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ORIGINAL RESEARCH ARTICLE

Development and Psychometric Evaluation of the Life Interference Questionnaire for Growth Hormone Deficiency (LIQ-GHD) to Assess Growth Hormone Injection Burden in Children and Adults

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Abstract

Background Current recombinant human growth hormone (r-hGH) replacement therapy involves long-term daily subcutaneous injections to treat growth hormone deficiency (GHD) in children and adults. Daily r-hGH injections can be burdensome, often resulting in poor treatment compliance. Clinical outcome assessments (COAs) can capture the burden of these injections from the patient (and caregiver) perspective and may demonstrate the benefit of a less-frequent r-hGH injection regimen, which may ultimately improve treatment compliance and long-term outcomes.

Objective To address this knowledge gap, qualitative research was conducted to inform the development of a new Life Interference Questionnaire for Growth Hormone Deficiency (LIQ-GHD), designed to measure the experiences of patients taking r-hGH GHD injections. A second objective was to evaluate the hypothesized factor structure and preliminary performance of the LIQ-GHD in a cross-sectional observational study.

Methods An empirical literature review and expert advice meetings were conducted to inform development of the draft LIQ-GHD (pediatric and adult versions). In-person concept elicitation and cognitive debriefing interviews were conducted with GHD patients (and patient dyads including caregivers) to explore and confirm concept coverage and evaluate respondents' ability to understand the questionnaire. The draft LIQ-GHD was then tested in a cross-sectional field study involving pediatric and adult patients receiving daily r-hGH injections for GHD. The factor structure, reliability, and validity were analyzed for the overall sample and for pediatric, adolescent, and adult subgroups.

Results Results from the literature review and input from six experts were used to develop and refine the LIQ-GHD, with content covering pen ease of use; regimen convenience; life interference due to regimen; benefit/satisfaction/willingness to continue treatment; regimen choice/preference; intent to comply with regimen; injection-related signs/symptoms; and reasons for missed injections. Twenty-one patient interviews confirmed comprehensive concept coverage and patient/caregiver comprehension of the LIQ-GHD. A total of 224 patients ($n = 70$ children/caregiver dyads, $n = 79$ adolescents/caregiver dyads, $n = 75$ adults) participated in the field study. While most items showed floor effects, confirmatory factor analysis fit statistics were good for the overall sample (root mean square error of approximation = 0.07, comparative fit index = 0.98) and for the full pediatric sample after dropping co-dependent questions from the model. Cronbach's alpha (α) ranged from 0.746 to 0.905 and intra-class correlation coefficients ranged from 0.761 to 0.918 for the overall sample on LIQ-GHD domains. Scores correlated as predicted with an existing criterion measure in the overall sample and LIQ-GHD domain scores distinguished known groups as expected.

Conclusions The LIQ-GHD is a new COA for the measurement of r-hGH injection treatment burden. This research provides evidence supporting its content validity, hypothesized factor structure, score reliability, and construct validity in pediatric and adult populations.

1 Introduction

The prevalence of pediatric growth hormone deficiency (GHD) is estimated at approximately 1:4000 to 1:10,000 [1–4]. The most apparent feature of GHD in children is growth failure or growth restriction. Metabolic consequences include impaired lipid metabolism, impaired protein synthesis, and impaired bone mineralization. GHD in children may also impact psychosocial development, resulting in poor self-image and social isolation. Short stature is also linked to a decrease in quality of life (QoL) [5–7].

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Key Points

The Life Interference Questionnaire for Growth Hormone Deficiency (LIQ-GHD) is a newly developed questionnaire to evaluate the burden of growth hormone injections in children (and their caregivers) and adults.

A robust scientific instrument development approach was followed, yielding a tool with evidence of score reliability and validity.

Additional analysis and on-going use of this questionnaire in clinical trials is recommended.

Recombinant human growth hormone (r-hGH) replacement therapy has been available to safely and effectively treat adults and children with GHD for the last several decades to (i) increase height during childhood; (ii) attain adult height targets; (iii) minimize adverse events; (iv) achieve cost-effective treatment [8]; and (v) improve QoL (since taller height in children is associated with a higher QoL) [9].

Therapy with r-hGH involves administration of subcutaneous injections given daily over the long-term (e.g., ≥5 years), until final height has been attained. Given the duration of r-hGH treatment, patients often do not optimally comply with treatment [10, 11], and non-compliance has been shown to be the most common cause of reduced height velocity in children [11–13]. Studies have also demonstrated a reduction in adherence over time [13].

There are many reasons for non-compliance, including complexity of regimen, difficulty in understanding potential treatment benefits, long-term treatment duration, perception of injections as painful, adolescence, and living in a busy, chaotic household [14–17]. However, the current literature suggests that little information exists describing the burden of administering daily growth hormone (GH) injections over the long-term. Further, there are currently no clinical outcome assessment (COA) measures available that can adequately assess the impacts and burden of r-hGH injections.

Since the administration of the injection to children often involves both the caregiver and patient, COA measures designed to evaluate r-hGH injection treatment burden should include feedback from both parties. A dyad approach to COA measurement (i.e., where the patient and caregiver read and answer questions together) may be useful to overcome concordance issues that arise in obtaining information from the caregiver or patient separately [18]. Although little research has been conducted to evaluate dyad-administered COAs, a study by Ungar et al. [19] suggested that a dyad approach could help children by enabling them to answer questionnaire items accurately, providing additional support in terms of comprehension or recall problems.

Thus, the overall goal of this research was to develop a new questionnaire, the Life Interference Questionnaire for Growth Hormone Deficiency (LIQ-GHD), to assess r-hGH injection treatment burden. The LIQ-GHD addresses an important measurement gap and offers versions for both adult and child–parent dyad administration.

The research summarizing the development and preliminary psychometric evaluation of the LIQ-GHD is presented here.

2 Objectives

The specific objectives of this research were to (i) establish evidence of content validity for the LIQ-GHD through qualitative research activities; and (ii) evaluate the hypothesized factor structure and preliminary score psychometric performance in a cross-sectional observational study.

3 Methods

As described in this section, the LIQ-GHD was developed and evaluated in a manner consistent with guidance provided by the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) "Pediatric Patient-Reported Outcome Instruments for Research to Support Medical Product Labeling: Report of the ISPOR PRO Good Research Practices for the Assessment of Children and Adolescents Task Force" [20–22].

3.1 Establishing Evidence of Content Validity

'Content validity' refers to the extent to which a questionnaire measures concepts of interest in ways that are relevant and understandable to patients, comprehensive, and appropriate for the questionnaire's intended context of use [20]. The target patient population for the developed questionnaire was adults (aged ≥25 years) as well as adolescents (aged 12–17 years) and children (aged 3–11 years). The period of 18–24 years of age is generally viewed as a 'transition period' in GHD, during which individuals with pediatric-onset GHD experience a slowed growth rate as they approach their adult height [25–27]. In order to avoid confounding the study results, and to clearly distinguish between pediatric and adult GHD populations, individuals aged 18–24 years were not included in the study population.

With this in mind, evidence for the content validity of the LIQ-GHD was developed through a targeted review of

empirical literature, advice meetings with clinical experts, and qualitative interviews with adults (age ≥ 25 years) and children (age 3–17 years) taking r-hGH injections for GHD.

3.1.1 Targeted Review of Empirical Literature

A review of empirical literature was conducted in March 2016 using PubMed (https://www.ncbi.nlm.nih.gov/pubmed). Searches were conducted to identify publications with potential relevance to dosing frequency and injection issues related to hGH, and other therapeutic areas with a similar treatment regimen in adult and pediatric populations. A supplemental literature search was also conducted through review of the reference lists of publications reviewed in the original search, conference proceedings, and Google and Google Scholar. A literature-focused conceptual model [23] was developed to represent r-hGH injection burden concepts and ultimately inform the selection of measurement concepts for the LIQ-GHD.

