Current HTA Experience with Real World Data

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EMA Cancer Medicines Forum

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HTA and Real World Data

- Ongoing discussion

- EUnetHTA Joint Action 3: Registry Evaluation and Quality Standards Tool (REQueST)
https://www.eunethta.eu/request-tool-and-its-vision-paper/

- EUnetHTA21 methods guidance

  - D4.6 Validity of Clinical Studies (practical guideline)
  https://www.eunethta.eu/d4-6/

  - D4.3. Direct and Indirect Comparisons (methodological guideline and practical guideline) https://www.eunethta.eu/d4-3/

Clarification of the question

We are not talking about

- Useful information from routine practice data, e.g.

  - size of a specific patient population

  - treatment patterns in clinical practisc

  - characteristics of patients with a given disease

  - costs of treatment in a patient group

  - …

We are talking about

- Treatment effects of new drugs

  - health outcomes causally related to treatments

  - comparative effectiveness comparing treatment outcomes of alternative interventions

B. Wieseler/IQWiG
Classified as public by the European Medicines Agency

HTA and Real World Data

- Recent publication by French HTA body HAS:

  - Vanier et al. Rapid access to innovative medicinal products while ensuring relevant health technology assessment. Position of the French National Authority for Health. BMJ Evidence-based medicine, Epub ahead of print https://ebm.bmj.com/content/early/2023/02/07/bmjebm-2022-112091

- Recent publication by German/Belgian HTA bodies IQWiG/KCE:

  - Wieseler et al. Replacing RCTs with real world data for regulatory decision making: a self-fulfilling prophecy? BMJ 2023;380:e073100 https://www.bmj.com/content/380/bmj-2022-073100
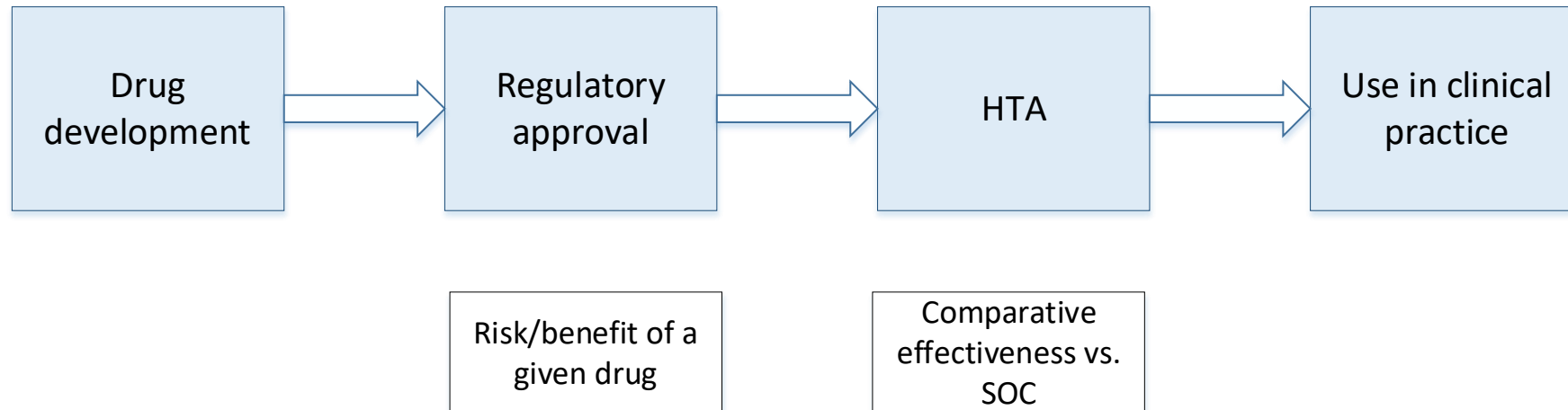
The problem: evidence available for the assessment of new cancer drugs

