The Statistical Abyss: Real-World Evidence for Health Technology Assessment

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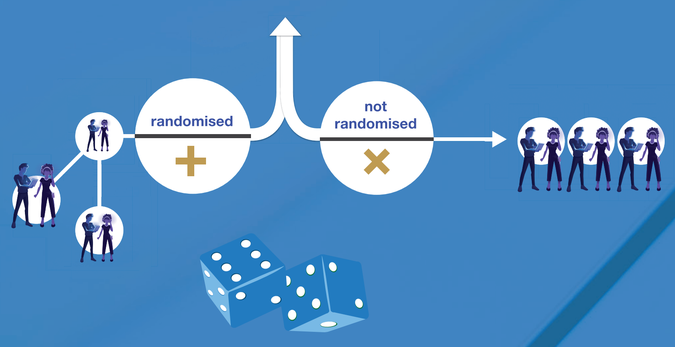
BACKROUND

The Statistical Abyss

Data from real world situations represent a considerable challenge. They are difficult to analyse and require the use of advanced statistical methods to draw valid conclusions. Another issue is data quality, which is often incomplete or inconsistent between treatment arms, thus making it considerably more difficult to interpret the data. We refer to these challenges as the 'statistical abyss'!



CHALLENGE

RWE and the EMA

The European Medicines Agency recognises the importance of real-world evidence in non-interventional studies (NIS), but emphasises the difficulties that are linked to various biases when drawing conclusions on causality between treatment groups:

> *"The non-experimental nature of NIS can lead to biases due to selection processes, misclassification and confounding factors, which should be identified and minimised in the design phase."*[*1]

CHALLENGE

RWE and Joint Clinical Assessment (JCA)

The EU HTA Coordination Group's methodological guideline for synthesising quantitative evidence also highlights the scientific challenges associated with non-randomised data:

> *"In the context of JCA, non-randomised evidence has a high potential for bias in the estimation of the relative effectiveness of treatments. This is due to the lack of interchangeability and the high risk of confounding factors."*[*2]

CHALLENGE

Analyses using RWD

Analyses that have to deal with the problem of selection bias are perhaps the most challenging to overcome. Methods such as propensity score adjustment, double robust methods and marginal structural modelling are often data-driven and not fully pre-defined, so there is a risk of potential subjectivity in the results. Consequently, the statistician is often faced with having to undertake a copious amount of sensitivity analyses, including QBA (Quantitative Bias Assessment).

Internal Validity of Different PICOs and their Risk Profile

PICO 1		PICO 2		PICO 3	
Type of bias	Risk	Type of bias	Risk	Type of bias	Risk
Selection bias	→	Selection bias	↑	Selection bias	↑
Confounding	↑	Confounding	↑	Confounding	↑
Immortal time bias	→	Immortal time bias	→	Immortal time bias	↑
Assessment bias	↓	Assessment bias	↑	Assessment bias	↑
Attrition bias	↓	Attrition bias	→	Attrition bias	→
Intercurrent event bias	↓	Intercurrent event bias	↓	Intercurrent event bias	↑
Trial bias	↓	Trial bias	→	Trial bias	↑

↑ = No bias → = Bias adjustment possible ↓ = Bias adjustment not possible

GUIDANCE AND PLANNING

It is advisable to develop a detailed plan at an early stage that clearly identifies how causality is to be proven using non-randomised, RWE data. This includes the preparation of RWE protocols and details of analyses that fall within the framework of EU HTA. These analyses should be conducted months prior to finalising the PICO assessment scope, ensuring they are completed well in advance of submitting the dossier to the JCA Subgroup.

Interdisciplinary collaboration between experts:
It is critical that statisticians advise clinical, HEOR and market access teams to reduce the number of comparisons to those that have the highest internal validity based on sound scientific principles.

ADVANTAGES

- **Improved prediction:** By using advanced statistical methods, more accurate estimation can be made regarding the effect of treatment.
- **More robust analyses:** Interdisciplinary collaboration leads to more robust and valid analyses that meet the stringent requirements of scientific and regulatory bodies.
- **Better decision making:** The integration of advanced statistical methods enables well-founded decisions based on a solid database.

SUMMARY

For regulatory authorities and HTA agencies, proof of causality is essential, with randomised controlled trials (RCTs) still considered the gold standard. Nevertheless, real-world studies (non-randomised, uncontrolled) for marketing authorisation and HTA, such as SATs, are increasing. However, real-world data (RWD) is often subject to noise, bias and confounding factors, which makes proving causality complex and time-consuming. This is not a task that can be done overnight!

Take home messages

- **Not all RWD analyses are equally feasible and scientifically sound.**
- **A gatekeeper is required.**
- **PICO requests should be carefully considered and prioritised based on sound scientific standards of internal validity.**

Given the demanding deadlines of the EU HTA JCA since 12 January 2025 for oncology and ATMPs, this is more urgent than ever.

References:
*[1]https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-use-real-world-data-non-interventional-studies-generate-real-world-evidence_en.pdf
*[2]https://health.ec.europa.eu/latest-updates/methodological-guideline-quantitative-evidence-synthesis-direct-and-indirect-comparisons-2024-03-25_en

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