Title: Patient Perspective on Acute Hepatic Porphyria with Sporadic Attacks: A Chronic Disease with Substantial Health-Related Quality of Life Impacts

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Concept Elicitation Interview Guide:
Characterizing the Patient Experience of Acute Hepatic Porphyria

| Site ID:       | Participant ID: |
|---------------|-----------------|
| Date of interview:       | Time of interview: |
| Type of interview:         |                 |
| □ In-person         |                 |
| □ Telephone         |                 |
| Location of interview (if applicable): | |
| Name of interviewer: | |

6 April 2020
Part 1: 
**Interviewer Instructions**

**Prior to the interview**

- Verify receipt of written informed consent and review for completeness
- Have the participant complete the questions in Appendix A and review for completeness
- Review Demographic and Health Information Form for completeness
- Confirm the type of acute porphyria (AP) that the participant has using the completed Screening Form:
  - Acute intermittent porphyria (AIP)
  - Variegate porphyria (VP)
  - Hereditary coproporphyria (HCP)
  - ALA dehydratase deficient porphyria (ADP)

**During the interview**

- This interview guide is semi-structured in nature and meant to serve as a basis for the discussion. Actively listen, probe as necessary, and take note of nonverbal communication (e.g., long pauses, facial expressions, gestures). Specifically, the interviewer should be aware of the following:
  - Probes (i.e., specific, targeted questions) are to be used to clarify ideas reported spontaneously by participants, as well as to explore concepts that participants have not reported in response to an open-ended line of questioning. Participants should be given sufficient time to respond to questions before more specific probes are used.
  - Non-verbal cues (e.g., facial expressions indicating rejection or acceptance of one of your questions) and communication (e.g., nodding or shaking their head, pointing to identify the location of a sign or symptom) can be informative, especially when discussing potentially sensitive information. Invite the participant to explain his/her feelings or actions and remind the participant that since the interview is being audio-
After the interview

- Thank the participant and ensure the he/she is compensated for his/her time.

- Write down brief overall impressions of the interview immediately after it is completed, making sure to note any issues encountered during the interview that may explain the quality or quantity of the data. Overall impressions can be extremely useful and informative for the subsequent interviews.
Part 2:
Study Introduction
[Duration: 5/90 minutes]

Introduction

- Thank you for your interest and willingness to be a part of this study.

- My name is [first name] and I work for Endpoint Outcomes, a research consulting company that works with pharmaceutical companies to understand patients’ experiences with various health conditions. I will be interviewing you today.

What to expect

- For this study, we are gathering information from people who have a type of acute porphyria, or AP. I will be asking you some questions in order to help us better understand your experience living with acute porphyria, including: your journey to diagnosis, the symptoms you experience, how those symptoms impact your life, and your treatment experience.

- The information you provide us will be used to better understand the experience of patients with symptomatic AP.

- Our interview is scheduled to last about 90 minutes.

- Please understand that there are no right or wrong answers. We welcome you to speak freely; your opinions and perspectives are appreciated. If you need to take a break or would like to stop the interview at any time, you are free to do so. You also do not have to answer any of the interview questions if you don’t want to.

- I, as well as other researchers involved in this study, have been trained to maintain participant confidentiality. Personally identifying information, such as your name and contact information, will remain with Endpoint Outcomes and will only be accessible to research staff. It will not be shared with the sponsor of this research, Alnylam Pharmaceuticals.
• [If applicable] A colleague of mine has been invited to observe this interview for training purposes, but they will not participate in this discussion. [He/she] will only observe our conversation.

• Our conversation today will be audio-recorded so that we have an accurate record of the discussion. Please speak clearly and loudly so that you can be heard on the audio-recording.

• Do I have your permission to audio-record this session?
  
  o [If yes:] Thank you. I will ask you again for the record once I have the audio-recorder turned on.

  o [If no:] Do not proceed with the interview.

• Do you have any questions at this point?

**Once the audio-recorder is turned on**

• This is interviewer, [state your name], here with participant [state participant’s ID].

