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A letter to editor – Critical appraisal on "Determining the cost-effectiveness of follitropin alfa biosimilar compared to follitropin alfa originator in women undergoing fertility treatment in France."

We read the article published by Lehmann et al. [1] with great interest. In this article, the authors performed a cost-effectiveness analysis of follitropin alfa biosimilar (Bemfola®, Gedeon Richter Plc, Budapest, Hungary) versus r-hFSH alfa originator (Gonal-F®, Merck KGaA, Darmstadt, Germany) in women undergoing in vitro fertilization/intracytoplasmic sperm injection treatment, based on unadjusted real-world evidence(RWE) from a French healthcare perspective. We feel compelled to highlight certain methodological concerns that, if overlooked, could potentially mislead readers.

The main outcome of the cost-effectiveness analysis (cumulative live birth [CLB]) relies on a non-interventional, retrospective, RWE study by Barriere et al., 2023 (REOLA), the objective of which was descriptive without any pre-determined statistical comparative analysis [2]. The authors of Barriere et al. [2] clearly stated that "doctors had treated patients as they felt appropriate" and therefore there was "considerable heterogeneity within populations". No statistical analysis was performed for correcting for confounding factors, but details on demographic/clinical characteristics, and confidence intervals (CI) were reported. The study did not find any difference in CLB between Bemfola® and Gonal-F® across various starting doses [2]. It may be interesting for the readers to know that a recently published comparative effectiveness analysis performed in France, from a nationwide French database over 7 years, with a sample 10 times larger than that of the REOLA study, found Gonal-F® to be 14 % more effective (in terms of CLB) than biosimilars, as a category, after correcting for confounding factors. These results were statistically significant [3].

Lehmann et al. [1] used point estimates (specific single values), rather than 95 % CIs, from an RWE descriptive study to estimate the effect size in their cost-effectiveness analysis. Hence, their analysis was based on unique numbers rather than a range of possible values. Additionally, they assumed that women were equally distributed across starting doses (<150 IU, 150–224 IU, 225–299 IU, >300 IU) for the biosimilar and the originator. The REOLA study showed a direct relationship of demographic/clinical characteristics with the starting dose, and the < 150 IU starting dose was the least commonly used (Bemfola®:9 %; Gonal-F®:20 %). It is notable that this is the only dosage in which there was a somewhat important difference in CLB between Bemfola® (30.5 %) and Gonal-F® (27 %), although with large and overlapping CIs given the small sample size for the former (see Fig. 1 in Barriere et al., 2023) [2]. It is worth noting that a weighted measure of CLB based on the percentages of patients in each group would have provided a more accurate CLB rate, which would have shown a favorable CLB for Gonal-F® compared to Bemfola® (21.6 % versus 19.9 %) (Table 1). Although the authors reported one-way sensitivity analyses, they did not perform any probabilistic sensitivity analysis. With large uncertainty in outcomes, as in this case, this should be the recommended approach [4].

For calculation of waste, the authors did not consider the partial dosing feature of Gonal-F® multidose pre-filled pens, which allows adaptation of doses and reuse of unadministered quantities, which clearly reduces unnecessary waste [5]. Instead, they compared a single dose delivery system for Bemfola®, limited in terms of dose adaptation and producing daily waste, to pre-filled pens for Gonal-F® using 3 different studies to derive mean, upper bound and lower bound levels.

Therefore, it is apparent that the conclusion of the cost-effectiveness analysis - that Bemfola® is more cost-effective than Gonal-F® - is driven

Table 1
Number of patients (N and %) and CLBR (%) in each treatment group distinguished in the REOLA study (section A) versus calculated weighted average of CLBR based on patients' distribution between treatment groups (section B).

Section	REOLA groups according to starting dose	Number of patients in REOLA study per arm *(Barrière 2023)* [2]				CLBR (%) per patient group *(Lehman 2024)* [1]	
[A]		Bemfola®		Gonal-F®		Bemfola®	Gonal-F®
		N	% of total	N	% of total	%	%
	TOTAL	**2319**		**4287**			
	< 150 IU	197	0.085	834	0.195	0.30	0.27
	150 −224 IU	698	0.301	1518	0.354	0.25	0.27
	225 −299 IU	527	0.227	730	0.170	0.21	0.2
	≥ 300 IU	897	0.387	1205	0.281	0.12	0.12
[B]	**CLBR calculated as weighted average based on number of patients in each group and their respective CLBR (by authors of this letter using data from section A)**						
	Bemfola®			Gonal-F®			
	0.199			0.216			

The same approach should have been used also for the calculation of costs and wastage.

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by the choice of clinical and wastage inputs that appear to be biased in favor of Bemfola®, thereby, deviating from ISPOR-SMDM Modeling Good Research Practices [6]. Considering unadjusted descriptive studies as source of causal evidence compromises the possibility of making valid comparisons, as already highlighted in a letter to editor by Montenegro et al., 2023 [7].

CRediT authorship contribution statement

Juan-Enrique Schwarze: Conceptualization, Supervision, Writing – original draft. **Vivek Chaudhari:** Conceptualization, Writing – original draft, Writing – review & editing. **Susana Montenegro:** Conceptualization, Writing – original draft, Writing – review & editing. **Claire Castello-Bridoux:** Conceptualization, Writing – original draft, Writing – review & editing. **Cristina Masseria:** Conceptualization, Writing – original draft, Writing – review & editing. **Claudia Roeder:** Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

Juan-Enrique Schwarze, Susana Montenegro, and Thomas D'Hooghe are full-time employees of Merck KGaA, Darmstadt, Germany. Vivek Chaudhari is a full-time employee of EMD Serono Inc., USA. Claire Castello-Bridoux is a full-time employee of Merck Santé, France, an affiliate of Merck KGaA, Darmstadt,Germany. Cristina Masseria, and Claudia Roeder are full-time employees of AESARA Europe, Zug, Switzerland.

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