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EXPLORING THE CONTENT AND PSYCHOMETRIC VALIDITY OF CLINICAL OUTCOME ASSESSMENTS IN PANCREATIC DUCTAL ADENOCARCINOMA VERSUS THE PATIENT REPORTED SYMPTOMS AND IMPACTS

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INTRODUCTION

- Pancreatic ductal adenocarcinoma (PDAC) is a leading cause of cancer-related deaths in most developed countries (estimated to be the fourth or fifth)[1]. Five-year survival is less than 8%[2].
- Diagnosis of PDAC is challenging as symptoms can be non-specific, such as pain in the abdomen and back, gastrointestinal problems, and tiredness/exhaustion[3,4]. As a result, nearly 80% of patients diagnosed with pancreatic cancer have locally advanced or metastatic disease[3].
- Health-related quality of life (HRQoL) appears to be an important prognostic factor in patients with PDAC5. Patients with lower quality of life (QoL) have a poorer prognosis than those with higher QoL, even after controlling for demographic characteristics, comorbidity, tumour size, cancer stage, and time since diagnosis[5].
- Capturing symptoms and HRQoL impacts can be obtained through use of patient-reported outcome (PRO) measures. Such measures are important as they ascertain, from the patient's perspective, their current health status and its impact on multiple aspects of their life (or health-related quality of life; HRQoL).
  - The EORTC QLQ-C30/PAN26, for instance, have been deemed highly relevant by patients since it assesses most aspects of their experience with the disease and treatment[4].
- The FDA's "Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims"[6] and the more recently released four-part "Patient-Focused Drug Development (PFDD) Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making"[7] outline principles for selecting appropriate PRO measures, developing and validating PROs, analysing data, and addressing regulatory requirements. The guidance documents emphasise the importance of PROs in capturing the patient perspective and enhancing understanding of treatment effects. The FDA has also released draft guidance specific to the use of PROs in oncology clinical trials[8].
- **This study aimed to build upon and extend prior research[4] by identifying the key symptoms and impacts of PDAC and evaluating the validity of existing patient-reported outcome (PRO) measures in alignment with FDA guidance for the specific context of use.**

METHODS

Methods ➔ Literature review

- A targeted literature review was conducted (PubMed & Google Scholar) to identify published studies or reviews related to:
  - Key symptoms, impacts, and characteristics of PDAC
  - PROs and digital measures used in PDAC studies

Methods ➔ PRO and Digital Measure Landscape Assessment

- Clinicaltrials.gov was searched to identify PROs used in current PDAC trials.
- DailyMed (FDA drug labels) and the EMA website (Summaries of Product Characteristics; SmPC) were searched to identify PROs used in the labels of drugs that treat PDAC.
- The Digital Medicine Society's (DiMe) digital endpoints library was searched to identify wearables and digital measures that were used in oncology studies that may be useful for use in patients with PDAC.
- The International HTA Database, the National Institute of Health and Care (NIHR) Journal of Health Technology Assessment, and the International Journal of Technology Assessment were searched to identify PROs used in HTA appraisals in PDAC or similar conditions.

Methods ➔ Gap Analysis and Concept Mapping

- A gap analysis on a short list of PROs assessed the development and measurement properties against the FDA guidance[6,7].
- Concepts identified as being relevant to patients with PDAC were used to extend an existing conceptual model of PDAC[4].
- Concepts from the conceptual model were then mapped to the items in the PROs to identify any gaps in concept coverage[6,7].

RESULTS – LANDSCAPE ASSESSMENT

Literature Review

- N = 6 studies indicated that PDAC has a significant impact on HRQoL.
- Key symptoms include pain, fatigue, nausea and appetite loss.
- These symptoms impact across HRQoL domains: emotional, physical, social and general activities of daily living.
- N = 8 studies contained N = 19 reported PROs (Figure 1).

