Improving Patient Access during Phase 2-3 Design - Things to Consider –

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BACKGROUND

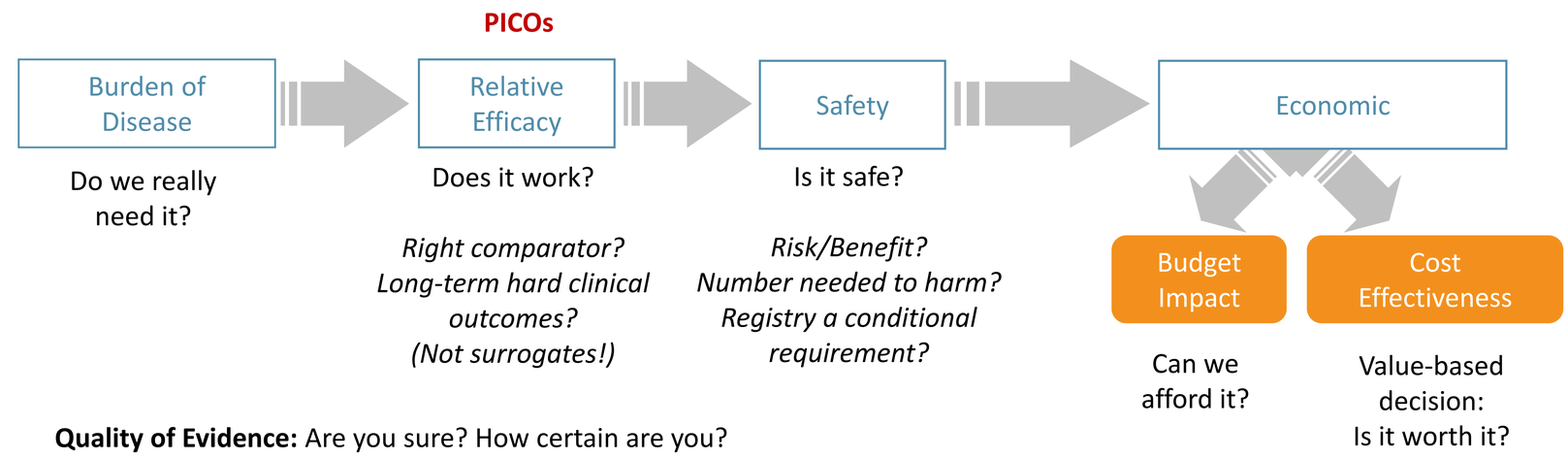
HTA (Health Technology Assessment)/Patient Access

A multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle. The purpose is to inform decision-making in order

- to determine the value of a health technology
- to provide guidance how these technologies can be used in health care systems
- to support the decision-making process at the policy level by providing evidence about given technologies

ASK: What are the health and cost consequences associated with your drug relative to what is already (reimbursed) in the market of country xy?

HTA/Payer Requirements at Launch: Clinical Data Play a Huge Role



Quality of Evidence: Are you sure? How certain are you?
Ability to Control Use in Correct Patient Population: Which patients benefit most?
Socio-political Impact of the Reimbursement Decision: Can we deny?

GOALS & ASKS from Payers are similar: However, **VARIABILITY** comes in through different Health care systems, Legal frameworks, PICO's, requirements (evidence, data, analyses methods), processes, etc.

PATIENT ACCESS: EFFORTS NEEDED

The PICO Framework

The PICO framework provides a standard format within HTA for the definition of a research question

P (opulation): the patients or population(s) in which the intervention under assessment should be used

I (ntervention): the therapeutic, diagnostic or preventive intervention under assessment (incl. setting)

C (omparator): the alternative intervention(s) against which the intervention under assessment should be compared

O (utcomes): the outcomes of interest (if relevant incl. minimum follow-up time)

