Do we need to mind the gap?: an analysis of the evidence base differences and alignment across regulator and HTA agencies

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Objective – Close alignment of evidentiary requirements and wider use of available data between HTA agencies and regulatory authorities could facilitate timely market access by optimising trial design and reducing the number of studies undertaken. This is particularly important in rare conditions with high unmet need, like haematological malignancies (HM), where patient sample sizes are challenging to achieve along with the emergence of adapted regulatory approval pathways which appraise less comprehensive and mature evidence.

The HARMONY Alliance is an Innovative Medicines Initiative public-private partnership project with over 90 organisations from 22 European countries with varying expertise in evidence development strategies to support new treatments and indications. To guide the consortium this study aimed to ascertain and analyse the alignment of the market access clinical evidence base assessed by regulators and HTA agencies for HM technologies.

Method – Clinical evidence data sources (clinical trials, observational studies, national statistics, registry data) and outcomes by domain (clinical event, time to event, response , patient reported) were extracted from EMA European public assessment reports (EPAR, n=12) and the publically available assessment reports from 8 national HTA agencies (France (HAS), Spain (AEMPS), Norway (NoMA), Sweden (TLV), England (NICE), Ireland (NCPE), Germany (G-BA), Poland (AOTMiT)) for 12 HM innovative products (n=59).

Results – Aggregated HTA and regulator clinical evidence showed overlap/commonality at 58% (range 28-67%) with variation by HTA agency (Figure 1). Primary EPAR efficacy study and pivotal trial for HTA effectiveness assessment were congruent in 92% of cases (Figure 2). Real world evidence was used in 15% (11/71) of reports with alignment in 2 cases. For individual assessments, 1/4 reached 100% congruence and 5% were 100% divergent. None overlapping evidence resulted from variation in HTA use of EPAR supportive data and HTA reporting additional studies from clinical trials (n=18). For outcome usage, HTAs reported a wider range of individual outcomes and used more time to event outcomes than the EMA (figure 3). Designated orphan products showed no difference in alignment of the evidence base compared with non-orphan products. Products with accelerated access conditional EMA approval had slightly higher rates of alignment, lower numbers of additional studies, almost double the rate of HTA negative/restrict decisions (60% compared to 36%), and earlier phase trials (figure 4).

