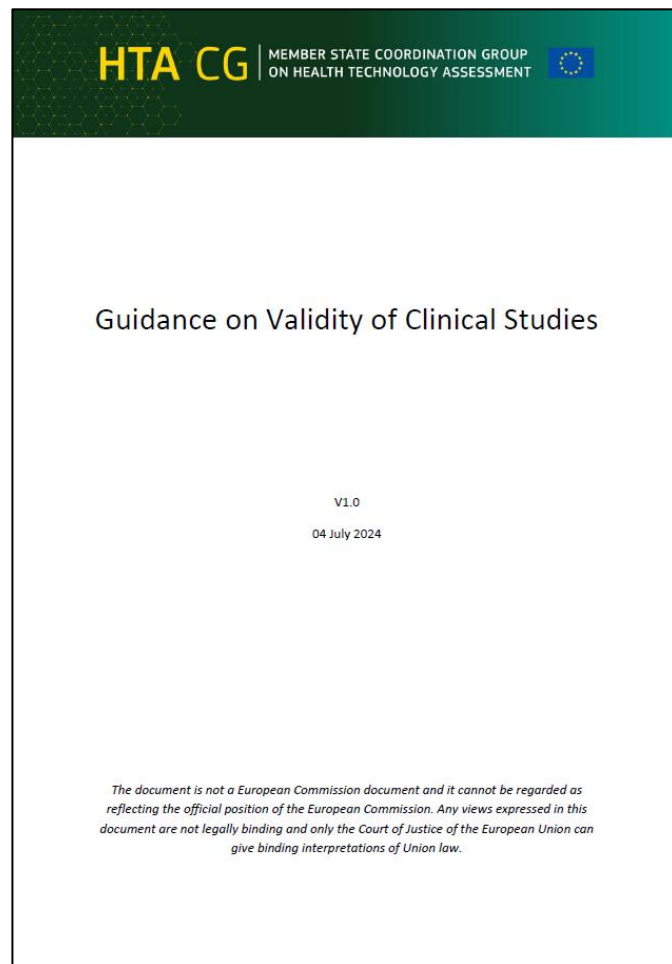
Context of health technology assessment

- Our question: comparative effectiveness (is there any difference between a new intervention and the current standard of care/best available treatment?)
- => inform treatment decisions, inform pricing and reimbursement decisions



- We often lack data to answer our question
- We need more and other studies to enable a description of comparative effectiveness

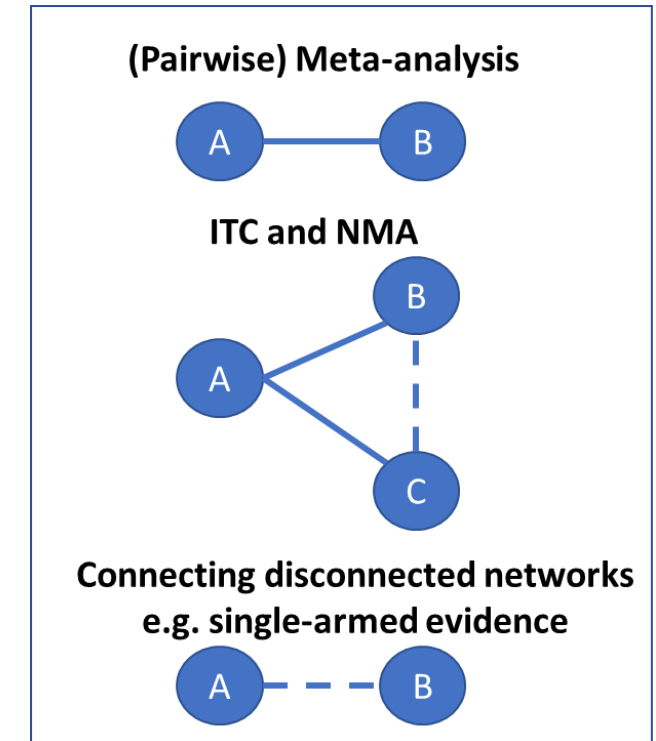
Guidance of the European HTA Coordination Group



https://health.ec.europa.eu/health-technology-assessment/key-documents_en?f%5B0%5D=topic_topic%3A225&f%5B1%5D=topic_topic%3A226&f%5B2%5D=topic_topic%3A227&f%5B3%5D=topic_topic%3A228

