

Development of Patient-Reported Outcome Measures (Symptoms and Impacts) in Adults with Pyruvate Kinase Deficiency

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BACKGROUND

- Pyruvate kinase (PK) deficiency is an ultra-rare hemolytic anemia caused by autosomal recessive mutations in the PKLR gene.¹
- An understanding of how signs and symptoms of pyruvate kinase (PK) deficiency can impact health-related quality of life (HRQoL) is important for optimal disease management and for determining how to measure the effects of interventions on HRQoL.
- A published evaluation of existing patient-reported outcome (PRO) measures recommended the European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (EORTC QLQ-C30) and Short Form 36-item Health Survey Version 2 (SF-36v2[®]) as appropriate for use in clinical trials in PK deficiency.²
- The SF-36v2[®] is a generic measure and the EORTC QLQ-C30 was developed for patients receiving treatment for cancer, so they may not be entirely relevant or applicable to patients with PK deficiency.

OBJECTIVES

- Primary: to develop de novo PRO measures for symptom and impact assessment in PK deficiency in accordance with the United States (US) Food and Drug Administration's (FDA) PRO guidance.³
- Secondary: to compare the newly developed PROs to the EORTC QLQ-C30 and SF-36v2[®].

METHODS

- Detailed methods regarding ethics approvals, recruitment processes, eligibility criteria, interview conduct, and analysis have been previously published.⁴
- Figure 1** summarizes the development of the de novo PRO measures.
- Items in the de novo measures were then compared to the domain structure, item concepts, and measurement characteristics of the EORTC QLQ-C30 and SF-36v2[®] to determine the degree of conceptual overlap and differences between the newly developed measures and recommended existing measures.

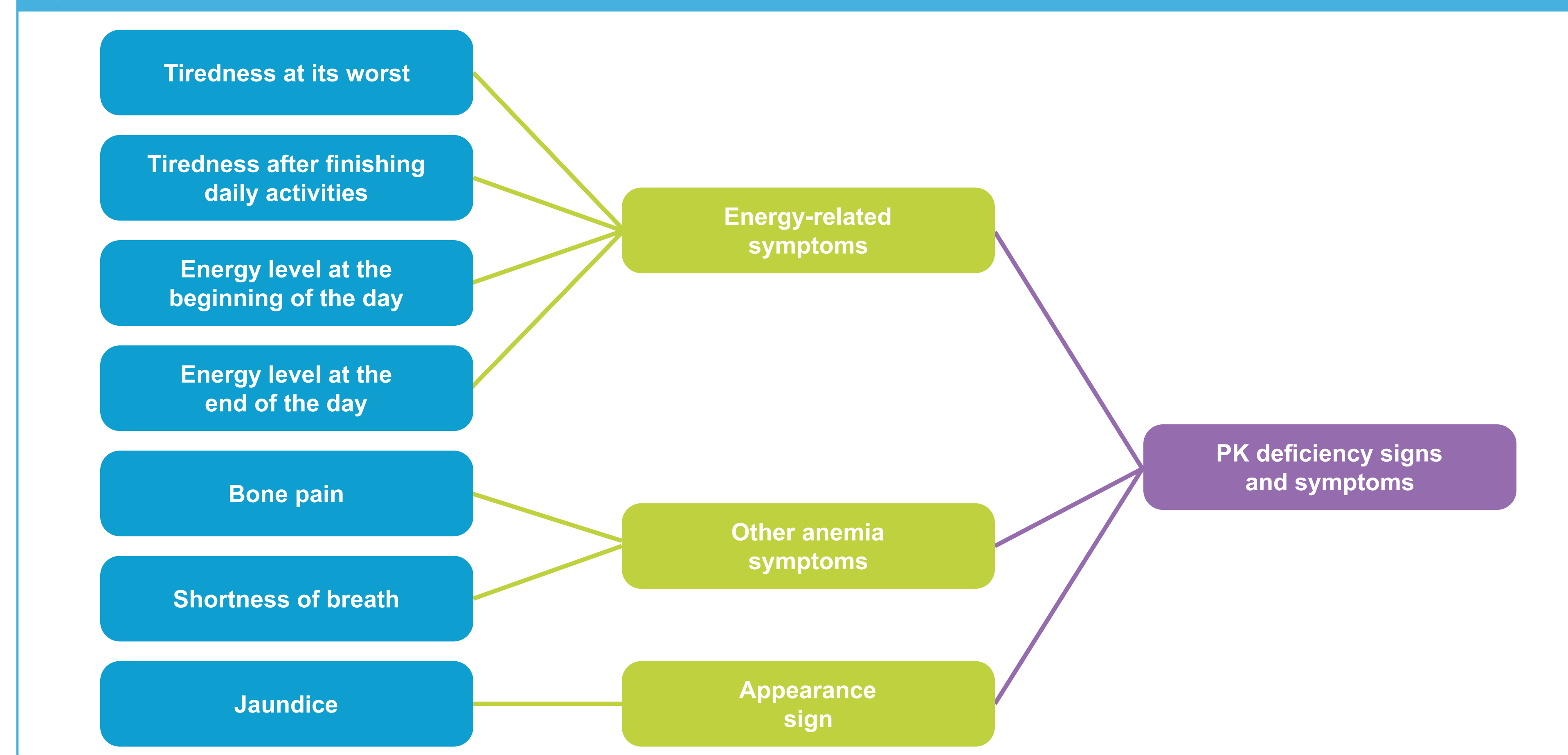
Figure 1. Overview of methods for PRO development^{4,6,7}