Cancer-Specific HRQoL N=9

- European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30), n = 5
- European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Pancreatic Cancer (EORTC-QLQ-PAN26), n = 4
- European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Palliative care (EORTC QLQ-C15-PAL), n = 1
- Functional assessment of cancer therapy - general (FACT-G), n = 5
- Functional assessment of cancer therapy - hepatobiliary (FACT-Hep), n = 5
- Functional assessment of cancer therapy - Hepatobiliary Symptom Index (FACT-FHSI), n = 1
- Cancer Linear Analogue Scales (CLAS1, CLAS2, CLAS3), n = 1
- Edmonton Symptom Assessment System, n = 2
- PDAC specific National Institute of Health Patient Reported Outcome Measurement Information System questionnaire (NIH Panc-PROMIS), n = 1

HRQoL N=8

- Short Form Health Survey (SF-36), n = 3
- Patient Health Questionnaire (PHQ9), n = 1
- Gastrointestinal QoL Index, n = 1
- Euro-QoL 5-dimension questionnaire (EQ-5D), n = 1
- Veterans RAND (VR-12), n = 1
- Professional Quality of Life Scale (PROQoL), n = 1
- Nepean Dyspepsia Index, n = 1
- Sickness Impact Profile, n = 1

Pain N=1

- Numerical Rating Scale for Pain (NRS), n = 1

Mental Health N=1

- Hospital Anxiety and Depression Scale (HADS), n = 3

Figure 1. PROs identified from published literature

PRO & Digital Measure Landscape Assessment

1. Clinicaltrials.gov search

- N = 9 out of 53 clinical trials named at least 1 PRO.
- The most frequently listed PROs were:
  - EORTC-QLQ-30 (N = 7 trials)
  - EORTC-PAN-26 (N = 3 trials)

2. Drug labels/SmPCs

- N = 54 labels were identified from the FDA; 0 reported a PRO.
- N = SmPCs were identified from the EMA; 0 reported a PRO.

3. DiME Digital Endpoint Library

- No PDAC-relevant digital endpoints were identified.
- However, N = 2 digital endpoints were identified that had been used among patients with breast cancer and unspecified cancer.
  - Activity monitors were reported as a primary (N = 1 trial) and a secondary (N = 1 trial) endpoint, respectively.

4. HTA databases

- N = 2 HTA appraisals were identified.
- The EQ-5D was reported in both appraisals in relation to cost-effectiveness.

RESULTS – GAP ANALYSIS

- N = 8 out of the 19 identified PROs were included in the gap analysis, of which N = 1 was pancreatic cancer specific (EORTC-PAN-26).
- When compared to the FDA's guidance for PRO evaluation, none of the PROs examined in the gap analysis met all the development and psychometric property criteria (Table 1).
- There was partial evidence of content validity in the PDAC population for the EORTC-QLQ-C30 and the EORTC-QLQ-PAN-26, however the majority of the PROs lack evidence of cognitive debrief interviews with patients with PDAC.
- Evidence based on a pancreatic cancer patient population was identified for the FACT-Hep, FACT-FHSI, EORTC-QLQ-C30 and the EORTC-QLQ-PAN-26 that met some of the measurement property criteria.
  - One of these PROs (the FACT-FHSI) appeared to meet all psychometric property criteria (listed by the FDA). However, no published content validation work was identified.
- The other identified PROs showed little to no evidence of psychometric validity. Cognitive debrief interviews would enhance the level of these PROs.