General methodological approaches covered

- Direct comparisons – individual studies, pairwise meta-analysis
- Indirect comparisons
 - Bucher's method for anchored indirect comparisons
 - Network meta-analyses
 - Population-adjusted methods for indirect comparison
- Comparisons derived from single-armed trials and other non-randomised evidence
- This range of approaches allows to address all types of products covered by the HTAR, including ATMPs and orphan drugs
- The lack of high-quality evidence does not in itself demonstrate the validity of results based upon less-reliable methods



The problem: evidence available for HTA

- Case study: new cancer drugs
- Sample: health technology assessments of cancer drugs started at IQWiG between June 2021 and December 2021
- HTAs covering 27 cancer drugs with 40 research questions

	Direct comparisons vs. SOC (RCT)	Indirect comparison vs. SOC	No acceptable evidence vs. SOC available	Total
HTAs of cancer drugs	19/40 (48%)	7/40 (18%)	14/40 (35%)	40/40 (100%)

No data submitted:
3/14

Single arm trials:
11/14

Single-arm study vs. RCT: a necessity or a choice?

Table 1 | Pivotal studies in approvals of treatments for late line relapsed or refractory diffuse large B cell lymphoma

	Pixantrone	Tisagenlecleucel	Axicabtagene ciloleucel	Polatuzumab vedotin	Tafasitamab	Lisocabtagene maraleucel	
Brand name	Pixuvri	Kymriah	Yescarta	Polivy	Minjuvi	Breyanzi	
Date of (first) approval	May 2012 conditional approval	Aug 2018 standard approval	Aug 2018 standard approval	Jan 2020 conditional approval	Aug 2021 conditional approval	Apr 2022 standard approval	
Indication	≥2 previous treatments	≥2 previous treatments	≥2 previous treatments	≥1 previous treatment, SCT ineligible	≥1 prior treatment, ASCT ineligible	≥2 prior treatments	
Orphan designation	no	yes	yes	yes	yes	no (withdrawn)	
ATMP	no	yes	yes	no	no	yes	
Pivotal studies	PIX301* RCT (phase 3)	C2201 single arm (phase 2)	ZUMA 1 single arm (phase 1/2)	G029365 RCT (phase 1b/2)	L-MIND single arm (phase 2)	017001 single arm (phase I)	BCM-001 single arm (phase 2)
Comparator arm	yes	no	no	yes	no	no	no
No. of patients enrolled in treatment arms	Pixantrone 70 (53 with DLBCL); Physician's choice 70 (51 with DLBCL)	147	111 (77 treated for DLBCL)	Polatuzumab+BR 40; BR 40	81	341	58
Primary endpoint	CR	ORR	ORR	CR	ORR	safety and ORR	ORR

* aggressive NHL including DLBCL. ASCT, autologous stem cell transplantation; ATMP, advanced therapy medicinal product; BR, bendamustine/rituximab; CR, complete response; NHL: non-Hodgkin lymphoma; ORR, objective response rate; RCT, randomised controlled trial; DLBCL: diffuse large B cell lymphoma, SCT: stem cell transplantation.



Difficulties with single-arm trials for HTA

- No evidence for comparative effectiveness
- Suggested ways to overcome the problem:
 - external control arms (including data from routine practice)
 - suggested methods uncertain (e.g. underlying assumptions often cannot be tested)
 - data required for effect estimation (confounders, endpoints) often not available in the required quantity and quality (especially not from routine practice data sources)
 - post-licensing evidence generation
 - randomised comparative studies with licensed drugs often difficult (due to perceived loss of equipoise)
 - shortcomings of observational studies as with external control arms
 - delays evidence-based health care