IQWiG

- 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%)
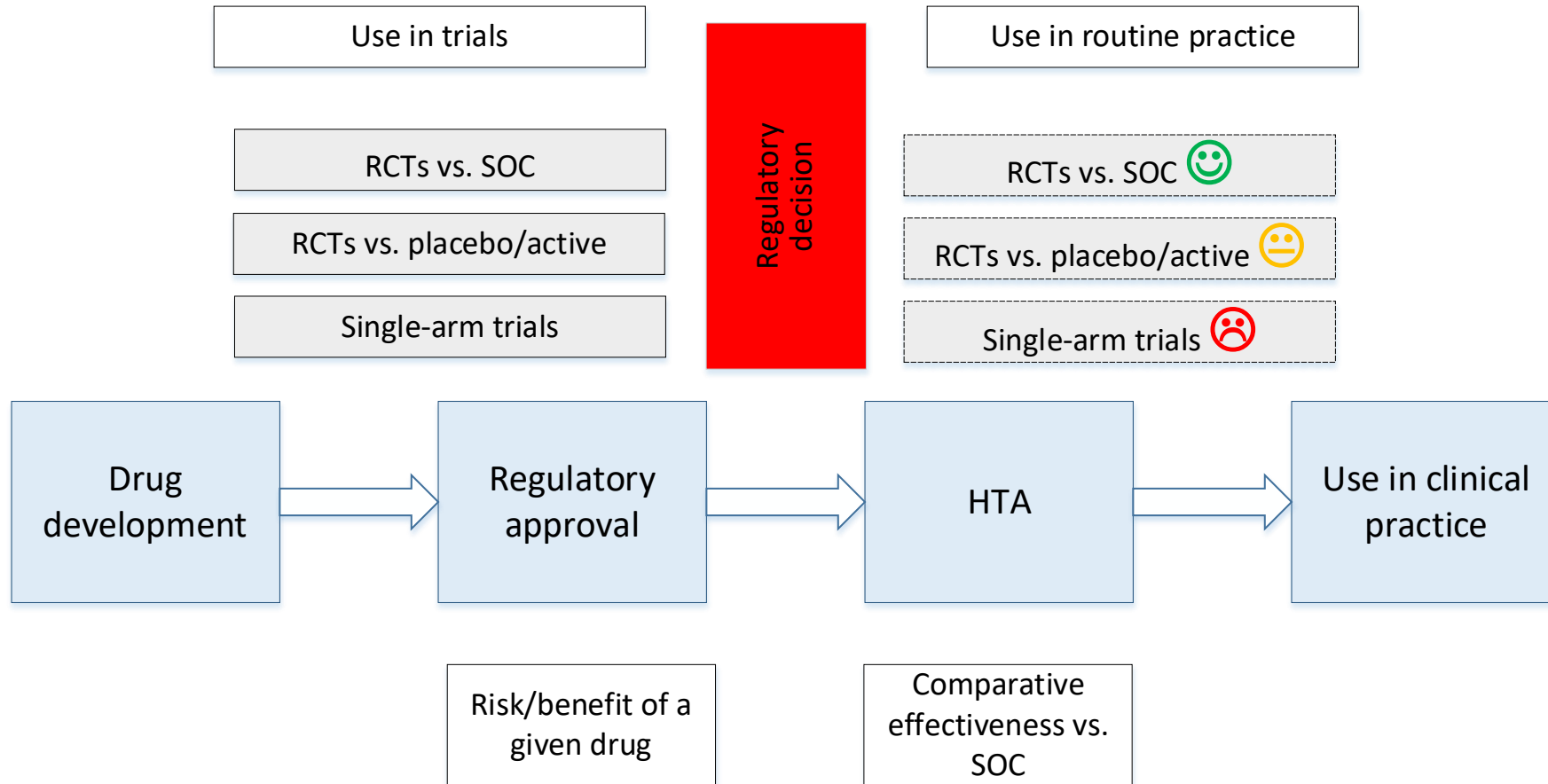
Difficulties with single-arm trials

- 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 percieved loss of equipoise)

    - shortcomings of observational studies as with external control arms

    - delays evidence-based health care

RCT vs. single-arm study: 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)	GO29365 RCT (phase 1lb/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.

Wieseler et al. BMJ 2023;380:e073100 https://www.bmj.com/content/380/bmj-2022-073100

Make RCTs
easier, faster and cheaper

Among other things
by conducting them
in a standing infrastructure in routine practice

FDA definitions

The FDA defines real world data as "data relating to patient health status and/or the delivery of healthcare **routinely collected from a variety of sources**," not restricting study designs. It defines real world evidence as "the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of [real world data]," which **can be generated using different study designs "including, but not limited to, randomised trials (eg, large simple trials, pragmatic trials), and observational studies (prospective or retrospective)."**

EMA definitions

The EMA defines real world data as "routinely collected data relating to a patient's health status or the delivery of healthcare **from a variety of sources other than traditional clinical trials**."

