Considerations for the Development of Treatment Efficacy/Benefit Attributes and Levels in Patient Preference Studies

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Background

- Regulatory authorities (e.g., Food and Drug Administration [FDA]) continue to highlight the importance of collecting patient experience data (PED) alongside establishing guidance on how to meaningfully collect PED and implement into decision-making; namely the FDA's Patient-Focused Drug Development (PFDD) initiative.[1]
- Patient Preference Information (PII) collected using fit-for-purpose stated patient preference methodologies may inform all stages of the medical product life-cycle (MPLC).[2]
- The value of PPI is becoming increasingly recognised by regulatory authorities in the context of benefit-risk evaluation, demonstrated by recent guidance by FDA,[3] and approvals by the European Medicines Agency (EMA).[4]
- Treatment efficacy and the likelihood that treatments will deliver a favourable outcome (benefit) are critical considerations for patients, HCPs and healthcare decision-makers.

Aims

- A breadth of best methodological practice recommendations and regulatory guidance exist for the design and conduct of patient preference studies (PPS). However, the development and incorporation of efficacy attributes into PPS presents unique challenges, given:
  - The diversity of efficacy outcomes in clinical studies including clinical events (e.g., mortality), patient-reported outcomes (e.g., pain and functioning), or relevant surrogates.
  - Trials often examine the effect of treatment on multiple efficacy endpoints.
  - Supportive data and statistical analysis of endpoints may vary (e.g., time-to-event, proportion of responders, mean change in scores)
- Common challenges and considerations in designing efficacy attributes are presented, to support methodological robustness and mitigate risk of confounding effects.

Concluding perspectives:

- The identification, development, implementation, and interpretation of efficacy attributes in patient preference studies necessitates a systematic, evidence-based process.
- Collecting and incorporating the patient perspective into preference survey design is paramount towards ensuring any efficacy attributes developed are fit-for-purpose.
- Preference studies intending to inform regulatory benefit-risk evaluation should consider early and continual engagement with regulatory bodies to ensure alignment is sought regarding the application of intended outputs, and to align on considerations or suitability of efficacy attributes.

1. SELECTING AN EFFICACY ENDPOINT

- In efficacy-focused PPS, researchers are tasked with devising attribute(s) which adequately represent and effectively communicate the desired endpoint(s) to the intended population.
- If relevant to the study objectives, efficacy attributes should align with the priorities of any decision-makers and stakeholders that the study outputs are intended for.[5]
- Clinical trials can include several efficacy measures in the endpoint hierarchy.

KEY CHALLENGE

PPS which aim to measure preference for efficacy endpoints across **comparator therapies** (e.g., investigational, competitor, standard of care) may find that **trials have utilised different efficacy endpoints** and/or applied different **endpoint definitions**.

Researchers may consider if a combined/composite attribute is appropriate

ADVANTAGES

- A composite attribute may be an effective compromise in instances where endpoint definitions are relatively comparable (i.e., composite attribute incorporates all pertinent information relevant to patients, the clinical field, and decision-making stakeholder[s]).
- For PPS involving combination therapies (e.g., 2 or more treatments are presented within each hypothetical treatment option), combining allows for 1 single attribute to be included.

CONSIDERATIONS

- A diligent approach must be taken to ensure aspects of all endpoints are adequately represented and not misrepresented (posing potential risk of bias that could invalidate outputs and limit generalisability of findings).
- Expert clinical input is strongly advised to ensure combining endpoints is an appropriate and clinically valid approach to take.

- PPS that intend to profile a range of treatment options may need to examine the efficacy data available for all options, with final selection being dictated by the availability of data.

KEY TAKEAWAY

PPS should ideally avoid measuring preference for multiple efficacy endpoints in a single experiment, especially if endpoint definitions are similar or intrinsically related; to avoid illogical combinations and limit attribute inter-dependence.

2. FRAMING OF AN EFFICACY ATTRIBUTE

- The manner in which an attribute is framed and communicated in a PPS is of critical importance, and vital to the ultimate interpretation of preference outputs.
- There are common challenges faced when attempting to ensure communication and framing of efficacy attributes is effective, often depending on the complexity of the specific endpoint definition and the needs of the intended population.

