

BACKGROUND

- Glycogen storage disease Ia (GSDIa) is a rare (~0.8 in 100,000), serious, and potentially life-threatening disease caused by mutation of a single gene, *G6PC*, which encodes the G6Pase enzyme. G6Pase is expressed primarily in the liver, as well as the kidney and intestine, and is essential for the final step in the release of glucose from both the gluconeogenic and glycogenolysis pathways
- Clinical features include hepatomegaly, non-ketotic hypoglycemia, lactic acidosis, hyperlipidemia, hyperuricemia, nephropathy, impaired platelet function, and hepatocellular adenomas. The hypoglycemia can be severe, and if inadequately untreated, can lead to seizures, coma, and death
- Acute complications of GSDIa include risk of severe hypoglycemia, seizures, and death, as well as a negative impact on health-related quality of life (HRQoL) and autonomy. Chronic complications include growth failure, osteoporosis, hepatic adenomas, hepatocellular carcinoma, renal failure, and neuropathy
- There is no available cure for GSDIa, and no approved therapies directly target the underlying cause of the disease. Current management consists of rigorous dietary control with frequent corn starch intake to maintain a supply of glucose and avoidance of fasting
- Uncooked corn starch is typically administered every 3 to 5 hours, including at night. Treatment-related side effects include obesity, gastrointestinal disturbances, and secondary hyperinsulinism