Can RWD solve the problem? Lisocabtagene case study

- Assessment of lisocabtagene maraleucel vs. an individualised treatment in r/r DLBCL considering patient characteristics (e.g. pre-treatment, ECOG-PS, course of disease etc.)
 - available data: comparison against external control arm from RWD (non-interventional retrospective study in various data sources: OTA, Flatiron, Guardian Research Network)
 - data on relevant patient characteristics missing in these data sources (e.g. 41% no data on ECOG-PS, 96% no data on IPI, 29% no Ann Arbor staging)
 - differences in time and type of treatment (start of treatment 2016-18 vs. unknown [first diagnosis since 2003]; 30% vs. 10% with SCT; low rates of newer treatment options in comparator arm)
 - data on confounders missing (12 out of 29 confounders not considered in the analyses due to >30% missing data)
 - only data on overall survival, no data on adverse events, no data on symptoms, no data on HRQoL

<https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/869/>

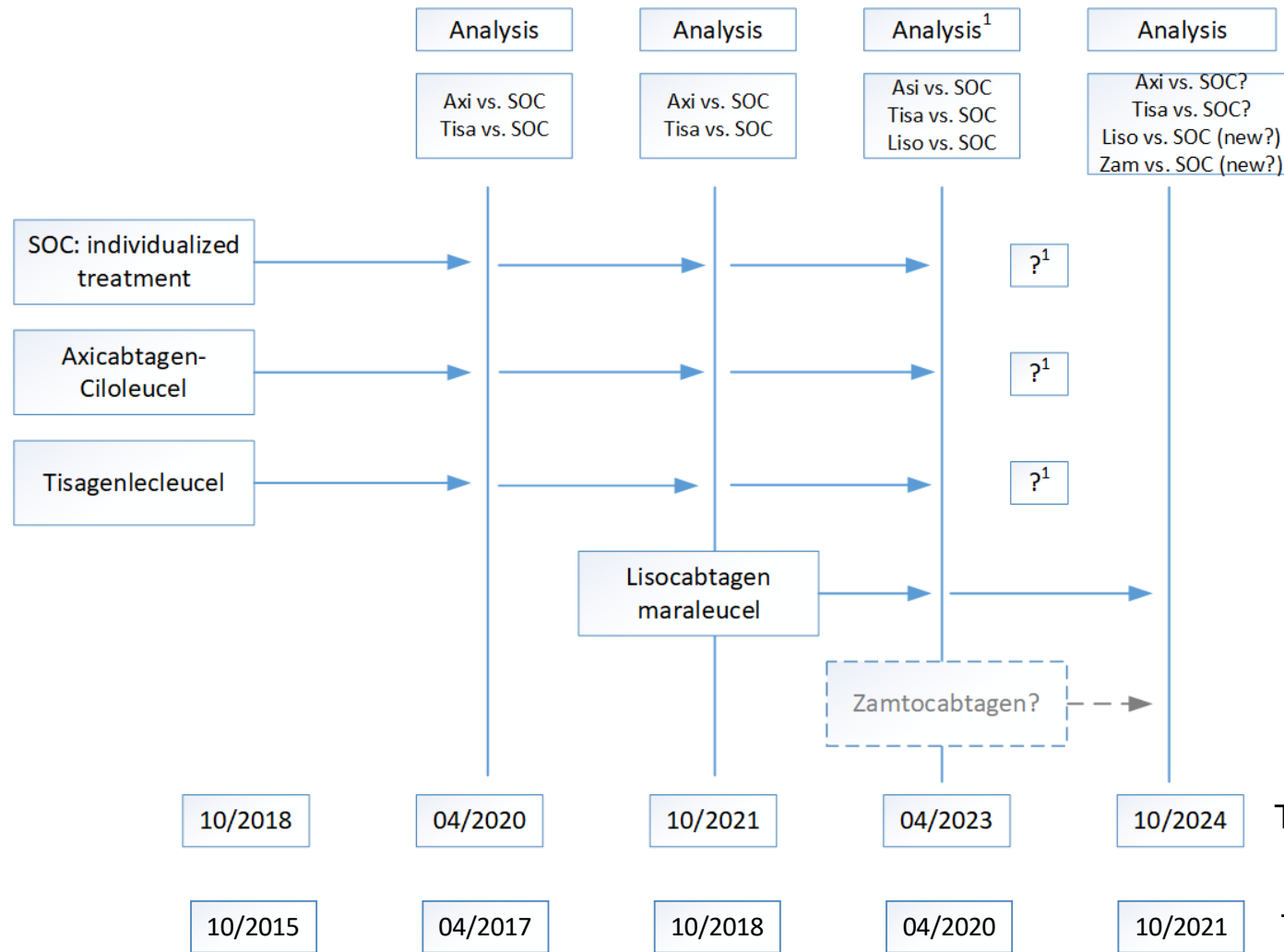
Can RWD solve the problem? Lisocabtagene case study