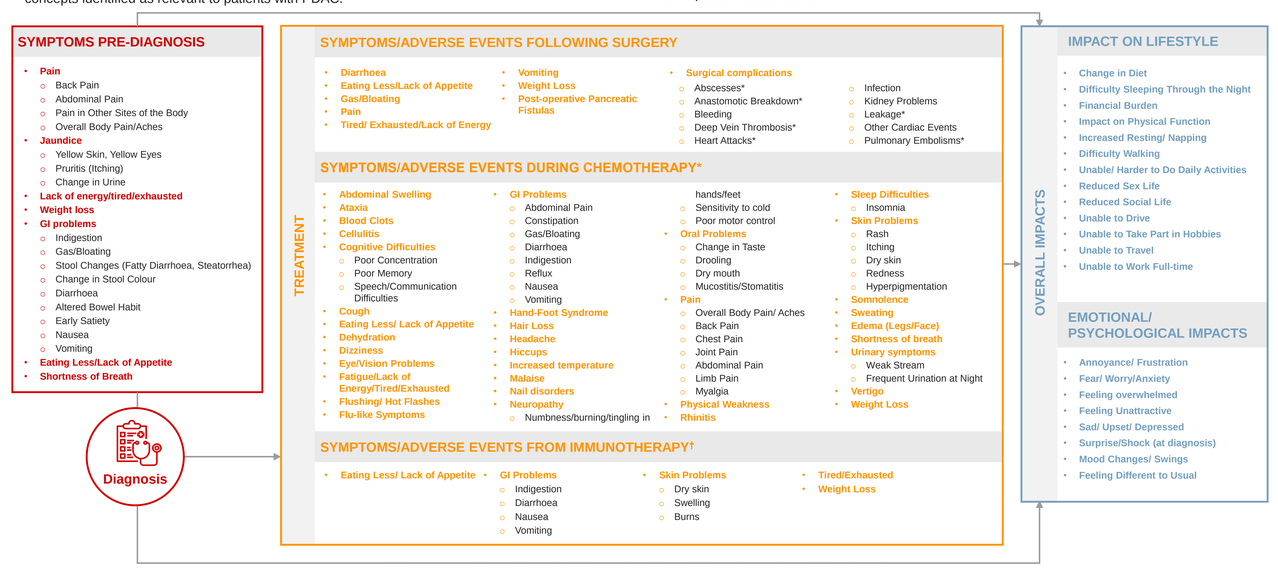
Table 1. Overview of measurement properties by shortlisted PRO

Measurement properties	FACT-G	FACIT Item GP5	FACT-Hep	FACT-FHSI	NFHSI-18	FACT-RNT	EORTC-QLQ-C30	EORTC-QLQ-PAN26	PRO-CTCAE	FACT-Hep
Content validity: Concept elicitation			✓		✓		✓		✓	
Content validity: KOL input			✓	✓	✓		✓		✓	
Content validity: Cognitive interviewing							✓		✓	
Internal reliability			✓	✓	✓		✓		✓	n/a*
Test-retest reliability			✓	✓						
Construct validity		✓	✓	✓	✓				✓	
Known-groups validity	✓		✓	✓				✓	✓	
Responsiveness/ability to detect change			✓	✓	✓					
Interpretability of scores (MCID)			✓	✓	✓					

*The PRO-CTCAE is an item bank used for contextual adaptation and therefore, cannot be generally tested for internal reliability.

CONCEPT MAPPING

- An existing conceptual model[4] was adapted from the findings of the literature review (Figure 2).
- The signs, symptoms and impacts identified were then mapped to the items of the shortlisted PROs.
- The goal of the concept mapping exercise was to assess the selected PROs for coverage of the concepts identified as relevant to patients with PDAC.
- The FACT-Hep and the combination of the EORTC-QLQ-C30 and PAN-26, which would be administered together, provide the best overall coverage of signs/symptoms.
- However, the combination of the EORTC-QLQ-C30 and PAN-26 provides the best overall coverage of impacts in all domains.



Model adapted from Herman et al [4]; *Chemotherapy treatments include FFX, Gemcitabine+Abraxane, Gemcitabine, 5FU+Leucovorin, Gemcitabine+Bevacizumab, GTX, and nab-paclitaxel

Figure 2. Preliminary conceptual model

KEY FINDINGS

- The advanced stage of pancreatic cancer causes significant symptoms and impacts. Frequently reported disease-related symptoms include pain, fatigue, nausea, appetite loss, weight loss, biliary complications, and gastrointestinal issues.
- The evidence points to a disease that has a substantial impact on patients' health-related quality of life.
- Further qualitative research with patients is needed on what is important to measure in patients with PDAC and how best to measure it.
- Based on the available evidence, the FACT-Hep, EORTC-QLQ-C30 and PAN-26 appears to be a leading contender for capturing symptoms and impacts of PDAC and treatment.
- Further validation of these measures within the specific context of use is needed.
- As therapeutic innovation evolves, further research is needed to capture the patient experience of not only the symptoms and impacts of PDAC but also the treatment impact to ensure instruments remain fit-for-purpose.

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