

Real World Data and Health Technology Assessment

Beate Wieseler

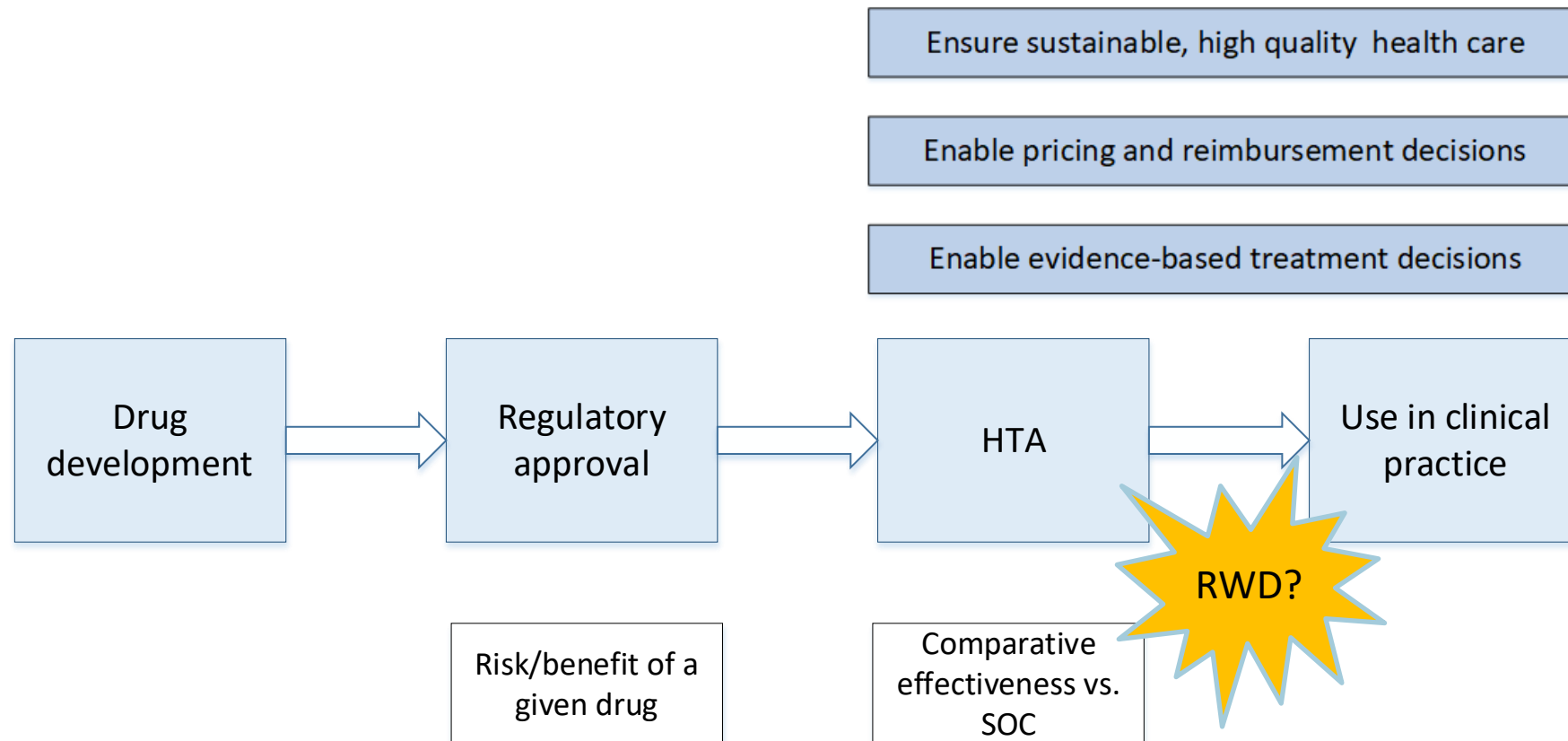
4th KCE Trials Symposium

Brussels, 25 May 2023

Agenda

- Context of decision making supported by HTA
- Current challenges and suggested RWD solutions
- IQWiG experiences with current RWD approaches
- Any other ideas?