3.1.2 Questionnaire Modification and Development

A full-day, in-person meeting was convened by the LIQ-GHD developers, including the study sponsor, health outcomes researchers, GHD clinical experts, and COA measurement scientists. Results from the empirical literature review were reviewed and used to incorporate concepts and items from two existing questionnaires (the Injection Pen Assessment Questionnaire [IPAQ] [18] and the Bother, Satisfaction, and Willingness to Continue [BSW] Questionnaire [24]) and to develop new items for inclusion in the LIQ-GHD. Response scales were developed to be appropriate to the concept measured, consistent among like items, sensitive enough to capture change, and easy to use. Items assessing ease of treatment and satisfaction used a 5-point Likert-type scale to capture the entire response range from easy/satisfied to difficult/dissatisfied. Items assessing frequency of experience used a 5-point verbal response scale, while items assessing sign or symptom severity used an 11-point numeric rating scale.

3.1.3 Advice Meetings with Clinical Experts

One-on-one, 60-min advice meetings were conducted by telephone with clinical experts from the USA and European Union (EU). During these meetings, experts were asked to describe reported patient experiences (patients as well as caregivers) related to daily r-hGH injections and their perspective on the injection-related burdens that patients experience. Experts were also asked to provide feedback on the relevance and comprehensiveness of the draft LIQ-GHD.

3.1.4 Translatability Assessment

Following advice meetings with clinical experts, and before conducting qualitative patient interviews, the translatability of the draft LIQ-GHD was assessed by an independent translation provider (TransPerfect; http://www.transperfect.com/), in order to identify any words or terms that may pose difficulty in translation. Any wording revisions made to the LIQ-GHD during the qualitative interviews were subsequently submitted for translatability assessment.

3.1.5 Qualitative Interviews with Patients and Caregivers

A series of in-person, 90-min qualitative interviews were conducted with patients (and, when appropriate, their caregivers) in the USA diagnosed with GHD and receiving daily rhGH injections. Ethics approval was received from Quorum Review. Participants were recruited from four clinical sites, and included adults (aged ≥ 25 years) and adolescents (aged 12–17 years) and children (aged 3–11 years) with their caregivers. The qualitative interviews comprised two parts: (i) concept elicitation during which participants were asked open-ended questions about the r-hGH injection treatment burden and impacts they experienced due to r-hGH injections; and (ii) debriefing during which participants were asked to provide feedback on the LIQ-GHD, to assess its relevance (i.e., does it assess concepts relevant and important to participants?), comprehensiveness (i.e., does it omit any relevant concepts?), and comprehensibility (i.e., can participants understand the LIQ-GHD as intended by the developers and select meaningful responses?). Interviews were conducted in three waves to allow time for questionnaire revisions, if needed. Participant compensation was distributed upon interview completion.

3.1.6 Questionnaire Revision

Based on the translatability assessments and feedback from patients with GHD (and their caregivers), further updates were made to both LIQ-GHD versions: wording and organization were revised, and some concepts for measurement were added prior to quantitative testing.

3.2 Evaluation of Hypothesized Factor Structure and Score Psychometric Performance

An online, cross-sectional observational study was conducted to evaluate the LIQ-GHD hypothesized factor structure and score psychometric performance. Participants were clinician-diagnosed adult and pediatric (child and adolescent) patients receiving daily r-hGH injections for GHD, recruited from eight endocrinology clinics. Ethical approval

was provided by Quorum Review and, where applicable, local ethical review boards. Consented participants completed the LIQ-GHD online at home. Questions related to the shared injection experience were completed by child and adolescent patients together with their caregiver (dyad administration). To enable test–retest analysis, the LIQ-GHD was completed twice in the same session with a brief interval between administrations, during which time participants completed a demographic form and the Self-Injection Assessment Questionnaire (SIAQ) [28]. Participant compensation was distributed upon questionnaire completion.

Analyses were conducted for the overall study sample and age-related subgroups (i.e., children, adolescents, and adults).

3.2.1 Factor Structure

Confirmatory factor analysis (CFA) was conducted to confirm the hypothesized factor structure of the LIQ-GHD (as summarized in Table 1 and presented in Fig. 1). The LIQ-GHD measures six hypothesized domains: Pen Ease of Use (PEoU; five items), Ease of Injection Schedule (EoIS; two items), Patient Life Interference (LI; five- or seven-item version), Satisfaction and Willingness to Continue Treatment (WtC; two items), Missed Injections (two items), and Injection Signs and Symptoms (SS; four items). Additional domains were hypothesized for the LIQ-GHD pediatric version: Injection Signs Reported by Caregiver (CS; two items), Caregiver Life Interference (CLI; five- or seven-item version), and Family Life Interference (FLI; five- or six-item version). CFA models were run for the overall sample and by age subgroup. Model fit was assessed with the comparative fit index (CFI) and root mean square error of approximation (RMSEA). CFI values can range between 0 and 1, with higher values indicative of better fit, and CFI >0.95 is considered to be a good fit. RMSEA values ranging from 0.08 to 0.10 are considered an indication of fair fit, and RMSEA values above 0.10 indicated poor fit [29]. The following models were run: Model 1—overall sample (excluding CLI and FLI items which are specific to only the pediatric subgroups); Model 2—overall sample (replicating Model 1, but run with LI [five items]); Model 3—combined pediatric sample (including the caregiver reported CLI and FLI items); Model 4—combined pediatric sample (excluding the caregiver-reported CLI and FLI items and the CS items); and Model 5—combined pediatric sample (excluding the CLI and FLI items and the SS items).

3.2.2 Psychometric Score Performance

LIQ-GHD item-level frequencies and descriptives, as well as domain-level descriptives, were calculated for the overall, child, adolescent, and adult groups. Descriptive statistics included the mean, median, and range for each statistic calculated.

Item-to-item correlations were calculated for each item against the other items using Spearman's rank order correlation coefficient (rho), with rho >0.80 indicating potential redundancy between items.

Item-total correlations were examined between items and hypothesized domains, as well as items and other domain scores, following the multi-method multi-trait paradigm [30]. Items should correlate ≥ 0.40 with domains to which they are hypothesized to belong, and demonstrate no or weak correlation with other domains [31].

Internal consistency reliability was estimated using Cronbach's coefficient alpha (α) [32], which ranges from 0 to 1, with $\alpha \geq 0.70$ being considered acceptable.

Intra-class correlation coefficients (ICCs) were calculated to assess test–retest reliability of the LIQ-GHD item and domain scores, using a two-way mixed model (Shrout and Fleiss ICC) [33]. The ICC ranges from 0.00 to 1.00 with a minimal acceptable level of 0.70 for group comparisons [34].

Construct-related validity was evaluated by generating convergent and discriminant validity correlation estimates and conducting a set of known-groups analyses.

For tests of convergent/discriminant validity, hypothesized relationships among LIQ-GHD and SIAQ variables were estimated using Spearman rho. Evidence for convergent validity was based on rho $\geq |0.40|$, and evidence for discriminant validity was based on rho $<|0.30|$ [30, 35].