RESULTS

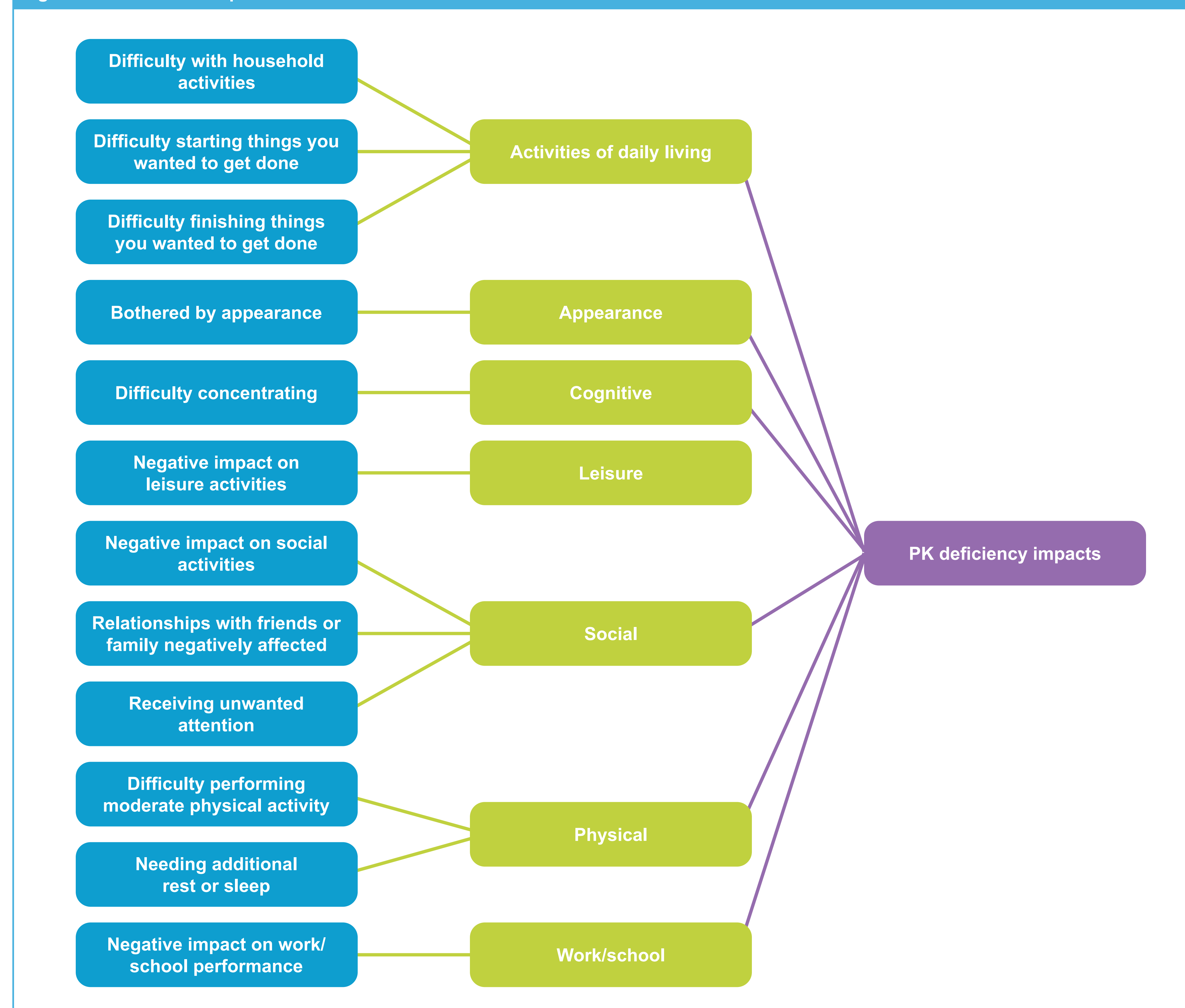
- The initial draft of the Pyruvate Kinase Deficiency Diary (PKDD) was an 11-item PRO measure of the core signs and symptoms of PK deficiency in adults, using an 11-point numeric rating scale (NRS) and a recall period of "over the past day."
 - Following the cognitive interviews, the description of the recall period was changed from "over the past day (from the time you woke up to the time you are completing this questionnaire)" to "today," as "today" is more appropriate for use in clinical trials, item-response scales were tweaked, and an item on worst overall tiredness was added.
 - Based on feedback from the FDA, an item measuring overall tiredness at its worst was added, the severity scale to measure jaundice was changed to a 5-point verbal descriptor severity scale, and the concepts "difficulty starting things you wanted to get done" and "difficulty finishing things you wanted to get done" were moved to the PKDIA.
- The second version of the PKDD following cognitive debriefing consisted of 7 items measuring 7 concepts. The revised conceptual model for the concepts and hypothesized domains are presented in **Figure 2**.

