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Background

- RCTs are the gold standard for health technology assessments (HTA) in many countries
- In indications with very small sample sizes or no existing treatments, randomisation is not an option and HTA need to be done based on single-arm trials.

Objectives

- To gain a better understanding of success factors and success rates if Real World data (RWD) was included in submissions versus use of other evidence as external control arm.

Methods

- Review of all HTA assessments, published by the German HTA agency “Gemeinsamer Bundesausschuss” (G-BA) between 01/2020 and 05/2022 and extraction of all submissions of single-arm trials (SAT) using either observational data (i.e. RWD), only clinical data or no data as external control.
- The findings were compared to the same single-arm trial-based assessments, published by the French agency Haute Autorité de Santé (HAS)

Results

- 27 G-BA and 20 corresponding HAS HTAs were identified
- RWD as ECs were used in 37% (10/27) of G-BA and 45% (9/20) of HAS submissions. Evidence from other clinical trials in 15% (4/27) (3/20) and no data in 48% (13/27) and 40% (8/20), respectively.

Conclusions

Consistent for G-BA and HAS, high requirements for SAT HTA lead to a low acceptance of adjusted indirect comparisons with a higher probability of acceptance if uncertainty is reduced due to stronger effects from the assessment of paediatric indications or where there is no active compound defined as the comparator. There is no clear evidence, considering the low numbers of accepted ITCs, whether RWD as external control had any advantages over other evidence

Excursus: further findings

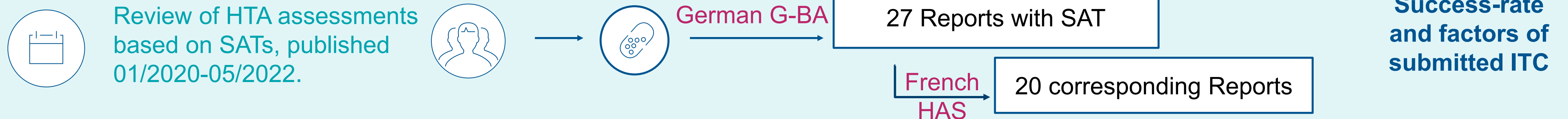
HTA outcome by ITC analysis type		
Analysis type		
Naïve	2	3
	4	8
MAIC	0	0
	4	3
IPD adjusted	0	0
	3	3

- Effort of adjusted ITC didn’t pay off
- In some procedures with positive HTA outcome RWE was used for the ITC. However, the ITC was not accepted and other reasons let to the positive outcome
- The key driver for HTA outcome is the effect size

Question

In how many HTA procedures with single-arm trials (SAT) was an indirect treatment comparison (ITC) considered and which success factors can be determined in procedures in Germany versus France?

Study design



Results

Table 1: HTA Assessments of SATs

Active substance	Indication		
Bedaquiline	MDR-TB, 12-18 yrs	X*	X*
Tisagenlecleucel	B-cell acute lymphoblastic leukaemia (ALL)	X*	X*
Tisagenlecleucel	Diffuse large B-cell lymphoma (DLBCL)	X*	X*
Ponatinib	chronic myeloid leukaemia (CML)		X*
Ponatinib	acute lymphoblastic leukaemia (ALL)		X*
Caplacizumab	thrombotic thrombocytopenic purpura (TTP), 12+ yrs	X	X*
Ledispavir/sofosbuvir	chronic hepatitis C, 3-11 yrs	X	✓
Sofosbuvir	chronic hepatitis C, 3-11 yrs	X	✓
Belantamab m.	4L+ RRMM *	X	X*
Sofosbuvir/velpatasvir	chronic hepatitis C, 3-17 yrs	X*	X
Avapritinib	gastrointestinal stromal tumour (GIST)	X	X*
Ivacaftor	cystic fibrosis (CF), gating mutation, 4-5 months	X*	✓
Blinatumomab	B-cell acute lymphoblastic leukaemia (ALL), Ph+ CD19+		X*
Brexucabtagene autoleucel	mantle cell lymphoma	X*	X*
Imlifidase	Desensitization (Kidney Transplantation)	X*	X*
Bedaquiline	pulmonary multidrug-resistant tuberculosis (MDR-TB), 5-17 yrs		X*
Pemigatinib	cholangiocarcinoma , FGFR2	X	X*
Risdiplam	5q spinal muscular atrophy (SMA), 2+ months	✓	✓
Atidarsagene autotemcel	metachromatic leukodystrophy (MLD), children	✓	✓
Tagraxofusp	blastic plasmacytoid dendritic cell neoplasm (BPDCN)	X	X*
Cemiplimab	locally advanced or metastatic basal cell carcinoma	X	✓
Selumetinib	symptomatic, inoperable plexiform neurofibromas, 3-17 yrs	X*	X*
Migalastat	Fabry disease, 12-15 yrs		X*
Tafasitamab	diffuse large B-cell lymphoma (DLBCL)	X	X*
Albutrepenonacog alfa	haemophilia B (congenital factor IX deficiency)		X
Sofosbuvir/velpatasvir/voxilaprevi	chronic hepatitis C virus (HCV), 12-17 yrs	X*	X
Elbasvir/grazoprevir	chronic hepatitis C virus (HCV), 12-17 yrs		X
TOTAL HTA reports available:		20	27
TOTAL HTA report with RWE submitted:		9	10

Key	Positive HTA outcome	Negative HTA outcome	Not assessed
V = ITC considered in the HTA X = ITC rejected / not made in the HTA X* = ITC rejected / not made, but still a positive HTA outcome			
CAVE: ITC received “considered” (V) only when explicitly stated in HTA commentary reports that it had positively contributed to a positive or restricted HTA outcome.			

Table 2: Success factors of considered ITC (see V in table 1)

Active Substance	Country	Pediatric indication	Strong Effects mentioned	Absence Active comparator / compared to natural history
Ledispavir/sofosbuvir	Ger	X	-	X
Sofosbuvir	Ger	X	-	X
Ivacaftor	Ger	X	-	X
Risdiplam	Ger/FR	X	X	X
Atidarsagene autotemcel	Ger/FR	X	X	-
Cemiplimab	Ger	-	-	X

Success factors for a positive HTA decision with rejected or not made ITC (see X* in table 1)

In Germany, the success factor is an orphan drug status (below a defined sales threshold this legally leads to a positive HTA outcome). In contrast, the reasons in France are multidimensional. Either there is an unmet need, a transfer of evidence was accepted, or a strong effect size was shown in a SAT.

Key take aways

The most influential success factor for getting an ITCs accepted seems to be the absence of an active comparator (“solist”), a pediatric indication and/or a strong effect size independent on whether RWD or any other evidence was used as the external control. Without an ITC the success factor in Germany is an orphan drug status, while in France it can be, among others, an unmet need or an accepted evidence transfer.

References

Information obtained from publically assessible HTA websites:
Haute Autorité de Santé – Médicament (has-sante.fr)
Nutzenbewertung nach § 35a SGB V – Gemeinsamer Bundesausschuss (g-ba.de)
- date of last access: 19.10.2022

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Abbreviations

RCT = Randomized controlled trial
HTA = Health Technology Assessment
SAT = single-arm trial
ITC = indirect treatment comparison
G-BA = gemeinsamer Bundesausschuss (German HTA)
HAS = Haute Autorite de Sante (French HTA)

Disclosures

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