Regulatory and HTA decision making



Clarification of today's question

We are not talking about

- Useful information from routine practice data, e.g.
 - size of a specific patient population
 - treatment patterns in clinical practice
 - 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

The problem: evidence available for HTA

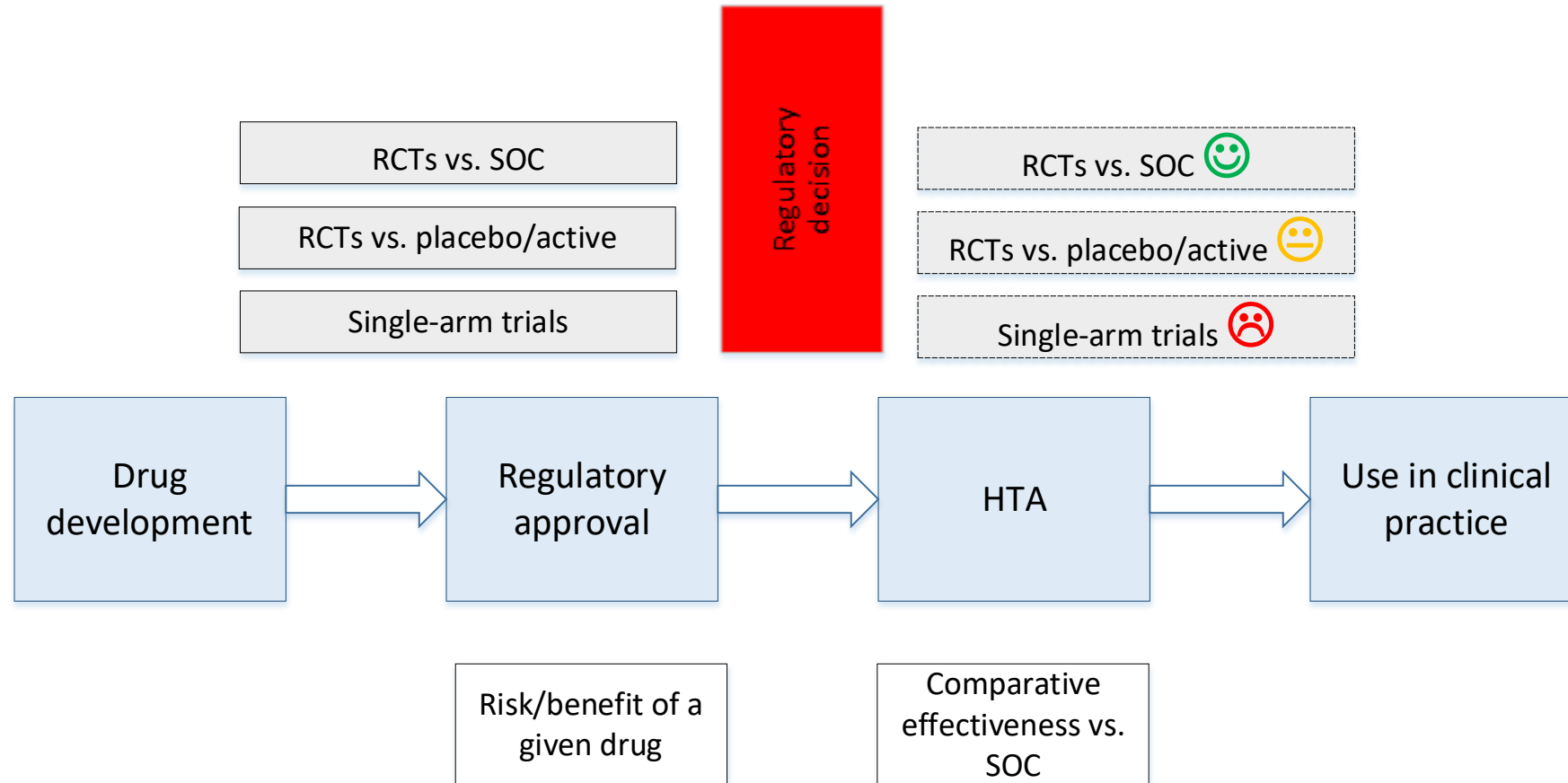
- Case study: new cancer drugs
- Sample: health technology assessments of cancer drugs started at IQWiG between June 2021 and December 2021
- HTAs covering 27 cancer drugs with 40 research questions

	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%)

