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EXPLORING THE CONTENT AND PSYCHOMETRIC VALIDITY OF CLINICAL OUTCOME ASSESSMENTS IN RENAL CELL CARCINOMA VERSUS THE PATIENT REPORTED SYMPTOMS AND IMPACTS

I Petit[1], L Eliasson[2], B Romero[3], C Patel[2], A Di Rosa[3], J Quinn[1]

[1]Debiopharm SA, Switzerland; [2]Sprout Health Solutions Limited, UK; [3]Sprout Health Solutions Limited, US

INTRODUCTION

- Renal cell carcinoma (RCC) is a histologically complex cancer. Outcomes range from very low survival rates for metastatic disease to excellent long-term prognoses for localised presentations[1].
- Patients with clear cell histology (ccRCC) can experience favourable outcomes; however, variations in disease characteristics (e.g., tumour size, localisation) impact patients' risk level and management approach.
- Regardless of RCC type, patients report high symptom and impact burdens, such as fatigue, pain, and shortness of breath, to social and mental health impacts, such as worry, irritability, and mood disorders[2].
- Capturing these symptoms and 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).
- It is currently not known which symptoms and HRQoL impacts are most meaningful for patients with ccRCC, or which PROs best collect outcomes of importance to patients in a clinical trial setting.
- It is also important to understand the extent to which PROs are fit-for-purpose for use with a ccRCC patient population.
- The FDA's "Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims"[3] 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"[4] 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 The FDA has also released draft guidance specific to the use of PROs in oncology clinical trials[5].
- **Therefore, this study sought to identify the key symptoms and impacts of ccRCC and to evaluate the validity of existing patient-reported outcome (PRO) measures that aligns with FDA guidance.**

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 ccRCC
  - PROs and digital measures used in ccRCC studies

Methods ➔ PRO and Digital Measure Landscape Assessment

- Clinicaltrials.gov was searched to identify PROs used in current ccRCC 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 ccRCC.
- 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 ccRCC.
- 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 ccRCC 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[3,4].
- Concepts identified as being relevant to patients with ccRCC were used to draft a *preliminary* conceptual model of ccRCC[4].
- Concepts from the conceptual model were then mapped to the items in the PROs to identify any gaps in concept coverage[4].

RESULTS – LANDSCAPE ASSESSMENT

Literature Review

- N = 4 studies indicated that ccRCC has a significant impact on HRQoL.
- Key symptoms include pain, fatigue and renal bleeding.
- These symptoms impact across HRQoL domains: emotional, physical, social and general activities of daily living.
- N = 8 studies contained N = 15 reported PROs (Figure 1).

Cancer-Specific HRQoL N=7	• Functional Assessment of Cancer Therapy – General (FACT-G) • Functional Assessment of Cancer Therapy – General Renal Cancer Subscale (FACT-G Renal Cancer Subscale) • Functional Assessment of Cancer Therapy – Kidney Symptom Index (FKSI-[15/19]) • Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms (FKSI-DRS) • European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) • MD Anderson Symptom Inventory (MDASI) • Edmonton Symptom Assessment System — Revised (ESAS-r)
HRQoL/utility N=2	• 36-Item Short Form Survey (SF-36) • Euro QoL 5 dimensions questionnaire – 3-levels and 5-levels (EQ-5D-3L/5L)
Fatigue and Sleep N=3	• Pittsburgh Sleep Quality Index (PSQI) • Brief Fatigue Inventory (BFI) • Functional Assessment of Chronic Illness Therapy–Fatigue Scale (FACIT-F)
Psychiatric N=3	• Center for Epidemiologic Studies Depression Scale (CES-D) • The Impact of Events Scale (IES) • Distress Thermometer (DT)

Figure 1. PROs identified from published literature

PRO & Digital Measure Landscape Assessment

1. Clinicaltrials.gov search

- N = 19 out of 61 clinical trials named at least 1 PRO.
- Apart from one trial, PROs were ranked as secondary outcomes.
- The most frequently listed PROs were:
  - EORTC-QLQ-30 (N = 8 trials)
  - FKSI-DRS (N = 7 trials)
  - EQ-5D (N = 7 trials)
  - FKSI-19 (N = 6 trials)

2. Drug labels/SmPCs

- N = 14 labels were identified from the FDA; 0 reported a PRO.
- N = 16 SmPC (comprising 9 compounds) were identified from the EMA; 1 SmPC reported PROs:
  - FKSI-DRS
  - EQ-5D

3. DiME Digital Endpoint Library

- No ccRCC-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 = 5 HTA appraisals were identified. Reported PROs were:
  - FKSI (-15 item / -19 item / DRS) (N = 3 appraisals)
  - FACT-G (N = 1 appraisal)
  - EORTC QLQ-C30 (N = 1 appraisal)
- The EQ-5D was reported in all 5 appraisals in relation to cost-effectiveness.

RESULTS – GAP ANALYSIS

- N = 11 out of the 15 identified PROs were included in the gap analysis, of which N = 3 were kidney cancer specific (FKSI-15, FKSI-DRS and NFKSI-19).
- When compared to the FDA's guidance for PRO evaluation, the gap analysis showed that evidence of full content validity in the ccRCC population was missing from all selected PROs. There was no evidence of concept elicitation or cognitive debriefing interviews with patients with ccRCC for any of the PROs.
- Evidence based on a kidney cancer patient population was identified for the FKSI-15, FKSI-DRS and NFKSI-19 that met some of the measurement property criteria (Table 1).
  - To note, a 12-item physical functioning subscale of the FKSI-DRS – the FKS-DRS-P – has been accepted into the FDA COA qualification programme[6].
- One of the PROs (the FKSI-15) appeared to meet all psychometric property criteria (as listed by the FDA).
  - The other identified PROs showed varying levels of psychometric validity. Cognitive debrief interviews would enhance the level of content validity for all PROs.
- While the FACT-G RCC is an RCC-specific subscale, this PRO is not listed as a measure on the FACIT website. No further information was identified on this PRO.