- Assessment of lisocabtagene maraleucel vs. an individualized treatment considering patient characteristics (e.g. pre-treatment, ECOG-PS, course of disease etc.)
 - comparison against external control arm from interventional retrospective study in various data sources: OTA, Flatiron, Flatiron Research Network)
 - data on relevant patient characteristics missing in various data sources (e.g. 41% no data on ECOG-PS, 96% no data on performance status, 96% no data on symptoms)
 - differences in time at risk of treatment 2016-18 vs. unknown [first diagnosis since 2003], low rates of newer treatment options in comparator arm)
 - data on confounders missing (12 out of 29 confounders not considered in the analyses due to >30% missing data)
 - only data on overall survival, no data on adverse events, no data on symptoms, no data on HRQoL

**External controls from
RWD not suitable
to solve the problem**

<https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/869/>

Randomised adaptive platform trial for CAR-T cells in r/r DLBCL



- Request such a study before approval?
- Conduct such a study in routine practise (registries) after approval (RWD)?

Faster access to evidence based health care



<https://kce.fgov.be/en/evidence-gaps-for-drugs-and-medical-devices-at-market-entry-in-europe-and-potential-solutions>

- Comparative trials before regulatory approval enable optimised treatment at market entry

Measures to enable RCTs in smaller populations

Box 2: Measures to enable RCTs in smaller populations

Improve study conduct, including patient recruitment

- Set up standardised patient registries for rare diseases and ensure data collection in routine care
- Set up a standardised trial infrastructure for studies in Europe and connect this infrastructure to networks outside Europe, as appropriate
- Identify patients for trials via patient registries³²
- Conduct RCTs linked to information stored in patient registries³³
- Use adaptive platform trials with master protocols across different treatment candidates³⁴

Mitigate small patient numbers

- Avoid narrow inclusion criteria; include broader patient populations reflecting the target population
- Increase proportion of patients (for a given disease) in clinical trials
- Perform multinational trials (increasing and speeding up patient inclusion)²⁷
- Use optimised study designs (such as adaptive designs) for trial efficiency³⁵
- Use common control groups (through platform trials)³⁶
- Apply statistical methods that tackle small patient numbers³⁵

General

- Optimise study designs for decision making by both regulators and health technology assessment agencies to avoid the need for a larger number of trials³⁷

- Involve patients in study design to ensure that the study conduct and information generated also meet their specific needs
- Maximise learnings from studies (in small populations) by routinely making individual patient data available to the EMA and use the individual patient data available from the FDA for additional analyses (also across studies)^{38 39}
- Accelerate clinical development by making new knowledge (including clinical study reports) publicly available as soon as possible⁴⁰

- Collection of suggestions discussed in the literature
- Additional suggestions include increased use of European Reference Networks, TWICS, linkage of RCTs with comparative data from routine practise ...

Wieseler et al. *BMJ* 2023; 380 doi: <https://doi.org/10.1136/bmj-2022-073100>

Orphan medicinal products regulation

- REGULATION (EC) No 141/2000 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL (December 1999) on orphan medicinal products, Recital 7:
 - patients with such conditions deserve the same quality, safety and efficacy in medicinal products as other patients; orphan medicinal products should therefore be submitted to the normal evaluation process

Conclusions

- To enable high quality care in sustainable health care systems we need appropriate evidence for decision making – also for patients with rare cancers
- Data and study designs must be fit-for-purpose for the research questions at hand – the trend towards single arm trials and observational study designs is not
- Conducting randomised studies in a standing infrastructure in routine practice can contribute to making RCTs easier, faster and cheaper (and might even be easier than improving data quantity and quality to the required level for observational studies)
- We need both appropriate requirements for commercial studies and a publicly funded trial ecosystems to achieve evidence-based patient care and to continuously optimise available treatment options

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