Known-groups-methods analyses characterize the degree to which scores produced by a target questionnaire can distinguish among the groups hypothesized a priori to be clinically distinct [20]. Known groups were defined in five ways: group (i) changes to life routine in order to deal with GH injections; group (ii) number of missed injections; group (iii) satisfaction with overall experience taking GH treatment; group (iv) GHD severity; and group (v) overall health rating. These five groups were selected with the expectation that subgroup members would differ clinically and/or that they would have a higher score in the LIQ-GHD. We expected the LIQ-GHD scores to reflect the differences within these groups. Between-group differences were evaluated using the *t* test or analysis of variance, or non-parametric analyses such as the Mann–Whitney *U* test or Kruskal–Wallis test when normality assumptions were not met. For parametric analyses, standardized effect sizes (Cohen's *d*, difference in means divided by pooled standard deviation [SD]) were calculated to quantify the magnitude of the differences between groups and interpreted as follows: $d = 0.2$ as a small effect size, $d = 0.5$ as a medium effect size, and $d = 0.8$ as a large effect size [36].

Table 1 Summary description of the Life Interference Questionnaire for Growth Hormone Deficiency (LIQ-GHD)

Hypothesized domain	Completed by	Question content	Response scale
Pen Ease of Use (PEoU), 5 items	Adult Dyad	(Recall: past 4 weeks) Overall pen ease of use Ease of use: prepare the pen Ease of use: set the dose Ease of use: inject the medicine Ease of use: store the pen	5-point Likert type
Ease of Injection Schedule (EoIS), 2 items	Adult Dyad	(Recall: past 4 weeks) Ease of injection schedule overall Convenience of injection schedule overall	5-point Likert type 7-point Likert type
Patient Life Interference (LI), 5 or 7 items	Adult Dyad	(Recall: past 4 weeks) Interference with usual daily activities Interference with social activities Interference with recreation and leisure activities Interference with spending the night away from home Interference with travel *7-item version includes these 2 additional items* Changes to life routine to deal with injections Bothered by growth hormone injections	5-point VRS
Satisfaction and Willingness to Continue (WtC), 2 items	Adult Dyad	(Recall: past 4 weeks) Satisfaction with overall experience taking growth hormone treatment Willingness to continue injection schedule	5-point Likert type 5-point VRS
Missed Injections, 2 items	Adult Dyad	(Recall: past 4 weeks) Number of missed injections Reason(s) for missing injections	Continuous Multiple choice
Injection Signs and Symptoms (SS) (patient reported), 4 items	Adult Pediatric patient (ages 8–17 years only)	(Recall: past week) Pain severity Stinging severity Bruising severity Bleeding severity	11-point NRS
Injection Signs (CS) (caregiver reported), 2 items	Caregiver of pediatric patient (all ages)	(Recall: past week) Bruising severity Bleeding severity	11-point NRS
Caregiver Life Interference (CLI), 5 or 7 items	Caregiver of pediatric patient	(Recall: past 4 weeks) Interference with caregiver usual daily activities Interference with caregiver social activities Interference with caregiver recreation and leisure activities Interference with caregiver spending night away from home Interference with the caregiver travel *7-item version includes these 2 additional items* Changes to caregiver life routine to deal with child injections Caregiver bothered by growth hormone injections	5-point VRS

Table 1 (continued)

Hypothesized domain	Completed by	Question content	Response scale
Family Life Interference (FLI), 5 or 6 items	Caregiver of pediatric patient	(Recall: past 4 weeks) Interference with family member usual daily activities Interference with family member social activities Interference with family member recreation and leisure activities Interference with family member spending night away from home Interference with family member travel *6-item version contains this additional item* Changes to family member life routine to deal with child injections	5-point VRS

NRS numeric rating scale, *VRS* verbal rating scale

4 Results

4.1 Establishing Evidence of Content Validity

4.1.1 Targeted Review of Empirical Literature

A targeted search of empirical literature yielded 315 potentially relevant abstracts for review. Abstracts were screened and additional publications were identified from supplemental searches, resulting in a total of 30 publications selected for full review (see Fig. 2). Concepts emerging from the reviewed publications primarily focused on ease or difficulty of injection device use, injection regimen, injection-related adverse effects, and injection-related impacts. The identified concepts were organized into a literature-based conceptual model (see Fig. 3) and used to inform questionnaire modification and development.

4.1.2 Questionnaire Modification and Development

Two existing questionnaires, the IPAQ (a questionnaire measuring r-hGH device ease of use) and the BSW (a questionnaire measuring benefit from, satisfaction with, and willingness to continue treatment) were modified, and included in the draft LIQ-GHD, for this study's context of use. New questionnaire content was developed to measure concepts identified during the literature review. Table 1 presents a summary of the LIQ-GHD item content and response option format.

4.1.3 Advice Meetings with Clinical Experts

Six clinical experts in the USA ($n = 3$) and the EU ($n = 3$) took part in advice meetings. All six experts had a minimum of 9 years' experience treating individuals with GHD, and half had more than 20 years' experience. During these meetings, experts were asked about their patients' experience with r-hGH injections and how r-hGH injections impact the lives of patients and caregivers. Experts reported many of the same concepts identified in the literature (see Table 2). Experts were also asked to review the draft LIQ-GHD and provide feedback. Although individual experts had suggestions for revising the LIQ-GHD, there were no consistent or fundamental issues identified that would call into question the appropriateness and comprehensiveness of the questionnaire.

4.1.4 Questionnaire Revision

Following the expert advice meetings, the LIQ-GHD was organized into two versions: the LIQ-GHD-Adult (intended for adults ≥25 years of age) and the LIQ-GHD-Pediatric (intended for children and adolescents 3–17 years of age and their caregivers). The LIQ-GHD-Adult is a patient self-reported outcome (PRO) measure. For most questions, the LIQ-GHD-Pediatric is a COA intended for 'dyad administration' in which the patient and caregiver read and answer questions together. LIQ-GHD-Pediatric questions asking about the severity of injection symptoms are administered only with children and adolescents capable of reliable self-report, while some observer-reported outcome (ObsRO) items are answered by the caregiver about his/her own experiences, experiences of the family, and observable behaviors of the child.

4.1.5 Translatability Assessment

While some minor recommendations for formatting and word choice were made to increase the translatability of the instruments across languages, the translatability assessment confirmed that the LIQ-GHD-Adult and LIQ-GHD-Pediatric could be effectively translated into a wide range of languages.