• Do I have your permission to audio-record this interview?
Part 3:
Overall Experience Living with AHP
[Duration: 5/90 minutes]

**Icebreaker and participant’s words**

- How do you typically refer to your condition?
- What does [participant’s preferred term for condition] mean to you? How would you describe it?
- What is it like to have [participant’s preferred term for condition]?
  - How has having [participant’s preferred term for condition] impacted your life?
  - What is a typical day like living with [participant’s preferred term for condition]? Week? Month?
  - When thinking about your overall experience living with [participant’s preferred term for condition], what has had the greatest impact on you?
Part 4:

AHP Attack Experience

[Duration: 15/90 minutes]

**Attack Experience**

- Are you familiar with the term *attack* as it relates to *[participant’s preferred term for condition]*?
  - *[If yes, ask]*: When you hear the word attack, what does that mean to you in terms of your AP? What does it feel like?
  - *[If no, explain]*: An attack is an episode of increasingly severe AP symptoms that may require hospitalization, urgent care intervention, or an increase use of medication used to manage your porphyria.
    - How do you typically refer to an attack?

*Note: Confirm that the participant understands the term “attack” as it relates to their AP, and note when necessary that you will be using this term throughout the rest of the interview.*

- When was your last porphyria attack? What happened during this attack?
- Think about all of the porphyria attacks you have experienced, when was your worst attack? What happened during this attack?
  - Are all attacks the same or are they different? Please explain.
    - *[If different, ask]*: How do the attacks differ? Are they different in terms of...
      - The symptoms experienced?
      - How bad or severe the attacks are?
      - How long the attacks last?
- Thinking about your overall experience with *[participant’s preferred term for condition]*, how would you describe the frequency that your attacks have occurred since the onset of your porphyria-related symptoms?
  - How many porphyria attacks have you had in the past year?
CE Interviews in AHP

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|---------|---|---|----------------|
| Project ID | Site ID | Participant ID |

- Has your **attack frequency** increased, decreased, or stayed the same since your diagnosis?
  - [If increased/decreased, ask]: What factors do you think contributed to the change in frequency?
- In general, what **typically happens during an attack**? For example, what symptoms do you typically experience during your attacks and how do you manage these symptoms when they occur.
  - [If not spontaneously mentioned, ask]: **During an attack**, do you **typically experience**...
    - Abdominal pain
    - Back pain
    - Arm/leg pain
    - Chest pain
    - Muscle pain
    - Other pain (e.g. skin)
    - Numbness
    - Muscle weakness
    - Headache
    - Fatigue or tiredness
    - Heartburn
    - Nausea
    - Vomiting
    - Constipation
    - Diarrhea
    - Loss of appetite
- Confusion (sometimes described as a “brain fog”)
- Anxiety
- Feeling sad
- Hallucinations
- Trouble sleeping
- Changes in urine color (e.g. darkening, brown or red in appearance)
- Rapid heart beat
- Sweating
- Skin rash
- Seizures
- Paralysis
- High blood pressure
- Other, please specify

**Note:** If the participant indicates that a given symptom does not typically occur during their attacks [participant’s preferred term for condition], ask the following questions.

- Since this symptom does not typically occur when you have an attack, have you ever experienced this symptom during any of your attacks?
  - [If yes, ask]: Please briefly describe the attack during which you experienced this symptom.
- Can you typically tell when you are about to have an attack or does it happen without warning? Please explain.
  - Do you know what typically triggers (i.e., brings on, causes) an attack for you?
    - [If yes, ask]: Is there anything you do to prevent an attack from happening?
      - What are your typical triggers?
• **How did you manage your most recent attack?** How did you manage your **worst attack ever?**
  
  o **What treatments did you use during your most recent attack? Your worst attack?**
    
    ▪ Intravenous pain medications?
    
    ▪ Glucose infusions?
    
    ▪ Hemin treatment?
    
    ▪ Were these used at home, or in a healthcare facility?

• **How do [participant’s preferred term for condition] attacks impact your life?**
  
  o Leading up to an attack?

  o At the time of the attack?

  o After the attack?
Part 4:

Chronic AHP Symptoms

[Duration: 30/90 minutes]

**Chronic symptoms of AHP**

*Note:* Use the tracking grid at the end of the interview guide to track the signs and symptoms of acute hepatic porphyria discussed by the participant.

- I’d like to learn more about your day-to-day experience living with [participant’s preferred term for condition]. In general, how do you feel on most days?
  - What is a **typical day** for you in terms of your [participant’s preferred term for condition]? Do you experience any symptoms of [participant’s preferred term for condition] on a regular basis?