Table 1. Overview of measurement properties by shortlisted PRO

Measurement properties	FACT-G	FACT-G item GP5	FACT-G RCC subscale	FKSI-15	FKSI-DRS	NFSKI-19	FACT-RNT	MDASI	EORTC-QLQ-C30	PRO-CTCAE
Content validity: Concept elicitation										
Content validity: KOL input			✓	✓	✓	✓				
Content validity: Cognitive interviewing										
Internal reliability				✓	✓	✓				
Test-retest reliability				✓						
Construct validity		✓		✓	✓	✓				
Known-groups validity	✓	✓		✓	✓	✓		✓		
Responsiveness/ability to detect change	✓			✓	✓	✓				
Interpretability of scores (MCID)				✓	✓					

CONCEPT MAPPING

- A preliminary conceptual model was developed 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 ccRCC.
- The NFKSI-19 provides the best overall coverage of the signs and symptoms of ccRCC.
- However, the MDASI and EORTC QLQ-C30 provide the best overall coverage of the impacts of ccRCC on daily life.

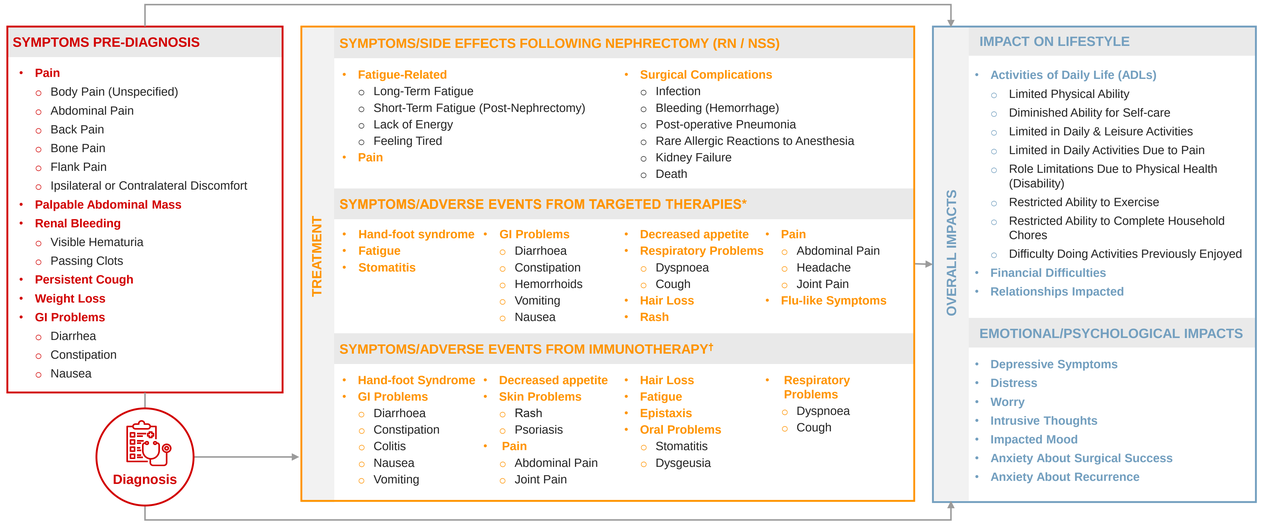

Figure 2. Preliminary conceptual model

KEY FINDINGS

- The patient experience of ccRCC is under-researched, and there are few published qualitative studies providing patient narratives about ccRCC symptoms and impacts.
- The evidence that exists, nonetheless, points to a disease that has a significant impact on patients' health-related quality of life.
- While ccRCC often presents with little or no symptoms at the early stages, advanced and metastatic disease cause significant symptoms and related impacts.
- Further qualitative research with patients is needed on what is important to measure in patients with ccRCC and how best to measure it.
- Based on the available evidence, the NFKSI-19, which includes the FKSI-DRS subscale, appears to be a leading contender for capturing symptoms and impacts of ccRCC and treatment. This is aligned with recommendations in the FDA draft guidance for core PROs for cancer clinical trials[5].
- Additional validation of these measures within the specific context of use is recommended.
- As therapeutic innovation evolves, further research is needed to capture the patient experience of not only the symptoms and impacts of ccRCC but also the treatment impact to ensure that instruments remain fit-for-purpose.

1. Ahmed et al. (2017). A new era and advances in renal cell carcinoma. Cancer Ther Oncol Int J, 6(4), 555692.
2. Harding et al. (2007). Symptom burden among patients with renal cell carcinoma (RCC): content for a symptom index. Health Qual Life Outcomes. 14;5:34.
3. FDA. (2009). Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. U.S. Food and Drug Administration. Retrieved from https://www.fda.gov/media/77832/download
4. FDA. (2024). FDA Patient-Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making. Retrieved from https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical
5. FDA. (2021). Core Patient-Reported Outcomes in Cancer Clinical Trials. Retrieved from https://www.fda.gov/drugs/clinical-outcome-assessment-coa-qualification-program/clinical-outcome-assessments-coa-qualification-program-submissions