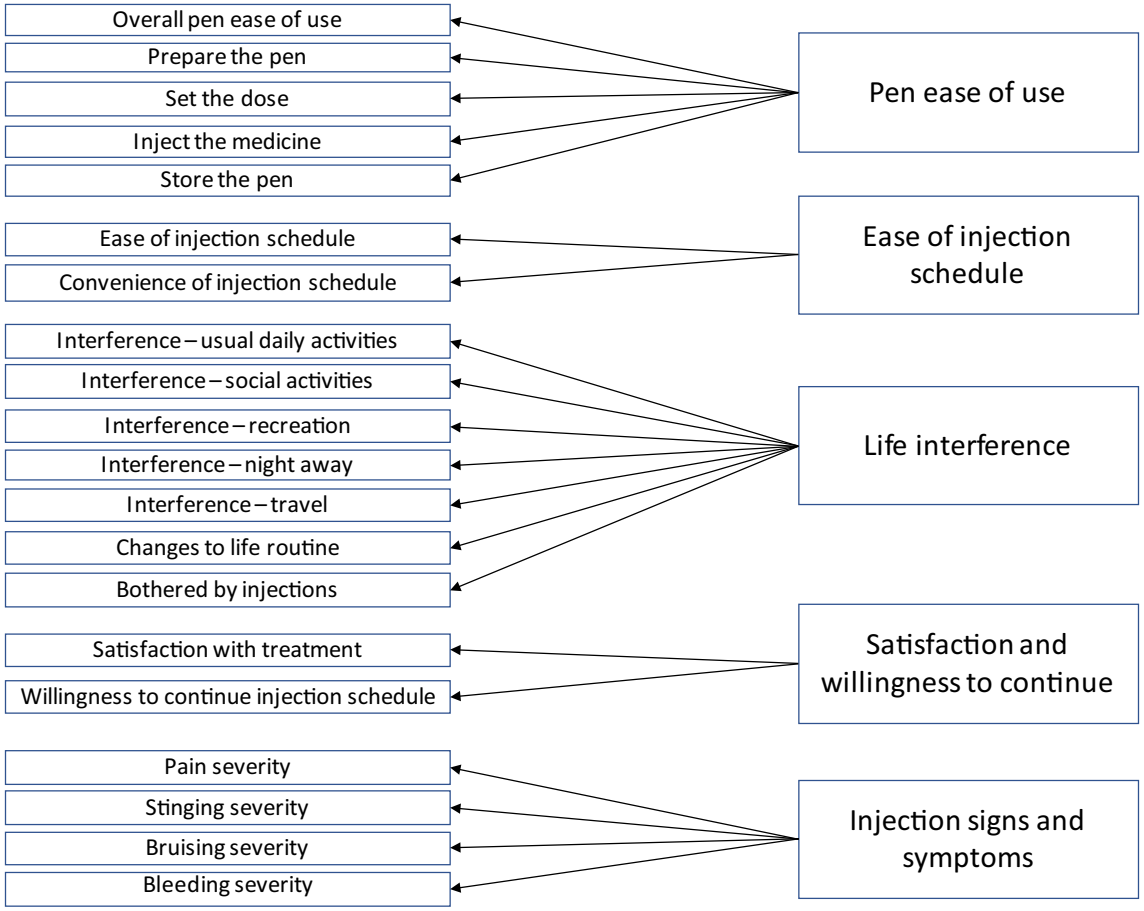

Fig. 1 Hypothesized domain framework evaluated by CFA

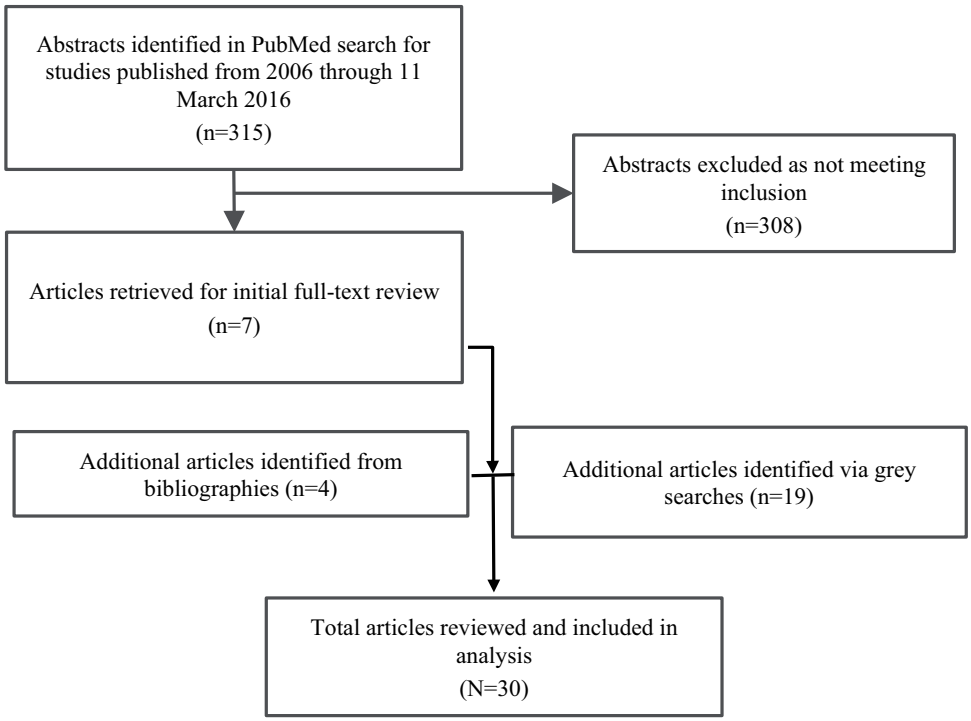

Fig. 2 Flow chart describing the identification of publications for the empirical literature review

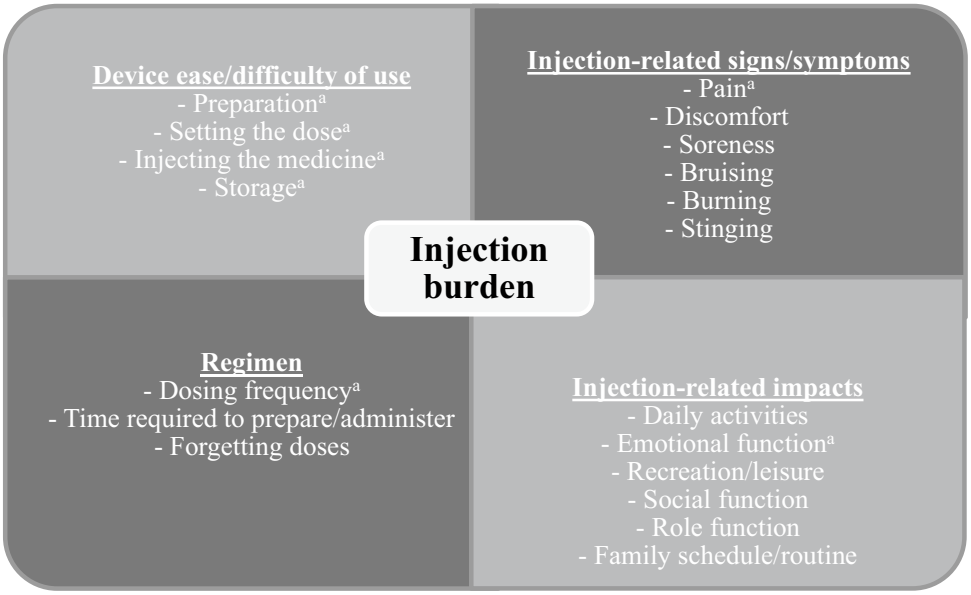

Fig. 3 Literature-based injection burden conceptual model

[a]Concepts referenced in articles related to adherence and preference

4.1.6 Qualitative Interviews with Patients and Caregivers

Qualitative interviews were conducted with 21 individuals with GHD (11 children < 12 years of age and their caregivers, four adolescents 12–17 years of age and their caregivers, and six adults ≥ 25 years of age). Table 3 presents participant demographic and health information.

Concept elicitation results confirmed that the LIQ-GHD comprehensively captures key aspects of the r-hGH injection experience (see Table 2 for a summary of concepts reported by patients and caregivers). All injection-related SS concepts reported by > 25% of the total sample were included in the LIQ-GHD, as were all impact domains reported by patients and their caregivers.

Cognitive debriefing results indicated that the LIQ-GHD instructions, items, and response options were generally well-understood. While a few of the younger children had comprehension issues, the nature of the dyad administration mitigated this finding (i.e., in these instances, the caregiver read the question to the child and arrived at a response together with the child). Minor wording revisions were made following these interviews in an effort to improve patient understanding. In addition, questions were added to assess bleeding, bother caused by injections, and number of and reasons for missed injections.

4.2 Evaluation of Hypothesized Factor Structure and Score Psychometric Performance

A total of 224 participants were included in the online observational study, including 70 children (age 3–11 years)/caregiver dyads, 79 adolescent (age 12–17 years)/caregiver dyads, and 75 adults (age ≥ 25 years). The patient sample ranged from 3 to 87 years in age. More than half of the patients were male (58%), and the majority were white (84%) (see Table 3).