Figure 2. Revised conceptual framework for the PKDD



- The initial draft of the Pyruvate Kinase Deficiency Impact Assessment (PKDIA) was an 8-item PRO measure of common impacts of PK deficiency experienced by adults, using an 11-point NRS and a recall period of "over the past seven days."
 - Following the cognitive interviews, one item was moved and another was slightly reworded for clarity.
- The second version of the PKDIA, following cognitive debriefing, consists of 14 items measuring 12 concepts, with 2 skip pattern items. The revised conceptual framework for the PKDIA is presented in **Figure 3**.

Figure 3. Revised conceptual framework for the PKDIA



Comparison to EORTC QLQ-C30 and SF-36v2[®]

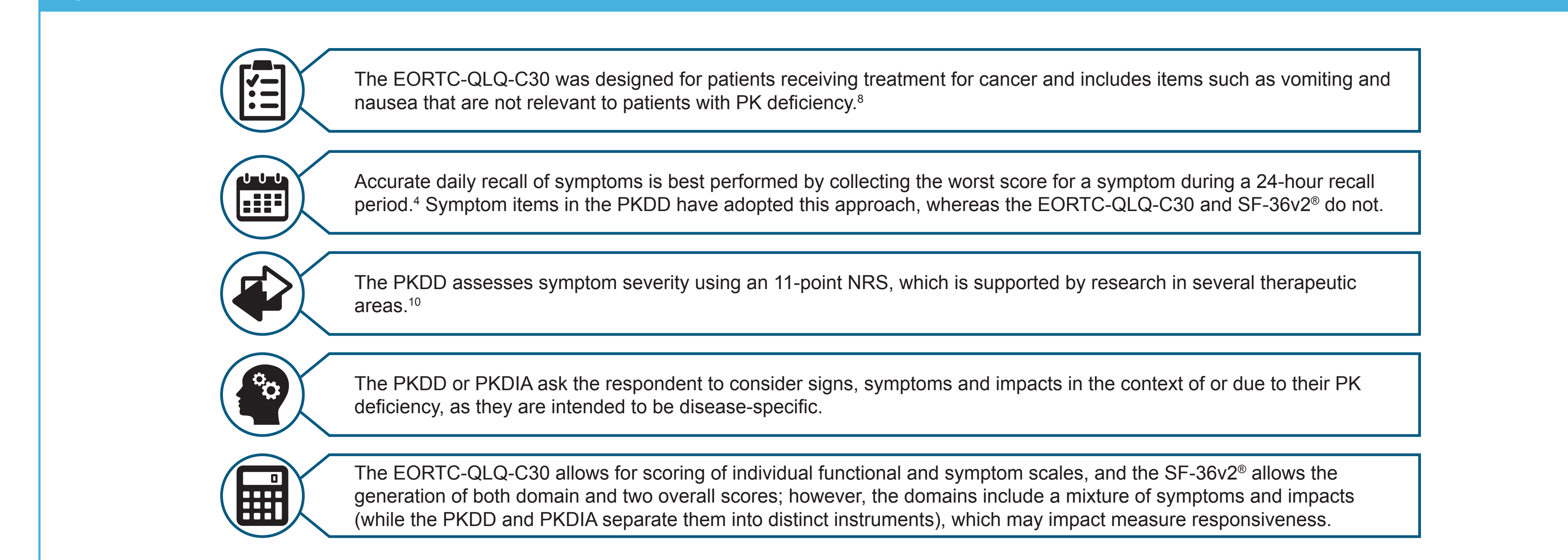
- The concepts included in the updated PKDD and PKDIA were compared to those included in the EORTC QLQ-C30 and SF-36v2[®], and organized by whether they were commonly represented in each assessment, a related concept is represented in the generic assessment, or the concept is not captured in the generic assessment (**Table 1**).

Table 1. Comparison of conceptual coverage of PKDD and PKDIA to EORTC QLQ-C30 and SF-36v2[®]

Measure	Domain	Concept	Included in EORTC QLQ-C30 ⁸	Included in SF-36v2 ⁷	Comparison summary
PKDD	Energy-related symptoms	Tiredness at its worst	Yes	Yes	<ul style="list-style-type: none"> Three of the 7 (43%) items in the PKDD were common to the EORTC-QLQ-C30, while 1 (14%) was related Four of the 7 (57%) items in the PKDD were common to the SF-36v2[®], while 1 (14%) was related
		Tired after finishing daily activities	Yes	Yes	
		Energy level at beginning of the day	No	Yes	
		Energy level at end of the day	No	Yes	