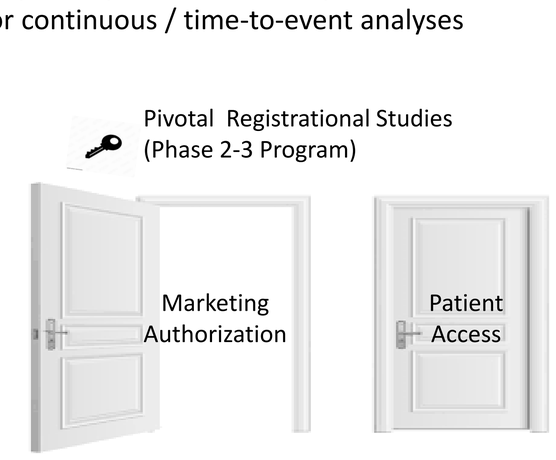
see also: PSI HTA SIG Webinar: Estimands, PICOs and Co. - Are we losing or gaining in translation?
https://www.psiweb.org/vod/item/psi-hta-sig-webinar-estimands-picos-and-co.---are-we-losing-or-gaining-in-translation

Consequences for Patient Access: complementary evidence requirements - additional analyses & data sources

Endpoint Level – e.g.,
- **Adverse Events**: comparative analyses, all required categories of AE, specifically AEs by SOC/PT, AEs of special interest
- **Patient Reported Outcomes**: responder analyses (different thresholds) and/or continuous / time-to-event analyses

Study Level – e.g.,
- **Subpopulations**: from PICOs
- **Subgroups**: additional subgroup analyses with interaction tests (efficacy & safety)
- **Sensitivity analyses**
- **Data Cuts**: additional timepoints

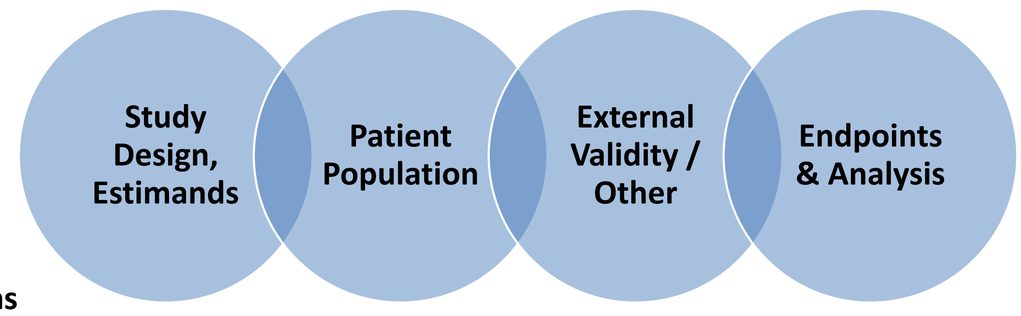
Synthesis Level – e.g.,
- **Meta-Analyses**: when more than one source of evidence is available, e.g., twin pivotal studies
- **Indirect Comparisons**: when comparator in study does not match PICO



KEY TOPICS TO DISCUSS DURING PHASE 2-3 PLANNING

- **Representativity**
- **Generalizability**
- **Extrapolation**
- **Devices**

- **Study duration & timepoints**
- **Comparator(s)**
- **Pre-specification**
- **Estimands**
- **Missing data**
- **Subgroups**
- **Indirect comparisons**



- **Endpoints**
- **Signs and Symptoms Outcomes**
- **Scales**
- **QoL/PRO Measures & Timing**
- **Utilities**
- **Economic models**
- **Instrument Validity**
- **Biomarkers**

- **Indication**
- **Patient Population**
- **Comorbidities**
- **Background Medication**

- *Currently, many registrational Phase 3 Programs do not satisfy all evidentiary needs for HTA & Patient Access purposes*
- *Planning for Patient Access should complement the clinical development plans prior to start of Phase 2 and 3 studies*
- *Clinical and HTA Statisticians have the opportunity to optimize Phase 2-3 study designs and evidence planning, thus enabling coherent and efficient decision making by Regulators and HTA bodies.*

Abbreviations:
AE = Adverse Event; HTA = Health Technology Assessment; PICO = Population, Intervention, Comparator, Outcome; PRO = Patient Reported Outcomes; PT = Preferred Term; QoL = Quality of Life; SOC = System Organ Class.

Both authors are members of the PSI/EFSPI **HTA Special Interest Group**

Want to get involved in this and similar methodology discussions?
Join the PSI/EFSPI HTA Special Interest Group today
– scan the QR code or email htasig@psiweb.org

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--- SUPPLEMENTAL MATERIAL ---

KEY TOPICS TO DISCUSS DURING PHASE 2-3 PLANNING - DETAILS

Study Design, Estimands

- **Study duration & timepoints**
  Are timepoints for measuring endpoints, minimal follow-up time sufficient for HTA purposes?
- **Comparator**
  Are active comparator arms included?
  If yes, are these the most relevant for patient access?
- **Pre-specification**
  Are secondary endpoints including PROs pre-specified, ‚sufficiently' powered and hierarchically tested (depends on the HTA requirements for a given country)?
- **Estimands**
  Are estimands of most interest in HTA included and their impact on the study design appropriately considered, e.g. ensure availability of data after intercurrent events (treatment discontinuation, rescue medication)?
- **Missing data**
  Are measures in place ensuring completeness of data as best as possible?
- **Subgroups**
  Are the number of subgroups for regulatory purposes restricted to a minimum?
- **Indirect comparisons**
  Would trial designs (including endpoints) enable indirect comparisons with main competitors?
  What is sufficient and necessary to conduct network meta-analyses?

Patient Population(s)

- **Indication**
  Is the study design appropriate to achieve target indication goal in all/the majority of geographies?
  Could the target population differ from the population identified by EMA/FDA and for what reasons?
- **Patient Population I**
  Do inclusion / exclusion criteria reflect the draft label population & disease definition, as well as HTA-defined (sub-) populations?

  Patient Population II
  Is the race & ethnicity composition appropriate to enable patient access
  What is its impact on the feasibility of indirect comparisons?
- **Comorbidities**
  Are comorbidities relevant for the disease are included?
- **Background Medication**
  Is Background medication used in-label and according to clinical practice / guidelines?

Endpoints & Analysis

- **Endpoints**
  Where novel endpoints are used, is it ensured that ‚traditional' endpoints can still be constructed to allow e.g., (indirect) comparisons to relevant older comparators?
- **Signs and Symptoms Outcomes**
  Are patients' signs and symptoms adequately captured, i.e., via accepted clinical disease measures (not surrogates)?
- **Scales**
  Are scales used in clinical practice included as well as key scales from competitor development studies?
- **QoL/PRO Outcomes & Timing**
  Are Patient reported QoL captured with sufficient power (at appropriate time points & follow up)?
- **Utilities**
  Are utilities needed for cost-effectiveness analyses (e.g., EQ-5D) collected?
- **(Early) economic models**
  Are all needs for cost-effectiveness models and associated evidence gaps identified and addressed?
- **Instrument Validity**
  Are instruments / measures (e.g., PROs) validated and accepted by HTA bodies?
- **Biomarkers**
  Is the use of biomarkers accepted (by HTA) and are there any conditions?

External Validity / Other

- **Representativity**
  Are a sufficient number of patients recruited in each geographical region / key markets?
- **Generalizability**
  Would RCT results be generalizable to individual country populations?
  Are local RWE data available and accessible to enable corresponding analyses?
- **Extrapolation**
  Is extrapolation to other populations accepted (by HTA) and under what conditions?
- **Devices**
  Are devices used in Phase 3 program same as later on after launch? If not, is this addressed from a patient access/ HTA perspective?

PSI HTA SIG Webinar: Estimands, PICOs and Co. - Are we losing or gaining in translation? Video-on-Demand (psiweb.org)

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