4.2.1 Confirmatory Factor Analysis

CFA using the overall sample demonstrated good-fit statistics for the hypothesized domain structure (without the family LI and caregiver LI items) using both the five- and seven-item patient LI domains (RMSEA = 0.07, CFI = 0.98 for each). CFA demonstrated good-fit statistics for both Model 1 (RMSEA = 0.07, CFI = 0.98) and Model 2 (RMSEA = 0.07, CFI = 0.98) in the overall group (with the travel and spending the night away from home [i.e., overnight] items correlated), supporting the hypothesized factor structure. Model 3 did not converge. CFA demonstrated good-fit statistics for Model 4 (five-item LI: RMSEA = 0.07, CFI = 0.97; seven-item LI: RMSEA = 0.08, CFI = 0.95) (with the travel and overnight items correlated). CFA demonstrated good-fit statistics for Model 5 (five-item LI: RMSEA = 0.07, CFI = 0.97; seven-item LI: RMSEA = 0.08, CFI = 0.96) (with the travel and overnight items correlated).

4.2.2 Item Distributions

The evaluation of item distributions for the full study sample demonstrated floor effects for most items of the LIQ-GHD,

Table 2 Patient and caregiver reported recombinant human growth hormone injection-related concepts

Concept	Frequency of patient report ($N = 21$)	Reported by clinical experts	Identified in reviewed literature	Included in LIQ-GHD
Signs and symptoms related to r-hGH injections				
Pain	Total: 15 (71.4%) Child[a]: 9 (81.8%) Adolescent[b]: 3 (75.0%) Adult[c]: 3 (50.0%)	✓	✓	✓
Bleeding	Total: 12 (57.1%) Child: 7 (63.6%) Adolescent: 3 (75.0%) Adult: 2 (33.3%)	✓		✓
Bruising	Total: 11 (52.3%) Child: 7 (63.6%) Adolescent: 2 (50.0%) Adult: 2 (33.3%)	✓	✓	✓
Stinging	Total: 7 (33.3%) Child: 5 (45.5%) Adolescent: 1 (25.0%) Adult: 1 (16.7%)	✓	✓	✓
Lumps	Total: 4 (19.0%) Child: 4 (36.4%) Adolescent: 0 (0.0%) Adult: 0 (0.0%)			
Mark on the skin	Total: 1 (4.8%) Child: 1 (9.1%) Adolescent: 0 (0.0%) Adult: 0 (0.0%)			
Cold sensation	Total: 2 (9.5%) Child: 0 (0.0%) Adolescent: 1 (25.0%) Adult: 1 (16.7%)			
Burning	Total: 2 (9.5%) Child: 0 (0.0%) Adolescent: 1 (25.0%) Adult: 1 (16.7%)		✓	
Dry skin	Total: 1 (4.8%) Child: 1 (9.1%) Adolescent: 0 (0.0%) Adult: 0 (0.0%)			
Edema	Total: 1 (4.8%) Child: 1 (9.1%) Adolescent: 0 (0.0%) Adult: 0 (0.0%)			
Itch	Total: 1 (4.8%) Child: 1 (9.1%) Adolescent: 0 (0.0%) Adult: 0 (0.0%)			
Sensation of pressure	Total: 1 (4.8%) Child: 0 (0.0%) Adolescent: 1 (25.0%) Adult: 0 (0.0%)			
Redness	Total: 1 (4.8%) Child: 1 (9.1%) Adolescent: 0 (0.0%) Adult: 0 (0.0%)			
Scarring	Total: 1 (4.8%) Child: 0 (0.0%) Adolescent: 0 (0.0%) Adult: 1 (16.7%)			

Table 2 (continued)

Concept	Frequency of patient report ($N = 21$)	Reported by clinical experts	Identified in reviewed literature	Included in LIQ-GHD
Withdrawal symptoms[d]	Total: 1 (4.8%) Child: 0 (0.0%) Adolescent: 1 (25.0%) Adult: 0 (0.0%)			
Impact domains related to r-hGH injections				
Impacts on travel	Total: 18 (85.7%) Child: 11 (100.0%) Adolescent: 3 (75.0%) Adult: 4 (66.7%)	✓	✓	✓
Emotional impacts	Total: 15 (71.4%) Child: 9 (81.8%) Adolescent: 2 (50.0%) Adult: 4 (66.7%)	✓	✓	✓
Limitations to overnight activities	Total: 9 (42.9%) Child: 7 (63.6%) Adolescent: 2 (50.0%) Adult: 0 (0.0%)		✓	✓
Limitations to usual daily activities	Total: 7 (33.3%) Child: 6 (54.5%) Adolescent: 1 (25.0%) Adult: 0 (0.0%)		✓	✓
Social impacts	Total: 3 (14.3%) Child: 2 (18.2%) Adolescent: 0 (0.0%) Adult: 1 (16.7%)	✓	✓	✓
Limitations to recreational/leisure activities	Total: 2 (9.5%) Child: 1 (9.1%) Adolescent: 1 (25.0%) Adult: 0 (0.0%)			✓
Work impacts	Total: 1 (4.8%) Child[e]: 0 (0.0%) Adolescent: 0 (0.0%) Adult: 1 (16.7%)	✓	✓	✓
Impacts on family	Total: 1 (4.8%) Child: 1 (9.1%) Adolescent: 0 (0.0%) Adult: 0 (0.0%)	✓	✓	✓
Impacts on relationships	Total: 1 (4.8%) Child: 0 (0.0%) Adolescent: 0 (0.0%) Adult: 1 (16.7%)	✓	✓	✓

LIQ-GHD Life Interference Questionnaire for Growth Hormone Deficiency, *r-hGH* recombinant human growth hormone

[a]Dyad interviews with 11 children aged 4–11 years, with their caregivers

[b]Dyad interviews with 4 adolescents aged 12–17 years, with their caregivers

[c]Interviews with 6 adults aged ≥ 25 years

[d]Physical symptoms experienced by one adolescent after several days without r-hGH injections

though no ceiling effects were observed for any items. For most items, all response options were used, although the upper end of the scale was not selected for some items. The findings for specific subanalyses based on patient age groups were similar to the overall sample. No missing data were observed as the electronic administration of the measure did not allow items to be skipped.

4.2.3 Item-to-Item Correlations

Evaluation of item-to-item correlations suggested possible redundancy between four sets of items in the LIQ-GHD: items assessing interference with spending the night away from home (i.e., overnight) and interference with travel, for patients, caregivers, and family members; items assessing

interference with recreation and leisure activities and interference with social activities, for caregivers and family members; items assessing patient-reported and caregiver-reported bruising; and items assessing patient- and caregiver-reported bleeding.

4.2.4 Item-Total Correlations

In general, the items correlated as expected with their hypothesized domains in the overall, child, adolescent, and adult groups and, for the most part, items correlated more strongly with their hypothesized domains than with other domain scores. There were some exceptions to this; for example, while the bother item correlated well with its hypothesized seven-item LI domain, it correlated more strongly with the WtC and patient-reported symptoms (SS) domains. Item-total correlations for the WtC domain were generally moderate to weak (i.e., <0.40 correlation). Not unexpectedly, moderate correlations were observed for patient LI and the caregiver LI and family LI items, and for the SS and caregiver-reported sign (CS) items.

4.2.5 Internal Consistency Reliability

For the overall study sample, internal consistency reliability was demonstrated for all domains (with Cronbach's α ranging from 0.746 to 0.905), with two exceptions (see Table 4). Similarly, all domains in all subgroups met the threshold of $\alpha \geq 0.70$ for internal consistency reliability, with few exceptions (see Table 4).

