Evolving Endpoint Strategies: Navigating New Therapies and Regulatory Acceptance

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SINGLE clinical trial endpoints often fall short in capturing the full scope of patient experience, particularly in complex conditions like sickle cell disease and haematologic malignancies. A European Hematology Association (EHA)-Patient Joint Symposium presented at the EHA2025 Congress, held in Milan, Italy, created space for multistakeholder discussions on topics with policy and regulatory implications. These topics are valuable to, and chosen by, patients. This particular session brought together perspectives from patient advocates, clinicians, regulators, industry, and health technology assessment (HTA) bodies to examine the limitations of single endpoints and explore how integrating patient-reported outcomes (PRO), demographic-specific measures, and multiple sources, including real-world data, can lead to more comprehensive and informative patient-centred evaluation frameworks.

LIMITATIONS OF TRADITIONAL ENDPOINTS AND THE NEED FOR EVOLUTION

Jenica Leah, President of the European Sickle Cell Federation (ESCF), opened the discussion by highlighting the current limitations of traditional clinical trial endpoints. Endpoints, by definition, are the specific metrics that researchers measure in a clinical trial to see if a treatment works. In the context of sickle cell disease, these typically include vaso-occlusive crisis frequency, healthcare utilisation, haemoglobin levels, and quality of life. However, Leah highlighted that such endpoints are not typically reflective of the majority of patients with sickle cell disease. For example, vaso-occlusive crises are self-reported and can be inconsistent, as many patients experiencing symptoms may not seek clinical care. Moreover, high haemoglobin does not always equate to fewer symptoms. Leah also flagged that quality of life does not always take into consideration the patient's mental health, fatigue, and social burden of disease.

How should endpoints evolve? Leah proposed an alternative approach, using mixed models that utilise both biomarkers and PROs. She also highlighted the possibility of demographic-specific endpoints and the importance of incorporating mental health, life-function, and fatigue at the forefront of the definition of clinical trial success and endpoint design.

To close, Leah highlighted several areas for improvement in addressing research gaps. Noting the increasing life expectancy of individuals with sickle cell disease, she stressed the importance of developing endpoints that reflect the needs and challenges faced by patients in later stages of life. She also emphasised the importance of raising awareness around clinical study failures, not just successes.

She concluded: "Going forward, patients should be asked what we want improved, and trials should be designed with the patients, not just for the patients, because sometimes what is looked for in a clinical setting as a positive endpoint may not necessarily be what a patient sees a good endpoint for their future."

HOW TO ALIGN CLINICAL RELEVANCE WITH THE LIVED PATIENT EXPERIENCE

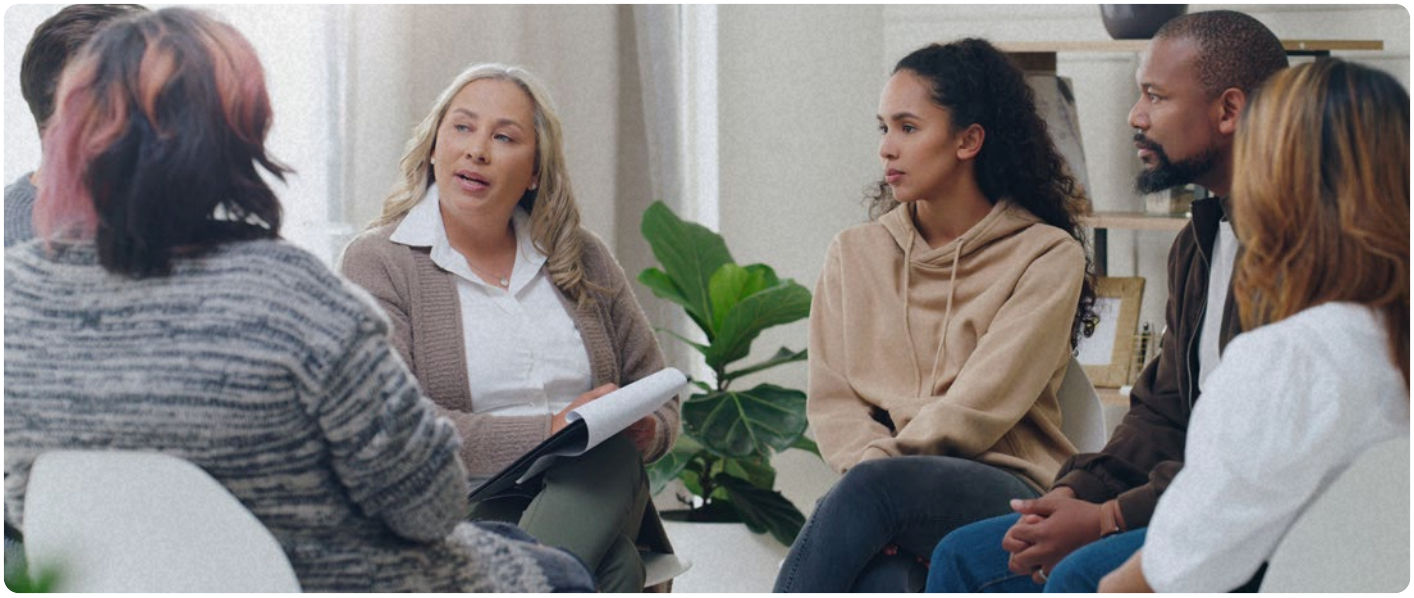
Lorenzo Brunetti, Hematology and Bone Marrow Transplant Unit, Ancona University Hospital, Italy, took the stage next to discuss the limitations of surrogate endpoints. Defined as measures used in clinical trials to substitute for direct, clinically meaningful outcomes, surrogate endpoints can help accelerate the development and approval of new therapies. However, as highlighted by Brunetti, surrogate endpoints are often tumour-centred rather than patient-centred, which can overlook toxicity and patient experience, and not always correlate with overall survival.

