

# KEY MEASUREMENT CONCEPTS AND APPROPRIATE CLINICAL OUTCOME ASSESSMENTS IN PEDIATRIC ACHONDROPLASIA CLINICAL TRIALS

eP252

Natalie V. J. Aldhouse<sup>1</sup>, Helen Kitchen<sup>1</sup>, Chloe Johnson<sup>1</sup>, Chris Marshall<sup>1</sup>, Hannah Pegram<sup>1</sup>, Sheryl Pease<sup>2</sup>, Sam Collins<sup>2</sup>, Christine L. Baker<sup>2</sup>, Katherine Beaverson<sup>2</sup>, Chandler Crews<sup>3</sup>, Kathleen W. Wyrwich<sup>2</sup>

<sup>1</sup>Clinical Outcomes Assessment, DRG Abacus (Part of Clarivate), Manchester, United Kingdom

<sup>2</sup>Pfizer Inc, New York, USA

<sup>3</sup>The Chandler Project, Little Rock, Alabama, USA

## BACKGROUND

- Achondroplasia is a rare genetic condition, in which bone growth is impaired. More than 250,000 people are affected worldwide [1].
- People with achondroplasia have short stature, short arms with a limited range of motion, short thighs, enlarged head, leg bowing, and hypermobile joints (hips, knees, shoulders) [2].
- Children and adolescents with achondroplasia (CWA) can experience complications including recurrent ear infections, sleep apnea, teeth crowding/misalignment and speech and hearing difficulties [3].
- Previous qualitative research has identified a substantial impact on how CWA feel and function [4].
- A literature review identified the Childhood Health Assessment Questionnaire (CHAQ) and Quality of Life in Short Stature Youth (QoLISSY) Brief as potential measures of the pediatric experience given their measurement of concepts related to physical functioning, activities of daily living, and well-being.

## OBJECTIVES

- To develop a conceptual model (CM) of the pediatric experience of achondroplasia.
- To evaluate the content validity and suitability of the CHAQ and QoLISSY-Brief in a population of CWA and/or their caregivers using cognitive debriefing.

## METHODS

- CWA in the United States (US) and/or their caregivers were recruited through a clinical database and advocacy organization to participate in 90-minute qualitative interviews. CWA aged 8-17 years were interviewed alongside their caregiver in a dyad interview, while caregivers of CWA aged 0-7 years were interviewed alone.
  - Participants were assigned a unique ID code to allow data to be reported anonymously, structured as follows:
    - [Recruitment number]-[Age group]-[Reporter: P, Pediatric participant or C, Caregiver].
    - For example, ID code '01-[8-11]-P' denotes a pediatric participant who is 8-11 years old and was given recruitment number 01, while '01-[8-11]-CG' is their caregiver.
- Interviews utilized concept elicitation (CE) methodology to explore CWA's experiences and caregivers' hypothetical perspectives of successful treatment outcomes.
- Cognitive debriefing (CD) methodology explored relevance and understanding of selected COAs.
  - Caregivers of CWA aged 0-7 years completed an observer-reported version of the CHAQ and QoLISSY-Brief. CWA aged 8-17 years completed a self-report version, if they were able, during the dyad interviews.
- CE data were subject to thematic analysis using ATLAS.ti version 7.5 software to identify concepts for inclusion in the CM.
- CD data were explored using framework analysis to identify the conceptual relevance and appropriateness of item wording, response scale/options and recall period of the COAs.

## RESULTS

### QUALITATIVE INTERVIEW PARTICIPANTS

- Thirty-six interviews were conducted:
  - n=8 interviews with the caregivers of children aged 0-2 years,
  - n=7 interviews with caregivers of children aged 3-7 years,
  - n=15 dyad interviews with children aged 8-11 years and their caregivers, and
  - n=6 interviews with adolescents aged 12-17 years and their caregivers.
- The demographic and clinical characteristics of the participants are presented in Table 1.

TABLE 1. PARTICIPANT CHARACTERISTICS

	CWA (N=36)	Caregivers (N=36)
<b>Age, Mean (SD) [Range]</b>	8 (4.4) [1-15]	40 (6.5) [26-50]
0-2, n (%)	8 (22)	
3-7, n (%)	7 (19)	
8-11, n (%)	15 (42)	
12-17, n (%)	6 (17)	
<b>Sex, n (%)</b>		
Male	23 (64)	7 (19)
Female	13 (36)	29 (81)
<b>Ethnicity, n (%)†</b>		
Caucasian or White	24 (67)	28 (78)
Black or African American	4 (11)	3 (8)
Asian	3 (8)	0 (0)
American Indian or Alaskan Native	1 (3)	0 (0)
Arabic	1 (3)	1 (3)
Prefer not to say	5 (14)	5 (14)
<b>Highest level of education completed, n (%)</b>		
High school, no diploma		1 (3)
High school diploma or equivalent		7 (19)
Associate's degree		5 (14)
Bachelor's degree		14 (39)
Graduate degree		9 (25)
<b>Age at diagnosis, n (%)</b>		
Before birth	16 (44)	
At/after birth	20 (56)	
<b>Treatment experience, n (%)</b>		
Vosoritide	1 (3)	
Surgery§	17 (49)	
Never treated	18 (50)	
<b>Comorbid conditions, n (%)</b>		
Respiratory disease	1 (3)	
None	35 (97)	