4.2.6 Test–Retest Reliability

ICCs for the LIQ-GHD domain scores ranged from 0.761 to 0.918 for the overall sample (see Table 5). Results were similar when analyzed by subgroup, with an ICC >0.70 being observed for most of the LIQ-GHD across age groups, with the exception of the EoIS and WtC in children (with ICC = 0.679 and ICC = 0.697, respectively).

4.2.7 Convergent and Divergent Validity

Table 6 presents correlations between LIQ-GHD and SIAQ domain scores for the overall group. As predicted, results demonstrated evidence of convergence between the PEoU and SIAQ Ease of use of the injection device scores, and between the WtC and SIAQ Satisfaction with self-injection scores. However, inconclusive results were found for the EoIS and SIAQ Satisfaction with self-injection scores and for the patient LI (five-item) and SIAQ satisfaction with self-injection scores. As predicted, inconclusive correlation results were found for caregiver LI (five-item) and SIAQ

Table 3 Participant demographic and health information

Demographic and health information	Qualitative interviews ($N = 21$)		Field study ($N = 224$)		
	Adults ($n = 6$)	Pediatric ($n = 15$)	Adults ($n = 75$)	Adolescents ($n = 79$)	Children ($n = 70$)
Age					
Mean years (SD)	47.8 (12.6)	9.7 (3.4)	50.3 (11.7)	13.9 (1.4)	8.7 (2.2)
Minimum–maximum years	32.0–62.0	4.0–15.0	28.0–87.0	12.0–17.0	3.0–11.0
Sex [*n* (%)]					
Male	4 (66.7)	11 (73.3)	25 (33.3)	60 (75.9)	44 (62.9)
Female	2 (33.3)	4 (26.7)	50 (66.7)	19 (24.1)	26 (37.1)
Race [*n* (%)]					
Asian	0 (0.0)	1 (6.7)	0 (0.0)	4 (5.1)	5 (7.1)
Black or African-American	0 (0.0)	0 (0.0)	1 (1.3)	2 (2.5)	2 (2.9)
American Indian or Alaska Native	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
White	6 (100.0)	10 (66.7)	71 (94.7)	63 (79.7)	55 (78.6)
Other	0 (0.0)	3 (20.0)	3 (4.0)	9 (11.4)	8 (11.4)
GHD severity [*n* (%)]					
Very mild	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)
Mild	1 (16.7)	3 (20.0)	6 (8.0)	7 (8.9)	2 (2.9)
Moderate	2 (33.3)	8 (53.3)	29 (38.7)	40 (50.6)	33 (47.1)
Severe	1 (16.7)	1 (6.7)	27 (36.0)	27 (34.2)	28 (40.0)
Very severe	2 (33.3)	0 (0.0)	13 (17.3)	5 (6.3)	7 (10.0)
Not answered	0 (0.0)	2 (13.3)	0 (0.0)	0 (0.0)	0 (0.0)

GHD growth hormone deficiency

Table 4 Internal consistency reliability estimates for the overall sample, and by child, adolescent, adult groups

Domains	Cronbach's alpha (α)			
	Overall sample ($N = 224$)	Child/caregiver dyads ($n = 70$)	Adolescent/caregiver dyads ($n = 79$)	Adult ($n = 75$)
PEoU ($k = 5$)	0.746	0.758	0.759	0.720
EoIS[a] ($k = 2$)	0.818	0.774	0.853	0.820
LI ($k = 7$)	0.853	0.730	0.884	0.874
LI ($k = 5$)	0.822	0.651	0.859	0.866
WtC[a] ($k = 2$)	0.589	0.346	0.579	0.788
SS[b] ($k = 4$)	0.757	0.807	0.706	0.579
CS[a,c] ($k = 2$)	0.653	0.552	0.718	
CLI ($k = 7$)	0.876	0.810	0.901	
CLI ($k = 5$)	0.846	0.767	0.877	
FLI ($k = 6$)	0.905	0.815	0.936	
FLI ($k = 5$)	0.885	0.755	0.927	

CLI Caregiver Life Interference, *CS* injection signs reported by caregiver, *EoIS* Ease of Injection Schedule, *FLI* Family Life Interference, *LI* Life Interference, *PEoU* Pen Ease of Use, *SS* Injection Signs and Symptoms, *WtC* Satisfaction and Willingness to Continue

[a]Results should be interpreted with caution as the domain score is based on only two items

[b]Patient-reported, ages 8–17 years and ≥ 25 years

[c]Caregiver-reported for children ages 3–17 years

Table 5 Test–retest reliability of Life Interference Questionnaire for Growth Hormone Deficiency (LIQ-GHD) domains, overall group

Domains	*N*	Time 1 [mean (SD)]	Time 2 [mean (SD)]	Reliability (ICC)	95% confidence interval	
					Lower	Upper
PEoU ($k = 5$)	224	1.3 (0.5)	1.4 (0.6)	0.761	0.700	0.811
EoIS ($k = 2$)	224	1.8 (1.8)	1.8 (1.9)	0.768	0.708	0.817
LI ($k = 7$)	224	1.7 (0.7)	1.7 (0.7)	0.857	0.818	0.888
LI ($k = 5$)	224	1.7 (0.7)	1.6 (0.7)	0.854	0.815	0.886
WtC ($k = 2$)	224	1.6 (0.6)	1.5 (0.7)	0.768	0.708	0.817
SS[a] ($k = 4$)	205	1.6 (1.4)	1.3 (1.4)	0.909	0.882	0.930
CS[b] ($k = 2$)	149	1.0 (1.2)	0.9 (1.1)	0.809	0.745	0.858
CLI ($k = 7$)	149	1.6 (0.7)	1.6 (0.6)	0.887	0.847	0.917
CLI ($k = 5$)	149	1.6 (0.7)	1.5 (0.7)	0.865	0.818	0.900
FLI ($k = 6$)	149	1.3 (0.6)	1.4 (0.6)	0.918	0.888	0.940
FLI ($k = 5$)	149	1.3 (0.6)	1.4 (0.6)	0.896	0.860	0.924

CLI Caregiver Life Interference, *CS* injection signs reported by caregiver, *EoIS* Ease of Injection Schedule, *FLI* Family Life Interference, *LI* Life Interference, *PEoU* Pen Ease of Use, *SS* Injection Signs and Symptoms, *WtC* Satisfaction and Willingness to Continue

[a]Patient-reported, ages 8–17 years and ≥ 25 years

[b]Caregiver-reported for children ages 3–17 years

Feelings about injections scores, and divergence was found between family LI (five-item) and SIAQ Feelings about injection scores.

For the child group, evidence of convergence among domain scores was not found; however, evidence of divergence was found between caregiver LI (five-item) and SIAQ Feelings about injections scores and between family LI (five-item) and SIAQ Feelings about injections scores.

For the adolescent group, evidence of convergence was found for PEoU and SIAQ Ease of use of the injection device scores and for the WtC and SIAQ Satisfaction with self-injection scores, but not for other domains, as predicted; evidence of divergence was found for family LI (five-item) and SIAQ Feelings about injection scores.