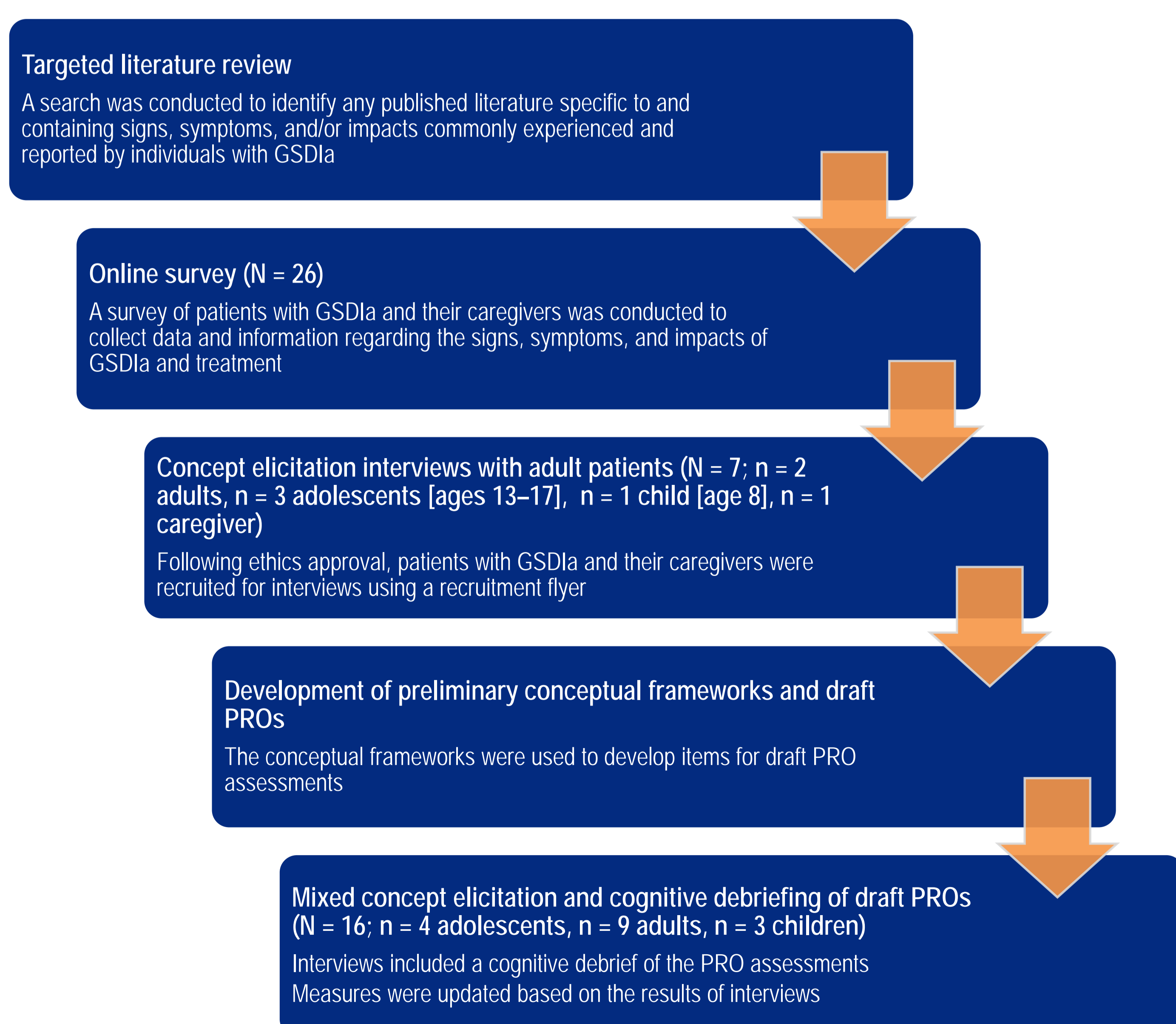
METHODS

- Results from an online survey, a targeted literature review, and concept-elicitation interviews were used to develop draft conceptual models
- Mixed-concept elicitation and cognitive interviews were conducted to debrief the draft questionnaires. All interviews were conducted with institutional review board/ethics approval
- Results from interviews were used to update the initial conceptual models and diaries
- Figure 1 presents the process used to develop the diaries

RESULTS

- Figures 2 and 3 are the preliminary conceptual frameworks from the initial literature review, survey, and N = 7 first-round concept elicitation interviews
- The GSD Functional Assessment Diary (FAD) was drafted to collect patient-reported occurrences of symptoms and impacts related to changes in blood sugar
- The GSD FAD consists of the GSDIa Morning Diary, designed to assess sleep and corn starch-related impacts after waking, and the GSDIa Evening Diary, intended to assess the energy-related, neurocognitive, and physical signs and symptoms of hypoglycemia physiology, as well as impacts on daily life (Figure 4)
- Thirteen hybrid concept elicitation and cognitive interviews were conducted with adolescent (n = 4) and adult (n = 9) participants to assess the content validity of the GSD FAD. Additionally, three children participated in cognitive interviews to debrief the pediatric version of the measures
- Overall, the instructions, items, and response options for the GSD FAD were interpreted as intended and were reported to be clear and relevant
- Based on the results of cognitive interviews, several concepts were removed from the GSDIa FAD due to lack of relevance or overlap with other concepts

Figure 1: Overview of methods



REFERENCES

1. U.S. Department of Health and Human Services. 2019. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rare-diseases-common-issues-drug-development-guidance-industry>. Accessed 17 October 2022.
2. Benjamin K, et al. *Value Health*. 2017; 20(7):838–55.

OBJECTIVES

- This research aimed to develop disease-specific patient-reported outcomes (PROs) for use in patients with GSDIa

Figures 2 and 3: Preliminary conceptual frameworks for signs and symptoms (left) and impacts (right) of GSDIa