KEY CHALLENGE

- Efficacy attributes may either be framed **positively** (e.g., survival) or **negatively** (e.g., mortality); and this framing is known to influence patient preferences.[6]
- Researchers must therefore diligently select the most appropriate communication format to minimise bias and mitigate untoward framing effects.[7,8]

2. FRAMING OF AN EFFICACY ATTRIBUTE - *continued*

CONSIDERATIONS

- For most PPS (particularly studies informing benefit-risk profiles), it is advised to align framing with the existing or expected endpoint definitions and data.
- Researchers should also consider aligning framing/expression of efficacy attributes to reflect how information is typically conveyed to patients in real-world treatment settings (e.g. drug labelling, patient-focused materials, and/or clinical practice discussion).
- For investigational therapies, whereby the patient population is not expected to be familiar with the efficacy endpoint definition, additional supplementary training may be required to facilitate upskilling and ensure participants respond to choice tasks in a well-informed manner.
- Well-designed and pre-tested educational tools such as videos or descriptive imagery may prove useful to support consistent interpretation and account for sample variation in health literacy and numeracy.

KEY CHALLENGE

Efficacy/survival outcomes are often a **highly influential** aspect of treatment decision-making, such as in cancer populations.[9] Researchers must identify and address potential **dominating attributes/grounding effects**.

CONSIDERATIONS

EARLY IDENTIFICATION OF DOMINANT EFFECTS

- For all PPS (particularly studies informing benefit-risk) early patient insights may be critical in ensuring the study design is appropriate for the specific research question.
- Early identification of potential attribute dominant effects is vital to ensure such effects can be handled and accounted for in the PPS design and analysis plan.

KEY TAKEAWAY

In-depth qualitative pre-testing (via patient interviews) is recommended to contextualise any dominance effects by identifying sample variables (demographic, clinical, personality) that may contribute to the magnitude of dominance effects or indicate preference heterogeneity.

RE-EVALUATE INCLUSION OF AN EFFICACY ATTRIBUTE

- Researchers may consider not including efficacy in a PPS if not considered a key focus or relevant to the research question.
- In these instances, efficacy must be held constant as part of upfront task assumptions to control for any unmeasured influence on preference.

CONSIDER EXPERIMENTAL DESIGN APPROACHES

- Experimental design can be constructed to mitigate, or account for, any dominant attributes. For example:
  - Two versions of each choice task may be shown – with and without efficacy, to observe the interactions efficacy could have on relative importance of attributes and trade-offs.
  - The ordering of attributes in a choice task may be systematically varied.
- However, such approaches may increase task burden and impact the quality of the data.

3. DEVISING ATTRIBUTE LEVELS

- PPS must ensure that attributes levels devised to reflect efficacy are understood, important and demonstrate a meaningful differentiation to the patient population.

KEY TAKEAWAY

Quantitative efficacy data (as opposed to qualitative is recommended; both to maximise precision of preference estimates, as well as ensuring efficacy is communicated unambiguously to patients.[10]

- Like all attributes, levels included in efficacy attributes must differentiate sufficiently to have a testable range in the PPS.

KEY CHALLENGE

The criteria used by researchers to identify **differentiating efficacy attributes** (i.e., a meaningful 'improvement' or 'worsening') and the **levels devised to reflect the data range** is a potential source of **experimental bias**.

EXAMPLE: Progression-free survival (PFS) data for Treatment 1 is **15 months;** Treatment 2 is **16 months;** Treatment 3 is **16.5 months;** Treatment 4 is **17 months.**
Is this difference meaningful to patients, clinically meaningful?

CONSIDERATIONS

- Researchers must proceed cautiously when examining numerical differentiation to inform attribute inclusion/exclusion.
- Researchers must also take caution when considering to 'merge' levels (e.g., devising a single '17 month' level to incorporate Treatment 3 and 4 shown above).

KEY TAKEAWAY

To minimise bias, input from the target patient population (via qualitative interviews, patients as research partners/advocates) and expert clinicians should support the selection of attributes and any constituent levels devised.

KEY CHALLENGE

Researchers must exercise caution when deciding on the level range, specifically the lower (minimum) and upper (maximum) levels.

CONSIDERATIONS

- The levels should capture the full range of data points identified from available product efficacy data (or expected data if trials are in early phases).
- However, efficacy data may change during the course of a study (e.g., long-term follow-up, maturing data), and certain trials (e.g., orphan indications) may present with statistical uncertainty due to sample size limitations.[2]
- Regardless, a balance must be struck to ensure any extended ranges are not implausible, unrealistic, or extreme; this may inadvertently result in efficacy becoming a dominant attribute.
- To maximise the utility of study outputs, it may be important to consider how to build in flexibility to estimate preference for anticipated future efficacy datapoints.

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Presented at ISPOR 2024, Atlanta, GA – May 5-8