For the adult group, evidence of convergence was found for all scores (PEoU and SIAQ Ease of use of the injection

Table 6 Correlations between Life Interference Questionnaire for Growth Hormone Deficiency (LIQ-GHD) and Self-Injection Assessment Questionnaire (SIAQ) scores, overall sample

LIQ-GHD domains	SIAQ domain scores[a]					
	Feelings about injections	Self-image	Self-confidence	Pain and skin reaction	Ease of use	Satisfaction
PEoU[b]	−0.214	−0.158	−0.090	−0.388	−0.429[c]	−0.371
EoIS[d]	−0.185	−0.152	−0.049	−0.245	−0.276	−0.323[e]
LI (7-item)[f]	−0.403	−0.337	−0.177	−0.527	−0.415	−0.437[c]
LI (5-item)[f]	−0.336	−0.294	−0.144	−0.439	−0.352	−0.368
WtC[g]	−0.254	−0.232	−0.191	−0.413	−0.340	−0.474[c]
SS[h,i]	−0.426	−0.338	−0.231	−0.683	−0.428	−0.402
CLI (7-item)[f]	−0.435	−0.303	−0.040	−0.462	−0.342	−0.343
CLI (5-item)[f]	−0.369[e]	−0.289	−0.040	−0.410	−0.283	−0.318
FLI (6-item)[f]	−0.230	−0.188	0.009	−0.297	−0.313	−0.258
FLI (5-item)[f]	−0.225[j]	−0.198	−0.030	−0.302	−0.302	−0.282

CLI Caregiver Life Interference, *EoIS* Ease of Injection Schedule, *FLI* Family Life Interference, *LI* Life Interference, *PEoU* Pen Ease of Use, *SS* Injection Signs and Symptoms, *WtC* Satisfaction and Willingness to Continue

[a]SIAQ domain scores range from 0 to 10, with higher scores associated with better experience with self-injection

[b]Adult and dyad LIQ-GHD items range from 1 to 5, with higher scores associated with greater difficulty

[c]Confirmed hypothesized convergent correlation

[d]Adult and dyad LIQ-GHD items range from 1 to 7, with higher scores associated with greater inconvenience

[e]Hypothesized correlation undetermined

[f]Adult and dyad LIQ-GHD items range from 1 to 5, with higher scores associated with more interference

[g]Adult and dyad LIQ-GHD items range from 1 to 5, with higher scores associated with less satisfaction

[h]Adult and dyad LIQ-GHD items range from a count over the past 4 weeks

[i]Patient-reported, ages 8–17 years and ≥ 25 years

[j]Confirmed hypothesized discriminant correlation

device, EoIS and SIAQ Satisfaction with self-injection domain, patient LI [five-item] and SIAQ Satisfaction with self-injection, and WtC and SIAQ Satisfaction with self-injection), as predicted.

4.2.8 Known Groups

For the overall sample, the LI (five-item) and EoIS domain scores differed significantly for groups reporting changes/no changes to life routine, satisfied/dissatisfied with treatment, and number of missed injections (see Table 7). Specifically, participants reporting frequent changes to life routine, dissatisfaction with treatment, and higher number of missed injections had higher LI and injection schedule difficulty (see Figs. 4, 5, 6 respectively). No significant differences were found based on self-rating of overall health or GHD severity level. Some similar results were observed in the child, adolescent, and adult group analyses; however, these analyses were limited due to small sample size.

5 Discussion

Results from this research, conducted in accordance with best practices [21, 22, 37, 38], provide evidence of the LIQ-GHD content and construct validity and score psychometric performance, based on a targeted literature review, expert advice meetings, interviews with patients and caregivers, and data from a quantitative field study.

The literature review revealed a paucity of data relating to r-hGH injection treatment burden (the most-cited references were related to diabetes [39–43]) and identified several functional health domains (e.g., emotional, role, travel, physical function) that may be impacted by daily injection treatment.

Results from the clinical expert advice meetings confirmed the literature findings and informed development of the draft LIQ-GHD.

Qualitative patient and caregiver interviews confirmed that the most important and relevant concepts related to r-hGH injection treatment burden were included in the LIQ-GHD, that participants understood and were able to answer the questions, and that it comprehensively covers

Table 7 Known-group analysis of the LI-5 and EoIS domain scores (overall group, $N = 224$)

Domain	Comparison group	*N*	Mean (SD)	Median	*p* Value		Post hoc tests[f]	SES[g]
					Parametric	Non-parametric		
Changes/no changes to life routine								
LI (5-item)	No changes	187	1.5 (0.54)	1.4	< 0.001[a]	< 0.001[e]		2.00
	Changes	37	2.6 (0.69)	2.6				
EoIS	No changes	187	1.5 (1.54)	0.8	< 0.001[a]	< 0.001[e]		1.05
	Changes	37	3.2 (2.31)	2.9				
Missed injections								
LI (5-item)	None (0)	78	1.5 (0.63)	1.4	0.056[c]	0.045[d]	1 vs. 2	0.35
	Few (1–3)	123	1.8 (0.73)	1.6				0.21
	Some or many (≥ 4)[h]	23	1.7 (0.73)	1.4				0.14
EoIS	None (0)	78	1.1 (1.37)	0.8	< 0.001[c]	< 0.001[d]	1 vs. 2, 1 vs. 3, 2 vs. 3	0.41
	Few (1–3)	123	1.8 (1.80)	1.7				1.46
	Some or many (≥ 4)[h]	23	3.4 (2.08)	2.9				0.87
Satisfaction with overall experience taking GHD treatment								
LI (5-item)	Satisfied	187	1.6 (0.64)	1.4	< 0.001[a]	< 0.001[e]		0.83
	Not satisfied	37	2.2 (0.81)	2.2				
EoIS	Satisfied	187	1.5 (1.58)	0.8	< 0.001[a]	< 0.001[e]		1.09
	Not satisfied	37	3.3 (2.11)	2.9				
Overall health rating								
LI (5-item)	Excellent	74	1.7 (0.70)	1.4	0.456[c]	0.466[d]		−0.02
	Very good/good	134	1.7 (0.72)	1.4				−0.35
	Fair/poor	16	1.5 (0.56)	1.3				−0.32
EoIS	Excellent	74	1.7 (1.65)	1.7	0.207[c]	0.399[d]		0.01
	Very good/good	134	1.7 (1.82)	0.8				0.48
	Fair/poor	16	2.5 (2.32)	1.9				0.44
GHD severity								
LI (5-item)	Mild or moderate	117	1.7 (0.72)	1.4	0.919[b]	0.442[e]		0.01
	Severe	107	1.7 (0.69)	1.4				
EoIS	Mild or moderate	117	1.8 (1.88)	0.8	0.602[b]	0.356[e]		−0.07
	Severe	107	1.7 (1.73)	0.8				

EoIS Ease of Injection Schedule, *GHD* growth hormone deficiency, *LI* Life Interference, *SD* standard deviation, *SES* standardized effect size

[a] *p* Values are from a Satterthwaite *t*-test comparing distributional differences between groups

[b] *p* Values are from a pooled *t*-test comparing distributional differences between groups

[c] *p* Values are from an analysis of variance comparing difference between mean scores between groups

[d] *p* Values are from a Kruskal–Wallis test comparing distributional differences between groups

[e] *p* Values are from a Mann–Whitney *U* test comparing distributional differences between groups

[f] Post hoc (Tukey) comparisons listed were significant at the 0.05 level

[g] Between-group SESs were calculated as the difference between group means divided by the pooled SD

[h] Respondents answering 'Some' (n = xx) or 'Many' (n = xx) on this item were combined into a single group for analysis. Statistical comparisons were presented but should be considered exploratory due to the small n

relevant concepts. Interview results also confirmed the overall feasibility of the dyad administration approach.

Results from cognitive debriefing provide evidence that the minimum age for reliable self-report on symptom questions is 8 years. Thus, the administrative instructions for the LIQ-GHD specify that symptom questions be administered only to respondents ≥ 8 years of age, and questions that assess observable signs (e.g., bleeding and bruising questions) be administered to caregivers.