	Other anemia symptoms	Bone pain	Related concept	Related concept	
		Shortness of breath	Yes	No	
Appearance sign	Jaundice	No	No		
PKDIA	Activities of daily living	Household activities	Yes	No	<ul style="list-style-type: none"> Five of the 12 (42%) items in the PKDIA were common to the EORTC-QLQ-C30, while 1 (8%) was related Two of the 12 (17%) items in the PKDIA were common to the SF-36v2[®], while 3 (25%) were related
		Starting things you wanted to get done	No	Related concept	
		Finishing things you wanted to get done	No	Related concept	
	Appearance	Bothered by appearance	No	No	
	Cognitive	Difficulty concentrating	No	No	
	Leisure	Negative impact on leisure activities	No	No	
		Negative impact on social activities	Yes	Yes	
	Social	Relationships with friends or family negatively affected	Yes	No	
		Receiving unwanted attention	No	No	
	Physical	Difficulty performing moderate (e.g., walking on an incline or up stairs) physical activity	Related concept	Related concept	
		Needing additional rest or sleep	Yes	No	
	Work/school	Work/school performance	Yes	Yes	

- A comparison of other measurement characteristics between the measures can be found in **Figure 4**.

Figure 4. Comparison of other measurement characteristics of PKDD and PKDIA to EORTC QLQ-C30 and SF-36v2[®]



CONCLUSIONS

- The newly developed PKDD and PKDIA are more relevant and specific to the PK deficiency patient population and may better measure the burden of disease and effect of therapeutic interventions than the EORTC-QLQ-C30 and SF-36v2[®].
- Planned future work includes the assessment of the psychometric properties of these measures.

Disclosures

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