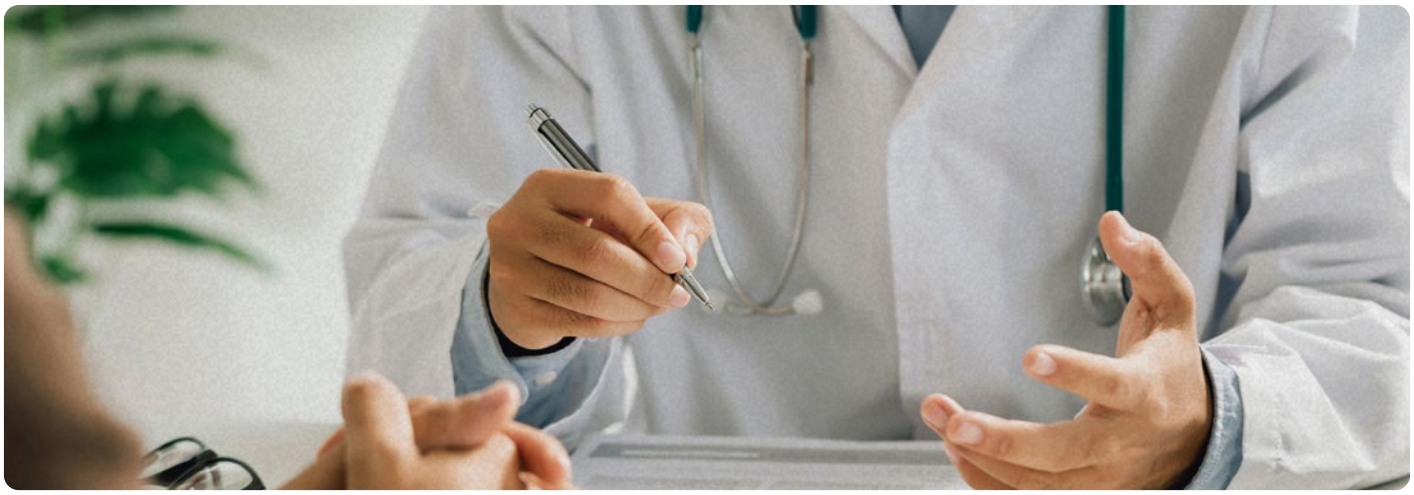
He spoke on the ALFA0701 study,[1] in which patients with acute myeloid leukaemia received either conventional front-line induction chemotherapy or chemotherapy in combination with a targeted immunotherapy, called gemtuzumab ozogamicin. The primary endpoint was a surrogate endpoint, event-free survival, which refers to the length of time after treatment begins that a patient remains free of certain defined events, such as disease progression, reoccurrence, or death. Secondary endpoints included overall survival and quality of life. Notably, although the event-free survival was improved in the treatment versus control arm, there was no significant difference in overall survival, and immunotherapy was associated with significant toxicities, including prolonged thrombocytopaenia.[1]

Brunetti also discussed the MAIA study,[2] which evaluated the effectiveness of adding daratumumab to the standard regimen of lenalidomide plus dexamethasone (D-Rd) for patients with multiple myeloma. The primary endpoint was again a surrogate endpoint; progression-free survival. After 28 months of follow-up, the test arm showed improved progression-free survival; however, no benefit in overall survival was observed.[2] In contrast to the ALFA0701 study, Brunetti highlighted how this study incorporated PROs which made the surrogate endpoint more meaningful. The D-Rd arm demonstrated faster and more sustained improvements in PROs compared to the standard treatment arm.[2]

To conclude, Brunetti advocated for a holistic approach to be taken in clinical research and trial design. Surrogate endpoints should be always coupled with patient-centred outcomes, as this integrated approach provides a more accurate and meaningful assessment of treatment benefit.