Following qualitative interviews, the LIQ-GHD was finalized and tested in a cross-sectional, observational field study. Results from the field study confirmed the hypothesized factor structure of the LIQ-GHD and yielded preliminary evidence of score reliability and construct validity in measuring treatment burden of daily r-hGH injections.

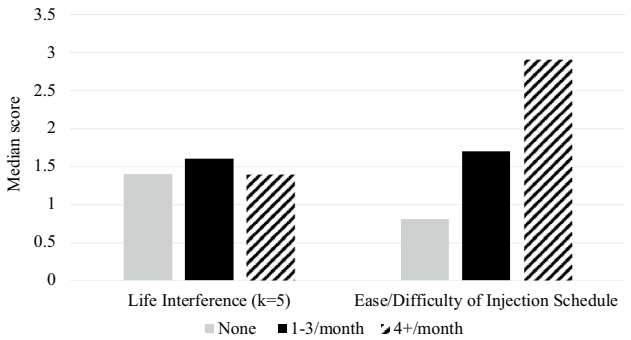

Fig. 4 Known-groups analysis: number of missed injections (key results). Higher scores represent more injection schedule interference and difficulty; for interference, $p < 0.05$ none vs. 1–3/month, Mann–Whitney *U* test; for difficulty, $p < 0.0001$ for all post hoc comparisons

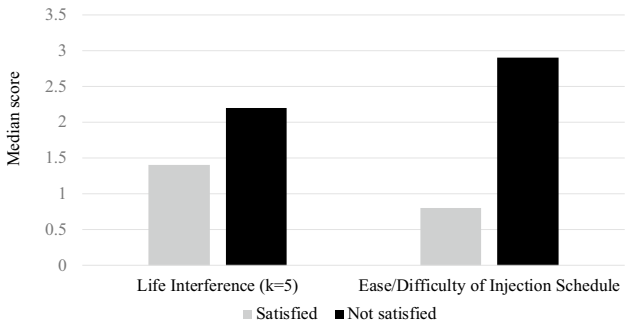

Fig. 5 Known-groups analysis: satisfaction or dissatisfaction with treatment (key results). Higher scores represent more injection schedule interference and difficulty; $p < 0.001$, Mann–Whitney *U* test

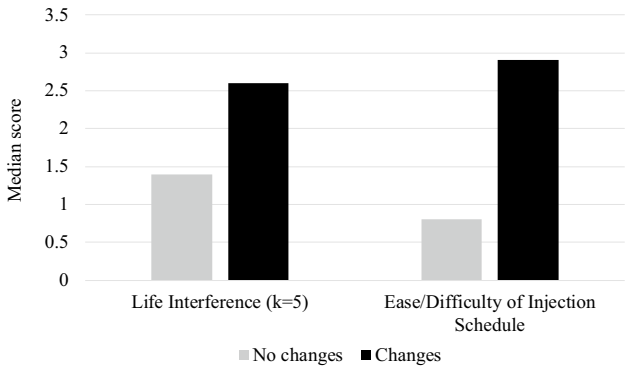

Fig. 6 Known-groups analysis: changes to routine (key results). Higher scores represent more injection schedule interference and difficulty; $p < 0.001$, Mann–Whitney *U* test

As observed in the literature review, evidence suggests that the burden of daily r-hGH injections has a negative effect on treatment adherence and thus on effectiveness. While data show that pediatric and adult patients with GHD may acclimate to daily r-hGH injections, they still continue to experience associated burden and impacts [44]. The availability of a less frequent injection schedule could address many of the burdens and barriers identified.

The research presented here adds to the r-hGH injection treatment burden evidence base and reinforces results from similar research undertaken by others that also identified daily injection LI, as well as emotional and social impacts [45, 46].

Evaluation of item frequency distributions identified a floor effect for many LIQ-GHD items, which is a possible study limitation and an important concern with regards to measurement. The floor effect was present but less notable for some questions (e.g., 'spending the night away from home' and 'travel' LI items, and the convenience question). Items with substantive floor or ceiling effects can limit the instrument's range of measurement (and thereby limit the responsiveness of the tool). One possible strategy to mitigate the potential consequences of a floor effect is to extend the lowest extreme response anchor. However, for most of these items, the lowest response category is 'Never'. One likely explanation for this finding is that most (if not all) patients in this target patient population follow a frequent (i.e., daily) r-hGh injection regimen, may have acclimated to that routine, and may not have any knowledge, exposure to, or experience with a less frequent regimen. Indeed, in this study's qualitative interviews, patients and caregivers indicated that they have made adaptations to their lives to deal with the burden of daily treatment injections. This may explain the floor effects observed on the LIQ-GHD items. While this may be the case, establishing a standardized method for the assessment of LI is important for these patients. The LIQ-GHD includes items that are written in such a manner that they may be used (or easily modified) to assess the patient experience with varied injection regimens. Future studies employing the LIQ-GHD should be powered (e.g., ensuring sufficient sample size to detect an effect or change) with these considerations in mind.

Another possible limitation is the short interval between the time 1 and time 2 LIQ-GHD administrations for the evaluation of test–retest reliability (although efforts were made for the participants to complete other questionnaires during the interval). Additionally, some of the known-groups analyses could not be completed due to the small sample size for grouping categories. Because this was primarily a cross-sectional study design, longitudinal analyses were not conducted to evaluate score interpretation. Future psychometric research should replicate these reliability and validity analyses and evaluate score interpretation.

One other possible limitation to the data is that the development and testing of this LIQ-GHD was only carried out with US patients and caregivers. However, there does not

appear to be evidence (e.g., from the literature) suggesting that the burden of daily r-hGH injections may differ substantially for patients residing in other parts of the world. Future research can confirm content relevance and performance of the LIQ-GHD in countries outside of the USA.

The benefits of a less frequent injection regimen might be further explored and elucidated in future research assessing the within-person difference in experience of more frequent (e.g., daily) versus less frequent (e.g., weekly) injections.

The LIQ-GHD may be useful for capturing and assessing aspects of the injection treatment burden of individuals receiving r-hGH injections. Addressing patient preferences for treatment may improve compliance, adherence, and, ultimately, clinical outcomes [47–49].

6 Conclusion

The LIQ-GHD is a new COA tool, designed for self- or dyad-administration, that has demonstrated evidence of content validity, reliability, and construct validity. The LIQ-GHD measures concepts that are important and relevant to patients (and their caregivers) and can be used to characterize the r-hGH injection treatment burden experienced by patients (and caregivers, where appropriate), to inform patient–healthcare provider communications and optimal individualized treatment decisions that may improve treatment compliance and adherence and long-term outcomes for GHD patients. The results of this research provide evidence that the LIQ-GHD is fit for use in clinical trials including adult patients (≥ 25 years of age), adolescents (12–17 years of age), and children (3–11 years of age) to establish treatment benefit in new GHD interventions.

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Compliance with Ethical Standards

Conflict of interest DMT-B, AY, REL, MK, EL, and AS are employed by Adelphi Values. JL and AP are employed by Pfizer. AMP is an independent research and evaluation consultant who was employed by Pfizer at the time of the research.

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Author contributions DMT-B, AY, AP, AMP, AS, and JL contributed to the design of the study. DMT-B, AY, AP, RL, MK, EL, and JL were involved in the acquisition and analysis of data for the work. All authors were involved in the interpretation of the results. DMT-B, AY, RL, and JL drafted the manuscript. All authors read, reviewed, and approved the final manuscript.

Data Availability Statement The data that support the findings of this study are available from Pfizer, but restrictions apply to the availability of these data, which were used under license for the current study and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of Pfizer. The authors can confirm that relevant data are included in the article.

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