Challenges in recruiting patients for the linguistic validation of PRO instruments developed for rare diseases: a case study with Alagille Syndrome

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OBJECTIVES

- Genetic liver diseases are common causes of severe cholestasis and progressive liver disease in children. Alagille Syndrome (ALGS) is a rare multisystem disorder due to defects in components of the Notch signaling pathway, mostly common due to mutation in AGT1 (ALGS type 1), but in a small proportion of cases mutation in NOTCH2 (ALGS type 2). Progressive familial intrahepatic cholestasis (PFIC) refers to a heterogeneous group of autosomal recessive disorders.1 The pathophysiology of cholestasis differs among these disorders. ALGS is associated with a paucity of interlobular bile ducts while PFIC is associated with defects in bile transporters.

- Itching is a key symptom in ALGS and PFIC, which can significantly impact a child's daily life.2

- Itch-Reported Outcome (ItchRO) instruments are a paired set of instruments:
  - ItchRO(Obs) is the parent/caregiver report on child’s itch-related symptoms.
  - ItchRO(P) is the patient self-report on itching.

- During validation in US English as electronic morning and evening diaries to assess itch-related symptom severity (rubbing, scratching, skin damage, sleep disturbances, or irritability) in pediatric patients suffering from rare cholestatic liver diseases such as ALGS and PFIC.

- Questions are designed as follows:

<table>
<thead>
<tr>
<th>ItchRO(Obs)</th>
<th>ItchRO(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary: Global assessment of itch signs and symptom severity</td>
<td>Itch severity</td>
</tr>
<tr>
<td>Exploratory: Severity of scratching</td>
<td>Sleep disturbance</td>
</tr>
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<td>Skin damage</td>
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</table>

- This research presents the recruitment challenges faced during the linguistic validation of the ItchRO into French, German, Polish, and Spanish (for Spain and the USA) in ALGS or PFIC patients.

METHODS

- The ItchRO instruments were translated following the Mapi linguistic validation process (Figure 1), which is in compliance with the ISPOR guidelines.4

- During the final step, cognitive debriefing interviews were to be performed with five children with ALGS (patient report) and five parents (observer report).

- Key inclusion criteria were: children aged 5-9 years with ALGS or PFIC who were also experiencing itching, and parents of the children interviewed.

RESULTS

- Given the rarity of the conditions, recruitment for the cognitive interviews was challenging and threatened to delay the clinical trial program. Thus, recruitment was extended to include children aged 3-17 years, and, in Spain and Germany, patients with alternative pathologies that manifested primarily with generalized pruritus were also included.

- The final sample of patients included 20 with ALGS (France n=5; Poland n=5; Germany n=3; Spain n=2; USA n=5), two with PFIC (Spain), two with atopic dermatitis (AD) (Germany) and one with contact dermatitis (CD) (Spain). In the total population, 44% (n=11) patients were female, and the average age was 8.4 (range 3-17), 84% (n=21) of caregivers were female, and the average age was 38.7 (range 25-48). 72% had a high school education, and 28% had some college or more. See Tables 1 and 2.

- The ItchRO translations were well understood. The general impression reported was favorable. On the whole, the translations were found to be clear, easily worded and of a reasonable length.

- No differential patterns in understanding were observed between those who met the original inclusion criteria vs. those who met the expanded inclusion criteria. In addition, the expansion of the recruitment criteria did not impact negatively on the quality of the cognitive debriefing methods.

CONCLUSIONS

- Children’s interpretation of items within a questionnaire can vary across age ranges, developmental ability and disease. Often children with a disease will understand difficult concepts, even at a young age, if the concept is relevant to their disease state.

- As a result, testing of pediatric patient understanding should be across age ranges within the patient population, rather than with lay people. However, in rare diseases pediatric patient recruitment across age groups can be challenging.

- Our results suggest that widening the recruitment strategy to broader age ranges and to diseases with similar symptom and impact characteristics does not negatively impact cognitive debriefing quality or results. Indeed, ensuring that children have a condition that manifests in similar ways can lead to a better understanding of the content validity of the questionnaire in pediatric populations.

- However, such a strategy should only be undertaken when the appropriate methods have been tried and when recruitment challenges may cause delays in clinical trial research for rare diseases where there is an urgent need for treatment.

Table 1. Demographic characteristics of patients involved in cognitive interviews

<table>
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<th>Germany</th>
<th>Poland</th>
<th>Spain</th>
<th>USA</th>
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<tbody>
<tr>
<td>Sex (M/F)</td>
<td>15/5</td>
<td>13/3</td>
<td>10/3</td>
<td>10/3</td>
<td>12/4</td>
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<tr>
<td>Age (yr)</td>
<td>10</td>
<td>12</td>
<td>8</td>
<td>9</td>
<td>8</td>
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<tr>
<td>Sex (M/F)</td>
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<td>30/20</td>
<td>27/3</td>
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Table 2. Demographic characteristics of patients involved in cognitive interviews

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REFERENCES


Disclosures

The study was funded by Lumenia Pharmaceuticals Inc., one of the Shire group of companies. C. Kennedy is employee of Shire, formerly Lumenia Pharmaceuticals.

L. Abetz-Webb is CEO of Patient-Centred Outcome Assessments, consulting for Shire.

J. Lambe is employee of Mapi. Oxford PharmaGenesis was funded by Shire to provide writing and editorial support to the authors.

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