- Do you experience symptoms when not having an AP-associated attack? Please explain.
  - Abdominal pain
  - Back pain
  - Arm/leg pain
  - Chest pain
  - Muscle pain
  - Other pain (e.g. skin)
  - Numbness
  - Muscle weakness
  - Headache
  - Fatigue or tiredness
  - Heartburn
  - Nausea
  - Vomiting
- Constipation
- Diarrhea
- Loss of appetite
- Confusion (sometimes described as a “brain fog”)
- Anxiety
- Feeling sad
- Hallucinations
- Trouble sleeping
- Changes in urine color (e.g. darkening, brown or red in appearance)
- Rapid heart beat
- Sweating
- Skin rash
- Other, please specify

**Note:** For each sign or symptom experienced between attacks, ask the following questions if it has not already been spontaneously reported by the participant.

- Differentiation: Do you also experience this [symptom] during attacks?
  - [If yes, ask]: How does this symptom differ when experienced during an attack versus in between attacks?

- Explanation: How would you describe [sign/symptom] to someone who has never experienced it? What does it feel like?

- Frequency: How often does [sign/symptom] occur? Daily? Weekly? Monthly?

- Duration: How long does [sign/symptom] last?

- Severity: How bad does [sign/symptom] get at its worst? On a scale of 0 to 10, where 0 is no [sign/symptom] and 10 [sign/symptom] as bad as you can imagine, how bad does it get?

- Location (if applicable): Where do you experience [sign/symptom] on your body?
Meaningful change: Thinking about an improvement in your [symptom], what would need to improve for it to be meaningful to you? Meaningful means an improvement in your health where you feel better – it does not mean that your [symptom] is completely cured.

- Frequency of [symptom]?
- Duration of [symptom]?
- Severity of [symptom]?

Treatment: How do you manage the [symptom]?

- Do you take any medications or other interventions to manage [symptom]?
- Do you see a health care provider for the treatment of [symptom] between attacks?

**Bothersome exercise**

*Note: Using the bothersome ratings sheet appended to the interview guide, list all of the signs and symptoms reported by the participant when not having an attack and provide the worksheet to the participant. If the participant is completing a phone interview, describe the bothersome rating scale prior to completing the exercise.*

- For the next part of the interview, I’d like you to tell me overall how much each symptom you experience when not having an attack due to [participant’s preferred term for condition] bothers you. A “0” means not bothersome at all and a “10” means extremely bothersome.

- When you hear the word bothersome, what does it mean to you in terms of your [participant’s preferred term for condition] symptoms? How are the symptoms bothersome?

- Of all the symptoms that you experience [list symptoms], which are the most important to treat? Why?

- Of all the symptoms that you experience [list symptoms], which ones impact your life the most? Why?

- Can you describe your experience with the treatment(s) to manage your [most bothersome symptom(s)]?
Part 5:
Chronic AHP Impacts

[Duration: 25/90 minutes]

**Impacts of acute hepatic porphyria**

**Note:** Use the tracking grid at the end of the interview guide to track the chronic impacts of AP discussed by the participant. If impacts were reported previously, begin with following-up on them.

- In **between** attacks, how has having [participant’s preferred term for condition] impacted your life?
- Earlier you mentioned [impact], could you please tell me a little more about that?
- How (else) does [participant’s preferred term for condition] affect your life **between** attacks?

**Note:** For each impact, ask the following questions if it has not already been spontaneously reported by the participant.

- **Symptoms:** Are there specific symptoms that cause [impact]? If so, which symptoms?
- **Frequency:** How often do you experience [impact]? Daily? Weekly? Monthly?
- **Attribution:** Do you think it is related to your [participant’s preferred term for condition]? Why or why not?
  - [If relatedness seems questionable from the interviewer’s perspective, ask]: Is there anything else that you feel this [impact] could be related to?
- **Severity:** How bad or severe is [impact] when you experience it?
- **Duration:** [When appropriate] How long does [impact] last when you experience it?
- **Meaningful improvement:** Thinking about improvement in your [impact], what would need to improve for it to be meaningful to you?
  - How often you have [impact]?
  - How bothersome the [impact] is?
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- How difficult it is to do [limitation, if applicable]?