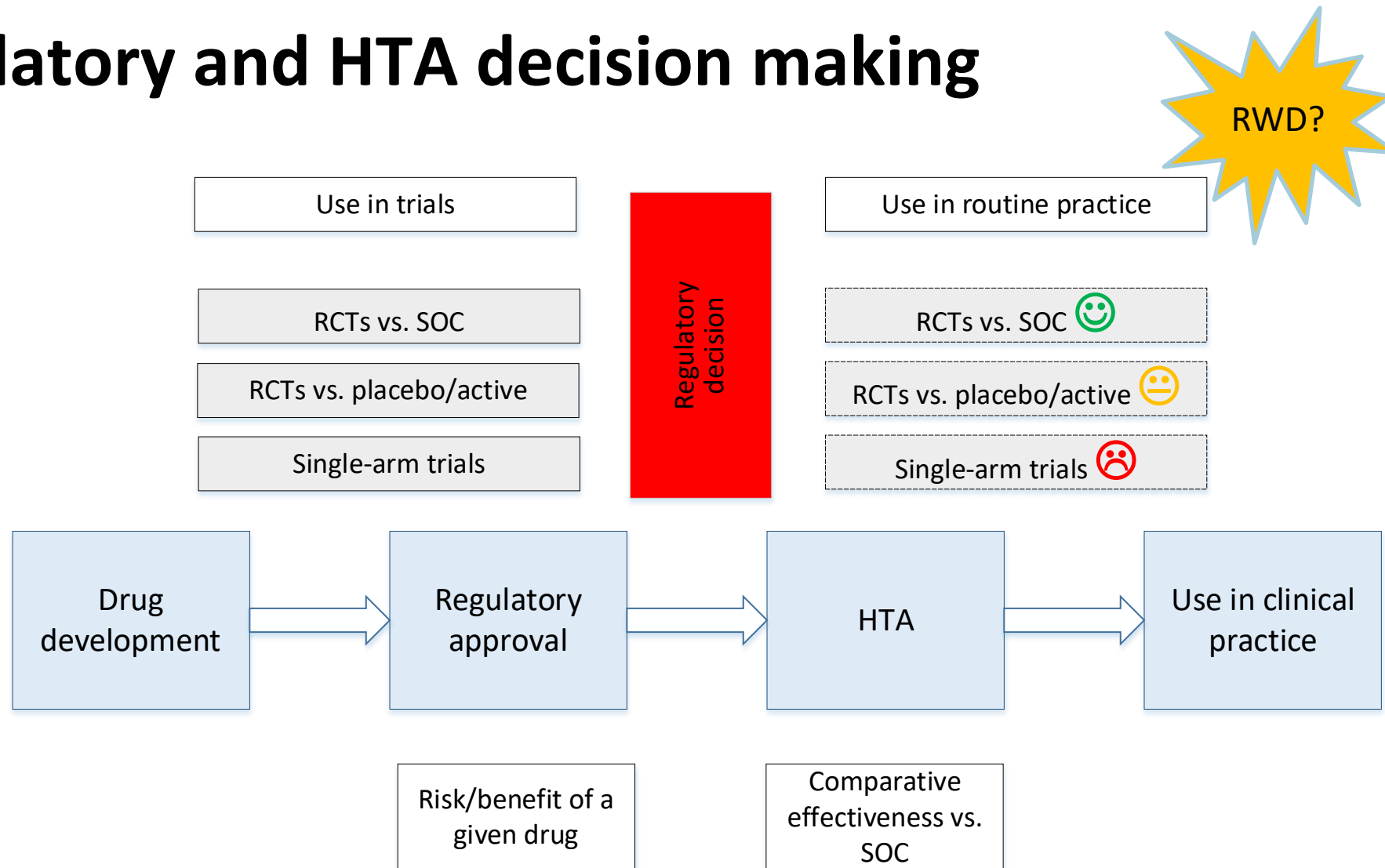
No data submitted:
3/14

Single arm trials:
11/14

Regulatory and HTA decision making



Regulatory and HTA decision making



Difficulties with single-arm trials in drug development

- 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

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.



Can RWD solve the problem? Lisocabtagene case study

- Assessment of lisocabtagene maraleucel vs. an individualised treatment considering patient characteristics (e.g. pre-treatment, ECOG-PS, course of disease etc.)
 - comparison against external control arm from non-interventional retrospective study in various data sources: OTA, Flatiron (Flatiron Research Network)
 - data on relevant patient characteristics missing in these data sources (e.g. 41% no data on ECOG-PS, 96% no data on Ann Arbor staging)
 - differences in time and treatment (start of treatment 2016-18 vs. unknown [first diagnosis since 2003]; 3% 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