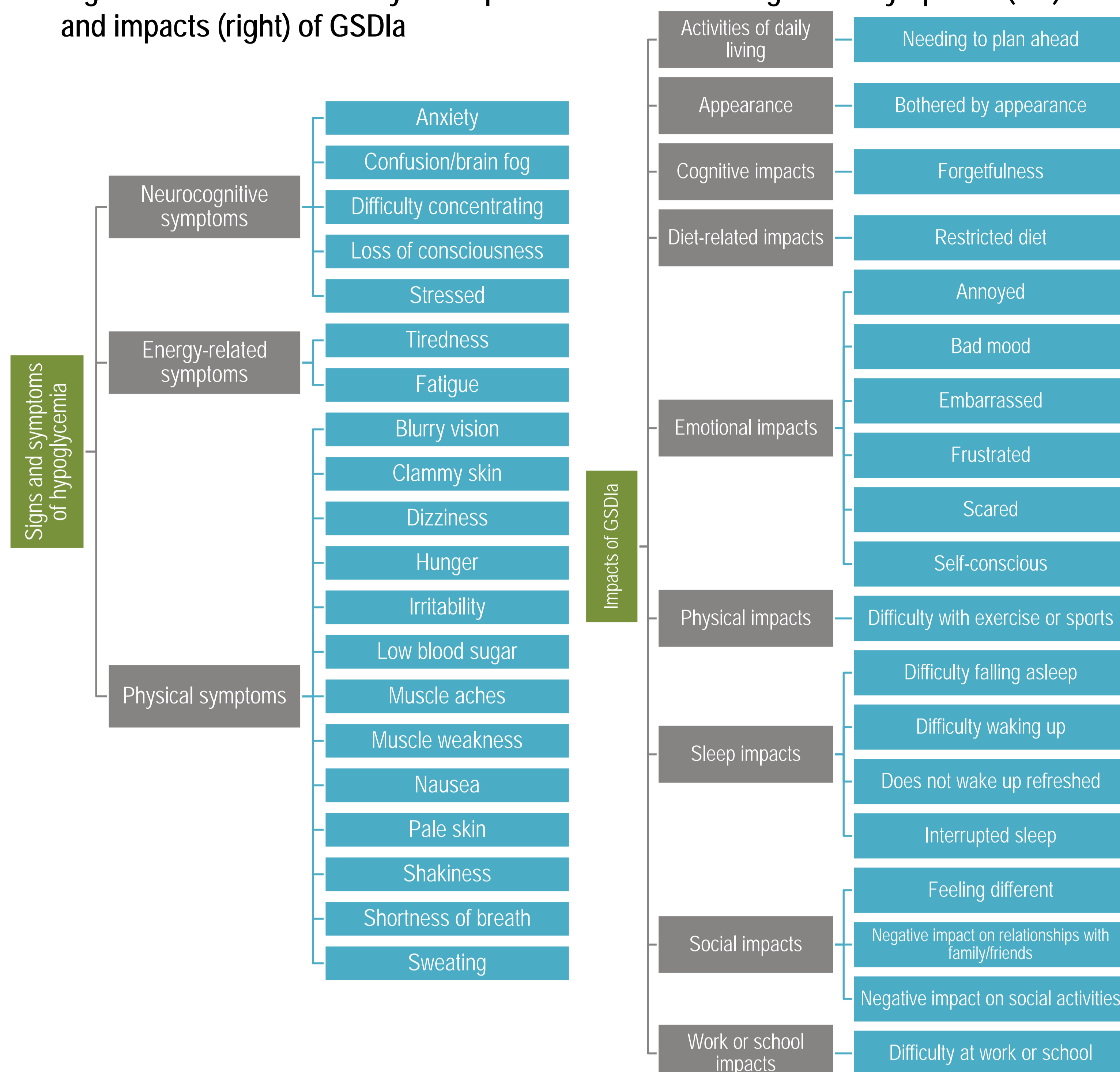


Figure 4: Overview of the GSD FAD following the conduct of the cognitive interviews

GSD FAD Morning Diary	GSD FAD Evening Diary (symptoms)	GSD FAD Evening Diary (impacts)
<ul style="list-style-type: none"> • Number of times woke up to take corn starch last night • Feel refreshed when waking* • Difficulty waking up • Feel tired after waking up 	<ul style="list-style-type: none"> • Number of times corn starch taken during the day • Feel like you had low blood sugar • Feel tired • Feel dizzy • Feel shaky • Clammy skin • Feel hungrier than usual • Trouble concentrating • Feel confused • Blurred vision • Feel sweaty when resting or standing still • Feel stressed • Trouble remembering things • Irritable • Muscle ache • Muscle weakness • Nausea • Pale skin • Trouble breathing 	<ul style="list-style-type: none"> • Feel different because you couldn't eat or drink what others had • Plan ahead due to GSDIa diet • Inconvenient to follow GSDIa diet • Difficult to play sports or exercise • Difficult to perform at work or school • Bothered by how appearance is affected by GSDIa • Feel annoyed • Feel frustrated • Feel scared • Feel self-conscious • Not participate in social activities • Negative impact on relationships with family and friends

Note: *, Strikethrough indicates the concept was removed based on the results of cognitive interviews. For the morning diary, the recall period is "from the time you went to bed last night until now". The response option for corn starch consumption is the "number of times", for the items on difficulty waking up and feeling tired the response options are "not at all", "a little bit", "somewhat", "quite a bit", "extremely".

For the evening diary, the recall period is either "today" or "the past 24 hours". The response option for corn starch consumption is the "number of times", for the majority of items the response options are "none of the time", "a little of the time", "some of the time", "most of the time" and "all of the time". Five items ("plan ahead", "follow your diet", "play sports or exercise", "bothered by appearance" and "perform at work or school") have different response options: "not at all", "a little bit", "somewhat", "quite a bit", "extremely" and the items on "play sports or exercise" and "perform at work or school" have "not applicable" options.

CONCLUSIONS

- A hybrid, pragmatic approach was taken for the development of the measures that incorporated the flexibility encouraged by the Food and Drug Administration Rare Disease Guidance for Industry, balancing the rarity of GSDIa with the rigor of valid PRO development
- Preliminary results demonstrate content validity suggesting that the GSD FAD captures the relevant concepts of hypoglycemic signs and symptoms from the patient perspective
- Study limitations include the small sample size, which was only an issue for the child version of the measures, as the adolescent and adult sample size of 13 was considered to be sufficient for a rare disease. Despite the study sample limitations, the GSDIa Morning Diary and GSDIa Evening Diary are the only measures specifically developed to assess the symptoms and impacts of GSDIa and tested for use in this population. The adolescent and adult version of the measures were debriefed with an adolescent as young as 13 years and the child version of the measures were debriefed with a child as young as 8 years; thus, the measures are considered to be appropriate for use in the intended age group
- Next steps will be to undergo psychometric validation utilizing a similar pragmatic approach