# The challenges of generating patient-relevant outcomes and other evidence sufficient to satisfy European HTA bodies in acute conditions managed in the ICU

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## Background

In recent years, there has been considerable discussion around the acceptability of surrogate endpoints, especially for oncology treatments [1]. A surrogate endpoint is defined as an indicator aiming to substitute a clinical endpoint that is expected to reflect a patient-centered outcome [2]. Regulatory agencies, including the European Medicines Agency (EMA), are increasingly approving new treatments based in surrogate endpoints as considered sufficient to achieve regulatory approval [3]. However, there has been controversy among payers and the different levels of acceptability across health technology assessment (HTA) organisations in Europe [4], which generates challenges for manufacturers.

Some European HTA organisations, such as NICE and IQWiG, have provided guidance relating to the acceptability of surrogate endpoints in oncology products [5, 6] as they have become more common in this clinical area [7]. However, surrogate endpoints are being used in clinical trials in other therapeutic areas. It is particularly challenging to measure treatment effects when conducting clinical trials in acute conditions in the intensive care (ICU) setting. This may be due to, for example, challenges achieving the required clinical trial size of patients to detect clinically meaningful outcomes, such as mortality rates [8]. Literature has highlighted difficulties associated with determining and validating meaningful surrogate endpoints in the ICU setting [8, 9], and a 2015 publication in Critical Care suggested the possibility of using economic surrogate endpoints to demonstrate the benefit in acute conditions in ICU patients [9].

## Objective

The objective of this research was to evaluate the acceptability of a surrogate endpoint related to arterial pressure for an ICU condition as a primary endpoint of the clinical trial and the impact in the HTA assessment across France, Germany, Italy, Spain and the UK.

## Method

Country-specific qualitative group discussions were conducted with a total of 15 (proxy) payers and 5 ICU setting leading clinicians (heads of ICU departments that have published in this space) (Figure 1). An online survey was then conducted with 10 payers from our internal stakeholder database to assess their perspective on the acceptability of surrogate endpoints for acute conditions managed in the ICU to support HTA submissions, as well as an exploration of the relevance of economic endpoints in this setting.

| Sample | FR | DE | IT | ES | UK | Total |
|---|---|---|---|---|---|---|
| Payers | 3 | 3 | 3 | 3 | 3 | **15** |
| Clinicians | 1 | 1 | 1 | 1 | 1 | **5** |

**Figure 1** Structure of group discussions with payers and clinicians

## Results

Payers acknowledge challenges associated with designing and conducting clinical trials for acute conditions in the ICU (Figure 2). Although payers' willingness to accept surrogate endpoints varied across countries in scope, none were very willing to consider them in their HTA, (Figure 3). Payers and clinicians aligned on the low acceptability of an arterial pressure-related endpoint as a primary endpoint, as this does not demonstrate any reduction in mortality and/or reduction in morbidity. Consequently, the surrogate endpoint evidence cannot be considered patient-relevant.

In France and Germany, the majority of payers would only consider endpoints in which the effect has been validated as clearly translating to a clinical benefit in patients. However, some payers in Italy, Spain and the UK showed an openness to considering alternative endpoints in cases where a treatment demonstrates no detrimental effect on mortality. A cost-minimization model showing the reduction in ICU stay among patients discharged alive could support the value of a treatment in budget impact (Italy and Spain) and cost-effectiveness (UK)-driven markets (Figures 4 and 5).

Fig 3: Total n = 9. HTA; Health Technology Assessment, Fig 4/5: Total n = 10.
ICU: Intensive Care Unit

**Figure 2**
Key challenges perceived by payers when designing/ conducting clinical trials for treatments use in the acute/ emergency setting in the ICU to ensure optional market access