**RWD not suitable
to solve the problem**

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

Make RCTs easier, faster and cheaper

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



FDA RWD definitions

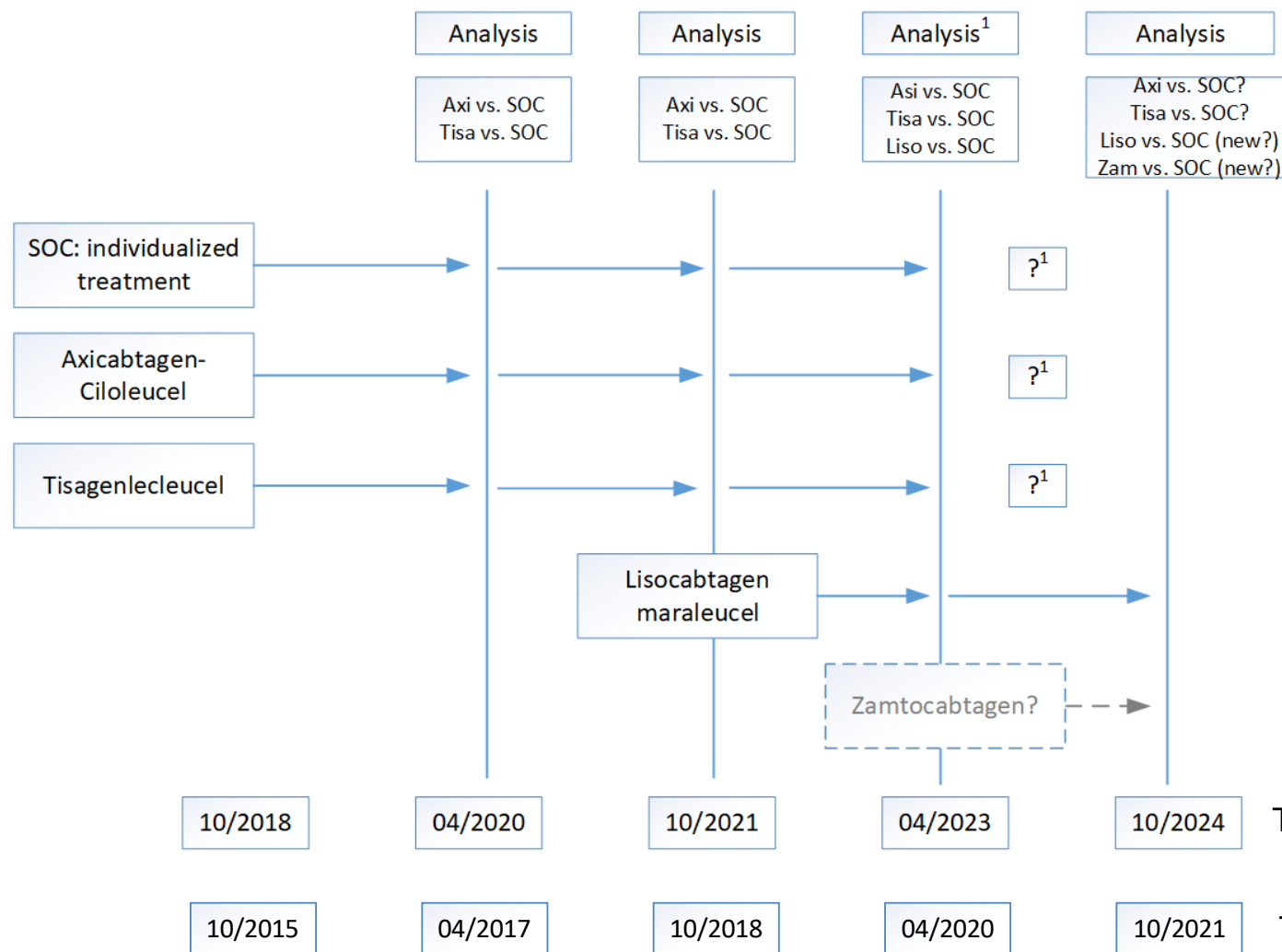
The FDA defines real world data as “data relating to patient health status and/or the delivery of healthcare **routinely collected from a variety of sources**,” not restricting study designs. It defines real world evidence as “the clinical evidence about the usage and potential benefits or risks of a 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 RWD 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



- Request such a study before approval?
- Conduct such a study in DARWIN after approval?

Conclusions

- To enable high quality care in sustainable health care systems we need appropriate evidence for decision making
- 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

Institute for Quality and Efficiency in Health Care (IQWiG)



Im Mediapark 8
50670 Köln

Telefon +49 221 35685-0
Telefax +49 221 35685-1

info@iqwig.de

www.iqwig.de
www.gesundheitsinformation.de
www.themencheck-medizin.de



@iqwig@wisskomm.social
@iqwig_gi@wisskomm.social