- **Situation** (if unclear): Is this mainly due to the attacks or the symptoms between the attack?

- **Treatment**: How do you manage the [impact]?
  - Do you take any medications or other interventions to manage [impact]?
  - Do you see a health care provider for the treatment of [impact] between attacks?

**Note:** After discussing impacts spontaneously described by the participant, ask the following questions. For each new impact reported, ask the series of questions listed above.

- Does your [participant’s preferred term for condition] change the way you do things? If so, how?
  - Does it stop you from doing things? What things? Why?

- Does your [participant’s preferred term for condition] affect your daily activities? If so, what activities?
  - Does your [participant’s preferred term for condition] affect activities you do in your free time? If so, how?

- Does your [participant’s preferred term for condition] affect your ability to engage in physical activities, such as exercise or sports? If so, how?

- Has your [participant’s preferred term for condition] caused or is it thought to be related to any additional medical complications, such as chronic high blood pressure, urinary dysfunction, liver dysfunction, liver cancer, pancreatitis, type II diabetes or chronic kidney disease?

- Does your [participant’s preferred term for condition] affect your mental state?
  - Do you ever have difficulty remembering things or concentrating? Please explain.

- Does your [participant’s preferred term for condition] affect your social life? If so, how?
  - Does it affect your relationships with:
    - Friends?
    - Family members?
- Spouse/partner?

- Does your [participant’s preferred term for condition] affect you at work or school? If so, how?

- Does your [participant’s preferred term for condition] affect you financially? If so, how?

- Does your [participant’s preferred term for condition] affect your appearance? If so, how?

- Does your [participant’s preferred term for condition] affect you emotionally? If so, how?
  - Does your [participant’s preferred term for condition] affect your mood? If so, how?

- Does your [participant’s preferred term for condition] affect your sleep? If so, how?

- Does your [participant’s preferred term for condition] affect your sex life? If so, how?

- Do you experience any other impacts related to your [participant’s preferred term for condition] that we have not discussed yet?

**Bothersome exercise**

**Note:** Using the bothersome ratings sheet appended to the interview guide, list all of the impacts reported by the participant and provide the worksheet to the participant. If the participant is completing a phone interview, describe the bothersome rating scale prior to completing the exercise.

- For the next part of the interview, I’d like you to tell me overall how much each impact bothers you. A “0” means not bothersome at all and a “10” means extremely bothersome.
Part 6 (if time allows):

Diagnostic Journey

(Duration: 10/90 minutes)

Diagnostic journey

- First, I would like to discuss your experience regarding your diagnosis. Can you describe how you were diagnosed with [participant’s preferred term for condition]?
  - When were you diagnosed with [participant’s preferred term for condition]?
  - What porphyria-related tests have you received?
    - Genetic testing?
      - Was this used to confirm your diagnosis?
    - Biochemical testing
      - Urinary ALA?
        - Was this used to confirm your diagnosis?
      - Urinary PBG?
        - Was this used to confirm your diagnosis?
    - Urinary porphyrins? Other?
      - Were these used to confirm your diagnosis?
  - Were you ever misdiagnosed or treated for something else before learning you had [participant’s preferred term for condition]?
    - [If yes, ask]: What were you diagnosed with? How were you treated (including medical intervention)?

- Did you experience any difficulties or challenges obtaining a diagnosis? If so, what were they?

Thank you!

- Thank you for your time. We appreciate you sharing your experiences and providing feedback.
Participant Handout: Bothersome Ratings for AHP concepts

Instructions: Please rate how bothersome overall each concept we’ve discussed is to you.

1. Overall, how bothersome to you is __________? 

Not bothersome at all: 0

Extremely bothersome: 10
### Interviewer Tool: Symptoms Tracking Grid

| Sign/Symptom | Location | Frequency | Duration | Severity | When | Trigger |
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**Interviewer Tool: Impacts Tracking Grid**

| Impact | Due to: [symptom] | Frequency | Duration | Severity | When |
|--------|-------------------|-----------|----------|----------|------|
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Appendix A: Pre-interview questionnaire

Please answer the following questions about your general health.