> **Surrogate endpoints should be always coupled with patient-centred outcomes**





CHOICE OF ENDPOINTS FROM THE PERSPECTIVE OF REGULATORS

Although speaking personally, Francesco Pignatti, Scientific Advisor for Oncology, European Medicines Agency (EMA), followed with a powerful opening statement: "I cannot remember any other topic in my long life as a regulator that would attract so much controversy and discussion." When deciding which endpoint to prioritise in a trial, you assess it against certain characteristics such as its relevance, validity, sensitivity, specificity, and precision. It is always a matter of balancing these various characteristics, and since individuals often have differing goals and preferences, clear-cut definitions are rarely possible. He stressed that in conversations regarding trial endpoints, the narrative should not be: 'What is the superior endpoint?'; but rather: 'How can we most comprehensively describe the effects of a drug, so that patients and others can make informed decisions?'

He highlighted the importance of patient preference studies, which aim to describe which endpoints and treatments patients favour, including the level of risk patients are willing to accept for certain benefits. A notable example was a study evaluating the preferences of adults and adolescents with alopecia areata undergoing treatment with JAK inhibitors. In this study, adults were willing to accept a mean 3-year risk of serious infection (7.4%; 95% CI: 5.5–9.3%), cancer (2.5%; 95% CI: 1.9–3.1%), and blood clots (9.3%; 95% CI: 6.4–12.2%) for a 20% increase in the likelihood of achieving 80–100% scalp hair regrowth.[3]

To conclude, he reinforced that we should move away from the quest for a single perfect endpoint and focus on the goal of communicating all the different effects and uncertainties we know about a drug, to help inform treatment decisions. If in doubt about what endpoints matter to patients, patient preference studies should be used to inform development and evaluation. Moreover, he recommended complementing conventional efficacy and safety summaries with an evaluation of health over time to better assess patients' experience.

ENDPOINTS: AN INDUSTRY PERSPECTIVE

James Ryan, Director HTA Policy, Oncology Business Unit, AstraZeneca, on behalf of the European Federation of Pharmaceutical Industries and Associations (EFPIA), then provided an industry perspective. He began by summarising data from 130 ongoing industry-sponsored Phase III haematology trials, highlighting the use of more patient-centric endpoints, such as overall survival, cognitive function, and quality of life. However, Ryan also noted the challenges in capturing overall survival within a defined time frame, especially given the heterogeneous experiences of patients. Quoting a patient who said: "It all depends on what you're looking for in your treatment, and what your goal is," he emphasised the importance of individual perspectives. Ryan then outlined key considerations in appraising endpoints, including how the sensitivity of a test affects interpretation, the magnitude of change required to alter

its perceived utility, how the direction of change in other endpoints should be evaluated, whether the absence of statistical evidence negates surrogate validity, and how to effectively incorporate patient experience data and patient preference studies.

To close, his key takeaways spotlighted the four main themes at play: how relevant are the endpoints to the different needs at play, the importance of continued validation of surrogate endpoints, maintaining a focus on patients and keeping them at the heart of all decisions, and finally, fostering collaboration between all stakeholders involved, whether that be clinicians, HTA bodies, industry, or patients.

HOW CAN ENDPOINTS BE IMPROVED TO SUPPORT HEALTH TECHNOLOGY ASSESSMENT DECISION MAKING

Finally, Beate Wieseler, Head of the Department of Drug Assessment at Germany's Institute for Quality and Efficiency in Health Care (IQWiG), provided an insightful look at the role of HTAs. Whilst regulators often look at the safety and efficacy of health technologies, ensuring they meet minimum standards for market authorisation, HTA bodies assess the value of health technologies, considering the clinical and cost-effectiveness. As highlighted by Wieseler, this is incredibly important, on an individual level for informing treatment decisions, on a population level with the deliverance of new clinical guidelines, and on a healthcare system level to inform pricing and reimbursement decisions.

She commented: "To answer the question if something is better than what we already have is important, because we usually would only like to pay higher prices if we have added benefit from this new drug, to keep our healthcare systems sustainable, and to allow for universal care for each and every patient."

Wieseler explained that the three main endpoints in HTAs are mortality, morbidity, and health-related quality of life. For the latter two, this can incorporate PROs, as the patient can report on any symptoms of complications from the treatment, as well as the impact of the disease and its treatment on physical, emotional, and social well-being. With these factors in mind, she urged for study programmes to be designed that consider all decision-makers from the start, including regulators, HTA bodies, and the patient. When studies do not address the questions for these parties, as explained, there are delays for the drug to enter the market and to achieve evidence-based care, as the uncertainty is so high.

CONCLUSION

The panel highlighted the need to move beyond 'one-size-fits-all' endpoints toward a more nuanced and inclusive approach to clinical trial design. Aligning regulatory, clinical, and patient perspectives will be key to defining endpoints that not only demonstrate efficacy, but also reflect true patient benefit, inform decision-making, and support the delivery of equitable and effective care. Importantly, all panellists expressed a strong willingness to hear from patients and understand what is meaningful to them. The challenge now lies in determining how to consistently and effectively incorporate the often-diverse patient perspective at every step of the process.

References

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