In recent publications, real world data and evidence **seem to be restricted to non-interventional** preauthorisation or postauthorisation **studies or sources other than RCTs. DARWIN EU**, EMA's main tool for the provision of real world data, is also **limited to observational data sources and non-interventional studies.**

Randomised adaptive platform trial for CAR-T cells in r/r DLBCL
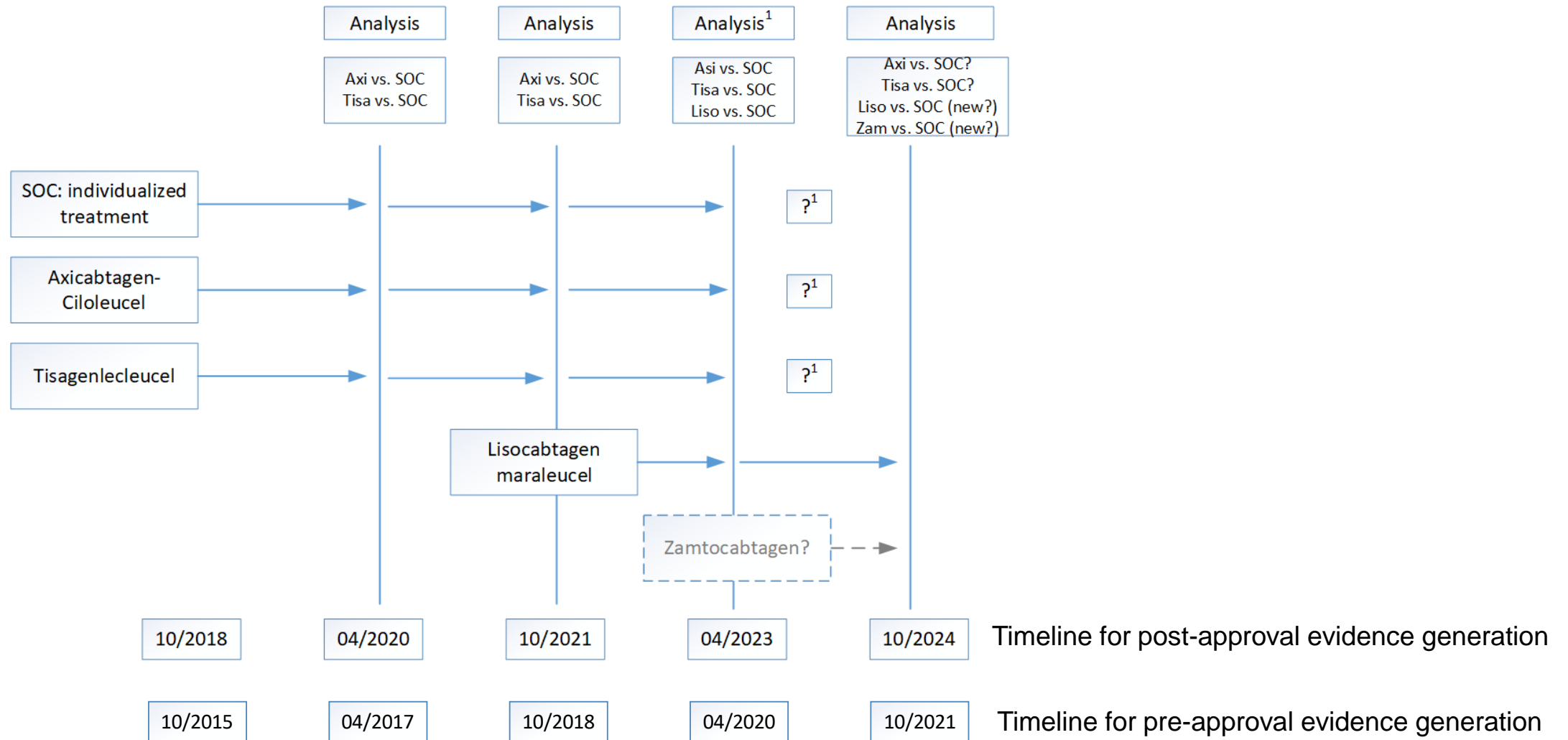
1: change comparator?

Enabling RCTs

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 registries[32]

- Conduct RCTs linked to information stored in patient registries[33]

- Use adaptive platform trials with master protocols across different treatment candidates[34]

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 efficiency[35]

- Use common control groups (through platform trials)[36]

- Apply statistical methods that tackle small patient numbers[35]

General

- Optimise study designs for decision making by both regulators and health technology assessment agencies to avoid the need for a larger number of trials[37]

- 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 possible[40]

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