Application of Evidence Generation and Synthesis Strategies to Gain Market Access & Reimbursement, and Deliver Value: Two Case Studies

Ramesh Arjunji,[1] Joseph Massey,[2] Natalie Japlon,[1] Karissa M. Johnston,[3] Shelagh M. Szabo,[3] Max Craig,[1] Benit Maru.[2]

[1]SSI Strategy, Parsippany, USA; [2]SSI Strategy, London, UK [3]Broadstreet HEOR, Vancouver Canada.

OBJECTIVE

- To illustrate using publicly available data the application of evidence generation and synthesis (EGS) strategies from early trial design stages to support product value proposition for multiple stakeholders at launch and beyond

INTRODUCTION

Summary

- Two case studies were selected to reflect situations requiring differing EGS approaches including drug development and real-world evidence strategies, based on disease prevalence, severity, availability of therapeutic alternatives, and likely volume of sales.

Case study 1: Zolgensma for SMA1

- SMA1 is a progressive monogenic neurologic disease that causes loss of motor muscle function, as well as bulbar muscle function essential for normal breathing and swallowing
- In severely affected infants, SMA1 results in functional decline by 12 months of age and ultimately, if untreated, leads to death or need for permanent ventilation by 2 years of age
- Zolgensma is a gene-replacement therapy that delivers a fully functional copy of the human survival motor neuron-1 (SMN1) gene to treat the genetic root cause of SMA through a one-time IV infusion[7,8]

Case study 2: Sleepio for insomnia

- Insomnia is a significant public health concern due to its high prevalence and associated increased healthcare resource use (HCRU) and costs, lower productivity, and increased accident risk. Insomnia is also associated with a substantial negative impact on health-related quality of life (HRQol) and an increased risk of conditions that are expensive to treat and include both cardiometabolic and mental health difficulties[9]
- Traditional and effective treatments for insomnia include prescribed sleep-promoting pharmacotherapy (e.g., benzodiazepines & non-benzodiazepines) and cognitive behavioral therapy (CBT)[9]
- Sleepio (Big Health, Inc.) is an evidence-based, fully automated digital CBT intervention for insomnia that offers a full-range of cognitive and behavioral techniques, highly personalised to individual users based on their responses.

ZOLGENSMA EGS CASE STUDY

Value Proposition Insights

- AVXS-101 value proposition for SMA1 is based on durable, long-lasting improvement in survival and HRQoL. Based on the Institute for Clinical and Economic Review (ICER) in the US, the lifetime incremental quality-adjusted life years (QALYs) gained for AVXS-101 vs best supportive care (BSC) was 11.77 years while the lifetime incremental total costs were $2,868,000 yielding an ICER (incremental cost effectiveness ratio) of $243,000/QALY
- Since data on the clinical effectiveness of AVXS-101 were based on a single-arm trial (CL-101; NCT02122952), as part of EGS, natural history studies (PNCR, NeuroNext -NCT01736553[6]) were used to show AVXS-101 offered improved event-free survival, quicker therapeutic benefit onset, robust achievement of motor-milestones and clinical and functional status. This body of evidence generation for AVXS-101 early on, helped establish the clinical effectiveness of AVXS-101 culminating in an “A” rating for SMA1 by ICER[1]

EGS Impact

- Because effective treatment of SMA1 requires early diagnosis, as part of the EGS for AVXS-101, efforts for communicating the value and cost-effectiveness of newborn screening for SMA were undertaken[3]
- Since AVXS-101 is a one-time therapy, as part of EGS, RESTORE, a prospective, multicenter, multinational observational disease registry was established early on (Figure 1) [4] so that vital information required in the immediate neighborhood of launch and beyond was made available to external stakeholders (payers, HTAs, and providers) with little/small or no commercial uptake
- Due to the high, one-time and upfront cost of AVXS-101, early cost-effectiveness modeling was undertaken[5] (Figure 2). The timely publication of evidence via abstracts, posters, and manuscripts, part of the EGS process, enabled the operationalization of the cost-effectiveness analysis model and help the firm successfully engage ICER for the SMA review
- In alignment with timing of FDA approval, ICER reported that Zolgensma’s $2.125MM price fell within the upper bound of ICER’s value-based price benchmark range for the pre-symptomatic population – a rare, positive outcome for an ultra-rare disorder drug exceeding $2M price and receiving approval with single-arm clinical trial evidence from 12 patients (Figure 3), followed by timeline and successful launches in Europe, APAC, Japan, and Latin America.

Figure 1: SMA RESTORE registry features

SMA RESTORE registry	
Data collected	• Long-term efficacy and safety associated with new/emerging treatments • Patient survival • Frequency of healthcare resource use • Caregiver burden • Patient functional status over time • Health-related quality of life over time
Data sources	• Individual *de novo* clinical sites • SMA Consortia • Managed Access programs • Expanded Access programs • Post-marketing Surveillance programs

Figure 2: Zolgensma EGS details

Key Zolgensma EGS: Early cost-effectiveness modeling	
Purpose	• Support pricing decisions • Perform ‘what-if’ analyses to uncover value drivers
Potential value drivers	• Choice of comparators • Country-specific health state utilities • Treatment patterns • Healthcare resource use/costs • Discount rates • Differential discounting between costs and benefits • Benefits of future health gains • Value of non-invasive ventilation vs. tracheostomy for best supportive care • Different survival extrapolation methods

SLEEPIO EGS CASE STUDY

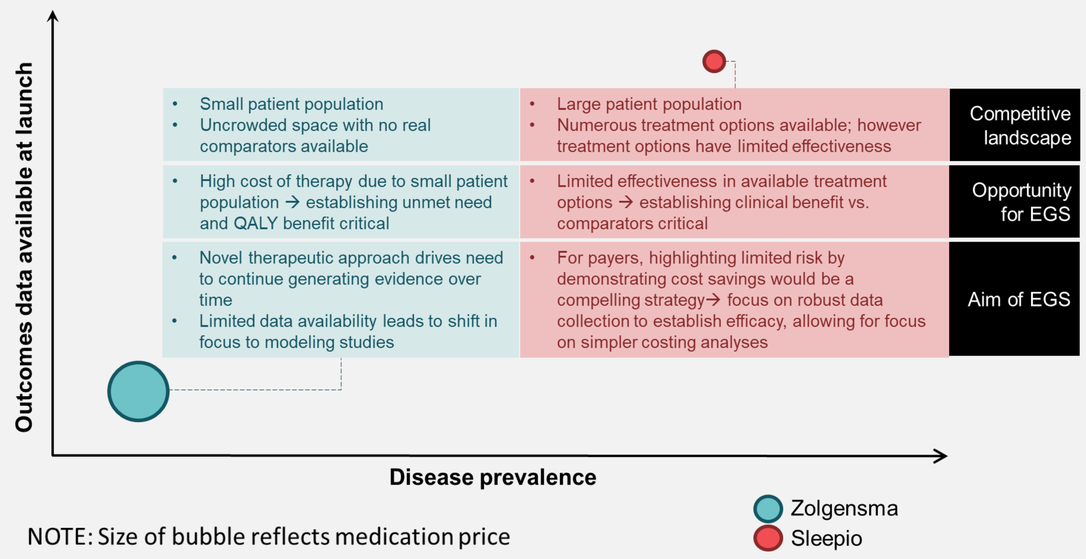
NICE Assessment for Sleepio Insights

- Data on the clinical effectiveness of Sleepio for CBT-I was robust and based on multiple, independent studies (28 studies, 12 of which are randomised controlled trials (RCTs), among which 10 used intention-to-treat analysis to control for the high drop-out rates)
  - This evidence base established clinical equivalence to “treatment as usual” and “face-to-face CBT”
  - Clinical equivalence to comparators enabled the company to focus exclusively on the reduction in total cost of care (a simpler, cost-minimisation approach as opposed to a more complex, cost-effectiveness approach)
- Robust data on the total cost of care reduction value proposition was delivered for Sleepio, and its rollout in a real-world setting due to real world evidence generated from a quasi-experimental and interrupted time series approach[12]. This reduced the need for complex models
  - Sampson et al.[12] was well accepted by the External Assessment Centre (EAC) as robust and pertinent input sources for the cost model

EGS Impact

- The approach taken with Sleepio highlights how tailoring the EGS approach to the product value proposition over the long-term is optimal for gaining market access and reimbursement
  - For Sleepio, the extensive 28 studies including the 12 RCTs gathered over a decade established clinical effectiveness and paved the way for a cost-minimisation only approach
  - Designing and executing the robust, quasi-experimental trial in a real-world setting [12] over two years enabled the company to validate the “total cost of care” reduction value proposition for Sleepio for CBT-I via a cost model leading to broad market access and reimbursement in the UK. Sleepio differentiated from numerous other digital therapeutics and conventional SOC through a robust, long run EGS strategy executed comprehensively (Figure 3), culminating in successfully penetrating the UK market for insomnia

Figure 3: A comparison of EGS, disease features and outcomes data available at launch between Sleepio and Zolgensma



CONCLUSION

These two case studies illustrate the critical role that a well-crafted EGS strategy plays in value proposition development; and that the EGS strategy needs to be initiated as early as possible. As the value proposition matures, the EGS strategy should be refined to highlight evidence gaps and model value drivers that are clinically validated and economically sound. Tailoring EGS to the attributes of the products and diseases under consideration is very important. Understanding cost offsets, the total cost of care reduction, and HRQoL balance for the intended population and comparators is important when synthesizing available evidence. Early planning, customisation and implementation of rigorous EGS approaches should be a cornerstone of evidence-based strategies to support market access and reimbursement.

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