Figure 1. Total alignment of EMA and HTA evidence base across 12 HM products

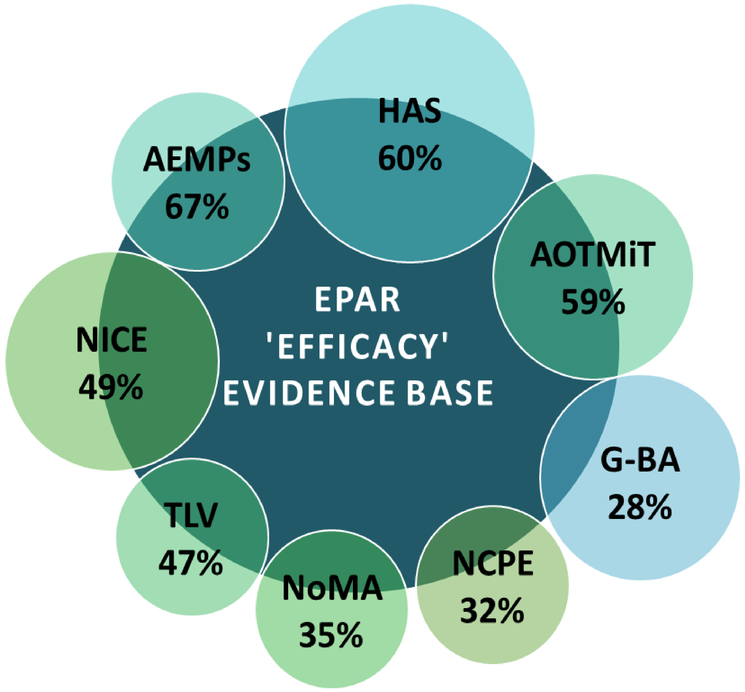


Figure 2. Alignment of HTA evidence base to EMA by specific elements

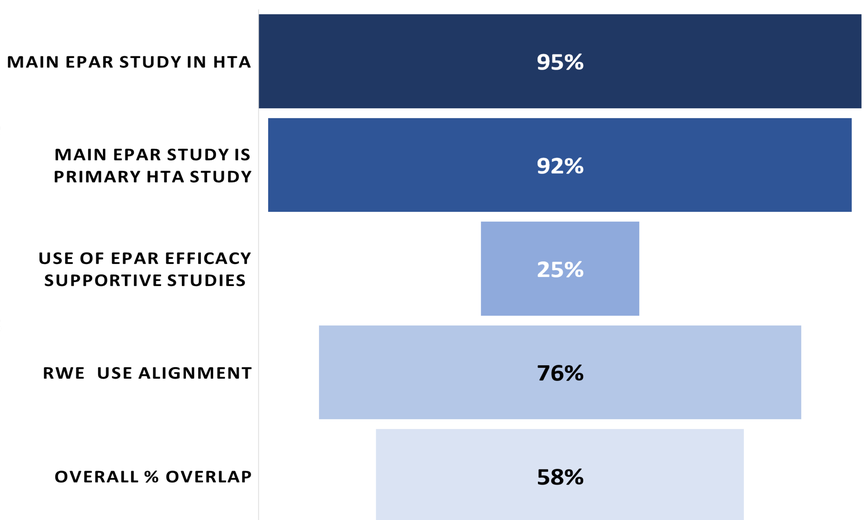


Figure 3. Total reporting of outcomes classified by domain across the 12 products for HTA and EMA

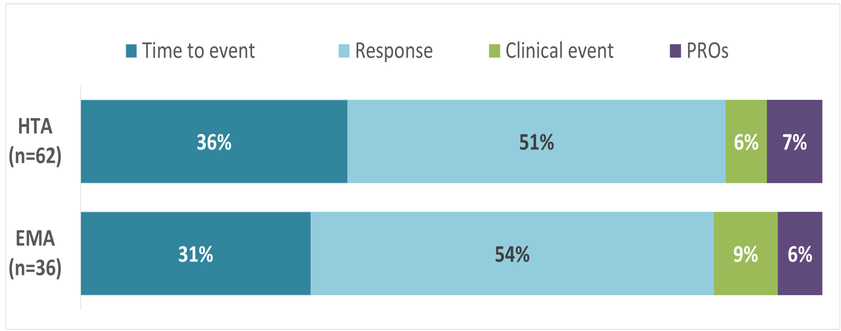
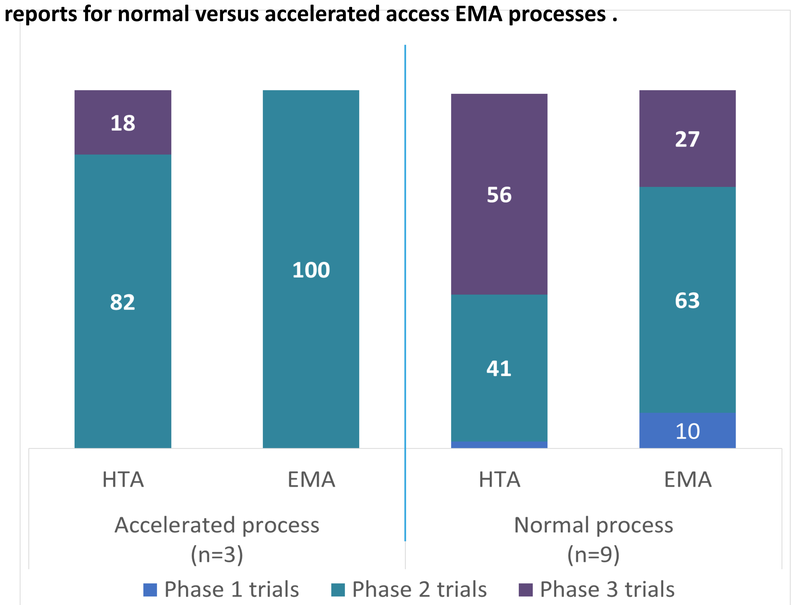


Figure 4. Percentage of evidence base within each clinical trial phase in HTA and EMA reports for normal versus accelerated access EMA processes .



Conclusion – Results indicate a closer evidence alignment than may be expected of the primary evidence source. According to our observations this suggests caution with regard to narrowing the evidence gap further, as seen in expediated assessments, if fewer additional evidence sources and earlier phase studies are used to meet HTA requirements this may lead to negative decisions.

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