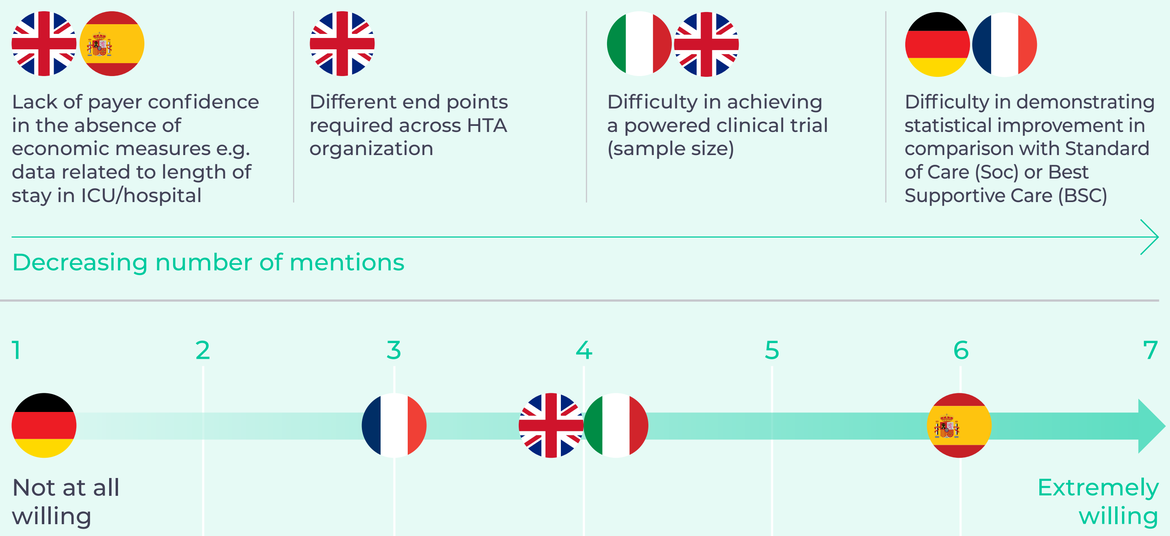
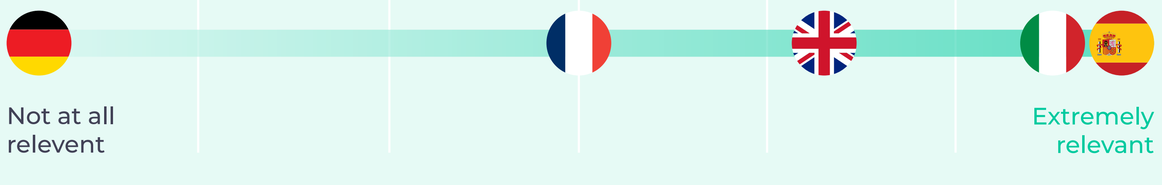



**Figure 3**
Willingness to accept surrogate endpoints in the Health Technology Assessment (HTA) of treatments for acute conditions in the ICU setting




**Figure 4**
Relevancy of a cost-minimization model to support the access of treatments for acute conditions in the ICU setting


**Figure 5**
Relevancy of reduction in ICU stay associated with a treatment used in the acute setting in the ICU to support its access




## Discussion and conclusions

For treatments where there are challenges associated with generating patient-relevant outcomes from clinical trials, such as those used in the acute / emergency ICU setting, there is a risk of negative pricing and reimbursement outcomes if the surrogate endpoints are used as payers may not deem them to be 'patient relevant'. Early engagement with European payers and health technology assessment bodies is therefore critical to understand their requirements prior to designing clinical trials and avoid these negative outcomes.

A cost-offset approach, demonstrating the potential savings to the healthcare system associated with use of a treatment for an acute condition in the ICU setting, could be taking into account by payers and acceptable in some European markets. Data such as reduced length of stay and earlier discharge may therefore be valuable data to collect as part of a treatment's incorporated into clinical development plan.

**REFERENCES:**
1. Ciani O et al. Validity of Surrogate Endpoints and Their Impact on Coverage Recommendations: A Retrospective Analysis across International Health Technology Assessment Agencies. Medical Decision Making (2021)
2. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework (2001)
3. Kordecka et al. Selection of Endpoints in Clinical Trials: Trends in European Marketing Authorization Practice in Oncological Indications (2019)
4. Kemp et al. Surrogate endpoints in oncology: when are they acceptable for regulatory and clinical decisions, and are they currently overused? (2017)
5. Davis S et al. A review of studies examining the relationship between progression-free survival and overall survival in advanced or metastatic cancer (2012)
6. IQWiG. Validity of surrogate parameters in oncology (Rapid report) (2011)
7. Beaver MD et al. A 25-Year Experience of US Food and Drug Administration Accelerated Approval of Malignant Hematology and Oncology Drugs and Biologics (2018)
8. Verghis E et al. Surrogate outcome measures used in critical care trials (2016)
9. Wilcox ME et al. Is critical care ready for an economic surrogate endpoint? (2015)

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