1. In general, would you say your health is:
   - □ Excellent
   - □ Very good
   - □ Good
   - □ Fair
   - □ Poor

Instructions: The following two questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

2. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf:
   - □ Yes, limited a lot
   - □ Yes, limited a little
   - □ No, not limited at all

3. Climbing several flights of stairs:
   - □ Yes, limited a lot
   - □ Yes, limited a little
   - □ No, not limited at all

Instructions: During the past 4 weeks have you had any of the following problems with your work or other regular activities as a result of your physical health?

4. Accomplished less than you would like:
   - □ Yes
   - □ No

5. Were limited in the kind of work or other activities:
   - □ Yes
   - □ No
**Instructions:** During the past 4 weeks, were you limited in the kind of work you do or other regular activities as a result of any emotional problems (such as feeling depressed or anxious)?

6. Accomplished less than you would like:
   - [ ] Yes
   - [ ] No

7. Didn’t do work or other activities as carefully as usual:
   - [ ] Yes
   - [ ] No

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?
   - [ ] Not at all
   - [ ] A little bit
   - [ ] Moderately
   - [ ] Quite a bit
   - [ ] Extremely

**Instructions:** The next three questions are about how you feel and how things have been during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks:

9. Have you felt calm and peaceful?
   - [ ] All of the time
   - [ ] Most of the time
   - [ ] A good bit of the time
   - [ ] Some of the time
   - [ ] A little of the time
   - [ ] None of the time

10. Did you have a lot of energy?
    - [ ] All of the time
    - [ ] Most of the time
    - [ ] A good bit of the time
    - [ ] Some of the time
    - [ ] A little of the time
    - [ ] None of the time
11. Have you felt downhearted and blue?

☐ All of the time
☐ Most of the time
☐ A good bit of the time
☐ Some of the time
☐ A little of the time
☐ None of the time

12. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

☐ All of the time
☐ Most of the time
☐ A good bit of the time
☐ Some of the time
☐ A little of the time
☐ None of the time
Please answer the following questions about your AP.

Over the past 2 years, how satisfied are with the management of your acute attacks?

|                                           | Very dissatisfied | Dissatisfied | Neither satisfied nor dissatisfied | Satisfied | Very satisfied | Not applicable |
|-------------------------------------------|-------------------|--------------|------------------------------------|-----------|----------------|----------------|
| 1. Knowledge of clinicians and other medical staff | □                 | □            | □                                 | □         | □              | □              |
| 2. Recognition of the problem             | □                 | □            | □                                 | □         | □              | □              |
| 3. Timely treatment                       | □                 | □            | □                                 | □         | □              | □              |
| 4. Treatment effectiveness               | □                 | □            | □                                 | □         | □              | □              |

5. Which of the following symptoms do you experience due to porphyria when you are not having an acute attack?

Please select the option(s) that apply to you:

- □ Nausea
- □ Pain
- □ Photosensitivity (e.g., pain, irritation and/or blistering after sun exposure)
- □ Skin lesions
- □ Trouble sleeping
- □ Trouble concentrating
- □ Fatigue or tiredness
- □ Weakness or paralysis
- □ Lack of coordination/falling
- □ Emotional distress (e.g. anxiety, depression)
- □ I experience other symptoms (please specify): ________________________________
- □ I do not experience any porphyria-related symptoms between attacks

Please indicate to what extent acute porphyria impacts the following aspects of your life:

|                  | Not at all | Slightly | Moderately | Severely | Extremely | Not applicable |
|------------------|------------|----------|------------|----------|-----------|----------------|
| 6. Social life   | □          | □        | □          | □        | □         | □              |
| 7. Pain/discomfort | □         | □        | □          | □        | □         | □              |
| 8. Mobility      | □          | □        | □          | □        | □         | □              |
Please indicate to what extent acute porphyria impacts the following activities:

|   | I have no problem doing this | I have slight problems doing this | I have moderate problems doing this | I have severe problems doing this | I am unable to do this | Not applicable |
|---|------------------------------|-----------------------------------|-------------------------------------|----------------------------------|-----------------------|----------------|
| 16. Self-care (i.e., washing and dressing yourself) | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 17. Work (i.e., the ability to perform your work as would be normally expected from someone in your function/role) | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 18. Household activities | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 19. Leisure activities | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |