Industry Perspective on PRO endpoint design and implementation in cancer drug development in the PFDD era

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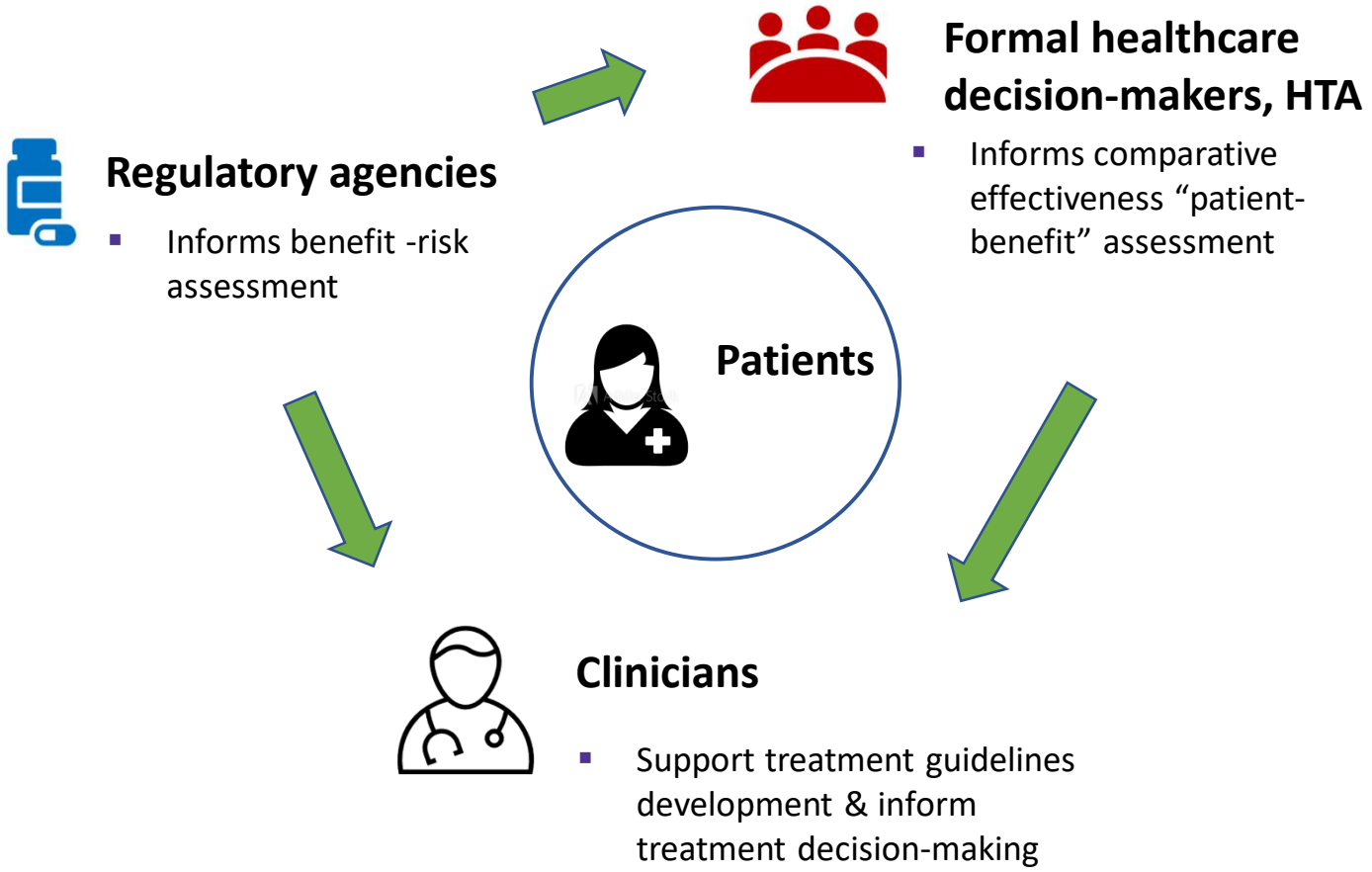
This presentation contains company proprietary information and the outcomes of the company's internal evaluations. The conclusions are my personal view and interpretation.

Outline

1. Background
2. Roadmap - implementation of PRO endpoints in cancer drug development
3. Case studies
4. Summary - challenges and opportunities

Background

Stakeholders for PRO data



Contextual Developments

- Increasing standardisation and rigor in implementation of PRO endpoints in cancer drug development
  - e.g. FDA CoE Oncology Core Outcomes domains, PFDD guidances
- A rapidly evolving anti-cancer therapeutics landscape, changing the treatment paradigm
  - emergence of immuno-oncologic therapies, tumor agnostic therapeutics
- Scientific and operational innovations
  - Novel models of pharma-patient engagement
  - Methodologic and technical advances in health outcomes measurement

PROs Roadmap:

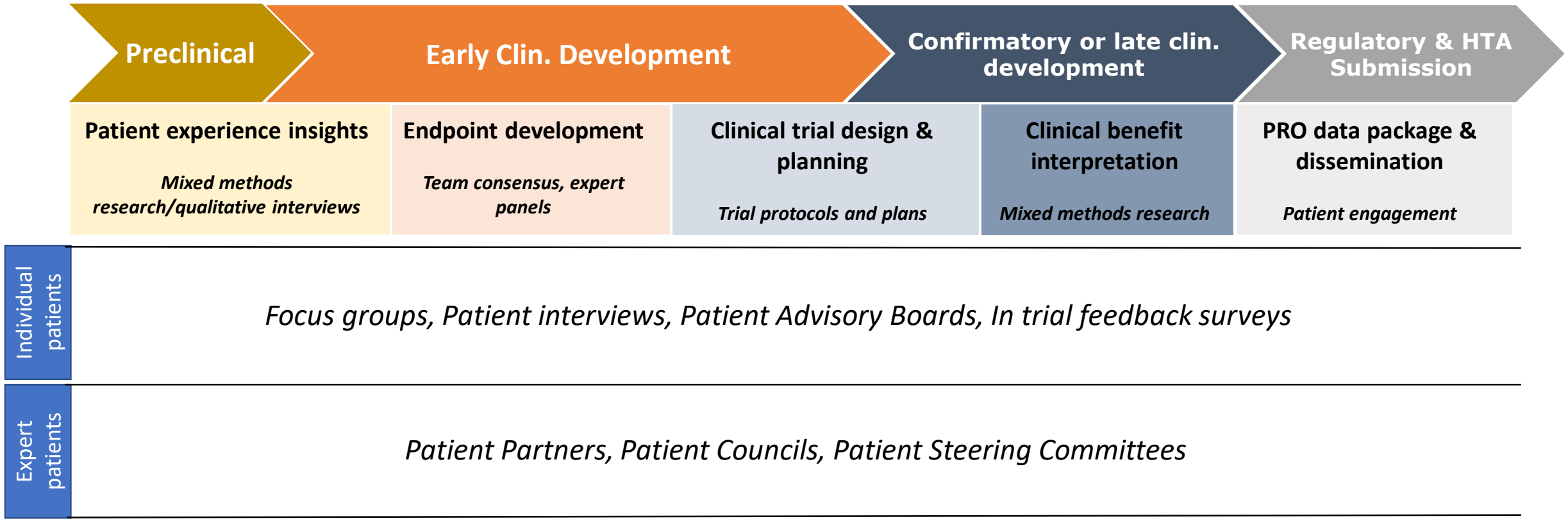
The design and implementation of PRO endpoints spans the full drug R&D continuum

Preclinical	Early Clin. Development	Confirmatory or late clin. development	Regulatory & HTA Submission
Patient experience insights ***Mixed methods research/qualitative interviews***	**Endpoint development** ***Team consensus, expert panels***	**Clinical trial design & planning** ***Trial protocols and plans***	**Clinical benefit interpretation** ***Mixed methods research***	**PRO data package & dissemination** ***Patient engagement***
• What outcomes are important for patients ? • What are expectations related to new treatment ?	• Which outcomes are most relevant and should be targeted, given MOA ? • What is the best way to measure the target outcomes ?	• What is the PRO-related research question for the trial • How can we best collect and analyse data on the endpoints to support our objectives ?	• What additional insights will support interpretation of PRO endpoints	• What is the relevance for observed clinical benefit for patients • Trial results dissemination
Target Product Profile and development plans incorporate PROs	Product team align on PRO strategy	Cross-functional alignment on PRO measurement	Internal governance approval of protocols	

Issue: Strong alignment across multiple layers of the organization on the value of PRO endpoints for asset and the necessary resource commitments are required

PROs Roadmap:

Patient engagement on PRO aspects, across the R&D continuum, now widely adopted!



Issue: Patient engagement requires careful planning and resources, still viewed as adding complexity

Case study 1, Bavencio ® (avelumab)

Included a PRO endpoint based on a measure from an analogous cancer type

Indication: Distant metastatic Merkel Cell Carcinoma (MCC)

Trials: JAVELIN Merkel 200 - single arm open label, Phase II Trial

PROs (exploratory): FACT-Melanoma was assessed at baseline, Week 7, Week 13, and Week 25.

Early Clin. Development	Regulatory & HTA Submission
• In-trial patient interviews – **Phase II trial:** – Concept elicitation/exploratory (at baseline) – On treatment experience (each follow-up visit) • **Phase II trial** data used to validate the FACT-Melanoma • Disease conceptual model developed – based on patient interview data	• PRO data and in-trial interviews from Phase II included in MA submission to regulatory agencies and HTA bodies

Issues: **1.** MCC's small population size made outside trial research challenging, **2.** Careful planning and substantial effort required for within trial validation of FACT-Melanoma

Notes: An ongoing longterm Phase II extension includes the FACT-M; no Phase III currently ongoing for BAVENCIO

Sources: Kaufman HL *et al*. Future Oncology. 2018 Feb;14(3):255-66**;** Kaufman HL, *et al.* The Patient-Patient-Centered Outcomes Research. 2018 Aug;11(4):439-49; Bharmal M *et al*. Health and quality of life outcomes. 2017 Dec;15(1):1-1.

Case study 2, illustrative HCC/NSCLS program

denovo PRO measure

Indication: HCC/NSCLC based on real development programs across industry

Trials: Phase I - III

PRO Endpoints (secondary): core disease symptoms and tolerability based on NSCLC-specific PROs

Preclinical	Early Clin. Development	Confirmatory or late clin. development	Regulatory & HTA Submission
Outside of trials: • Clinician interviews • Exploratory patient interviews **Phase I trial** included multiple PRO measures to explore most appropriate concepts	• Target PRO concept defined/selected • Measure newly drafted or derived from item banks e.g., PRO-CTCAE • Cognitive patient interviews • draft PROs included in **Phase II trial** for validation • PRO endpoint formulated	Plan **Phase III** trial designs • PRO objectives, hypothesis defined • Supportive in-trial interviews	Outside of trials: • Patient surveys on benefit-risk ratio preferences for treatments MCID estimates confirmed in phase III trial	• PRO data package submissions • Input on product labelling • Dissemination of clinical trial results e.g., novel patient platforms

Issues: 1. Long lead time adds to development risks, 2. Substantive effort and resources investment required upfront

Notes: CTCAE, Common Terminology Criteria for Adverse Events (CTCAE)

Sources: This illustrative case study is based on multiple development programs, including Tagrisso Case Study in Advanced NSCLC presented at 5th Annual Clinical Outcome Assessments in Cancer Clinical Trials (COA-CTT) Workshop, Project Patient Voice – Session 04, ASCO-FDA Center of Excellence Oncology, August 2020

Summary - challenges and opportunities

1. Transferability of evidence and generalizability of validity across settings
   - Various constraints necessitate appropriating evidence from other disease stages or analogous cancers to support endpoints e.g., *lack of natural history data, small populations*
2. Special consideration for mechanism of action
   - Treatment goals may differ based on the assets MOA
   - Emergence of tumor agnostic therapies requires special considerations
3. Practical issues in collecting supportive evidence for PRO endpoints
   - denovo PROs associated with long lead time and substantial upfront investments – often perceived as risky during early development

Discussion Topics

1. How can we increase transparency on the trade-offs between ensuring validity in given setting or target population, and generalizability of validity across settings e.g., disease stages or analogous cancer types ?

2. How may a structured approach for addressing mechanism of action (MOA) look like ? Is standardization possible ?

3. What approaches and strategies would help to address the risks associated with PRO endpoint development work during early clinical development stages