Abbreviations: CWA, Children/adolescents with achondroplasia; SD, standard deviation

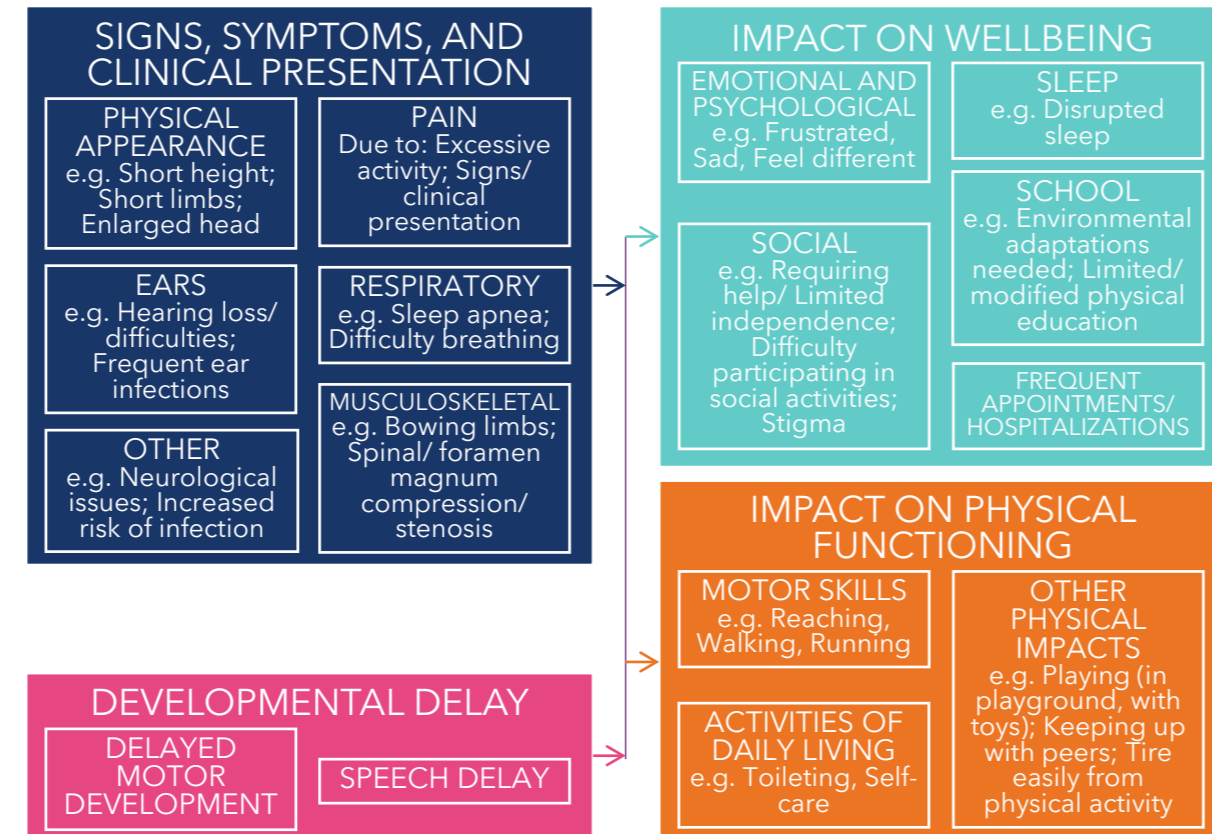
† Not mutually exclusive; participants could select multiple responses

‡ Including: adenoidectomy (n=8, 22%), decompression surgeries (n=8, 22%), tonsillectomy (7, 19%), ear tube insertion (6, 17%), and others (not mutually exclusive).

## CONCEPTUAL MODEL

- Discussion of the symptoms and impacts of achondroplasia identified pain (n=25, 69%) as the most frequently reported symptom of achondroplasia, and difficulties reaching (n=36, 100%), walking (n=34, 94%), and toileting (n=32, 89%) as commonly reported impacts on physical function and activities of daily living (ADL).
- An abbreviated CM is presented in Figure 1, and shows the concepts most frequently reported by participants.

FIGURE 1. (ABBREVIATED) CONCEPTUAL MODEL

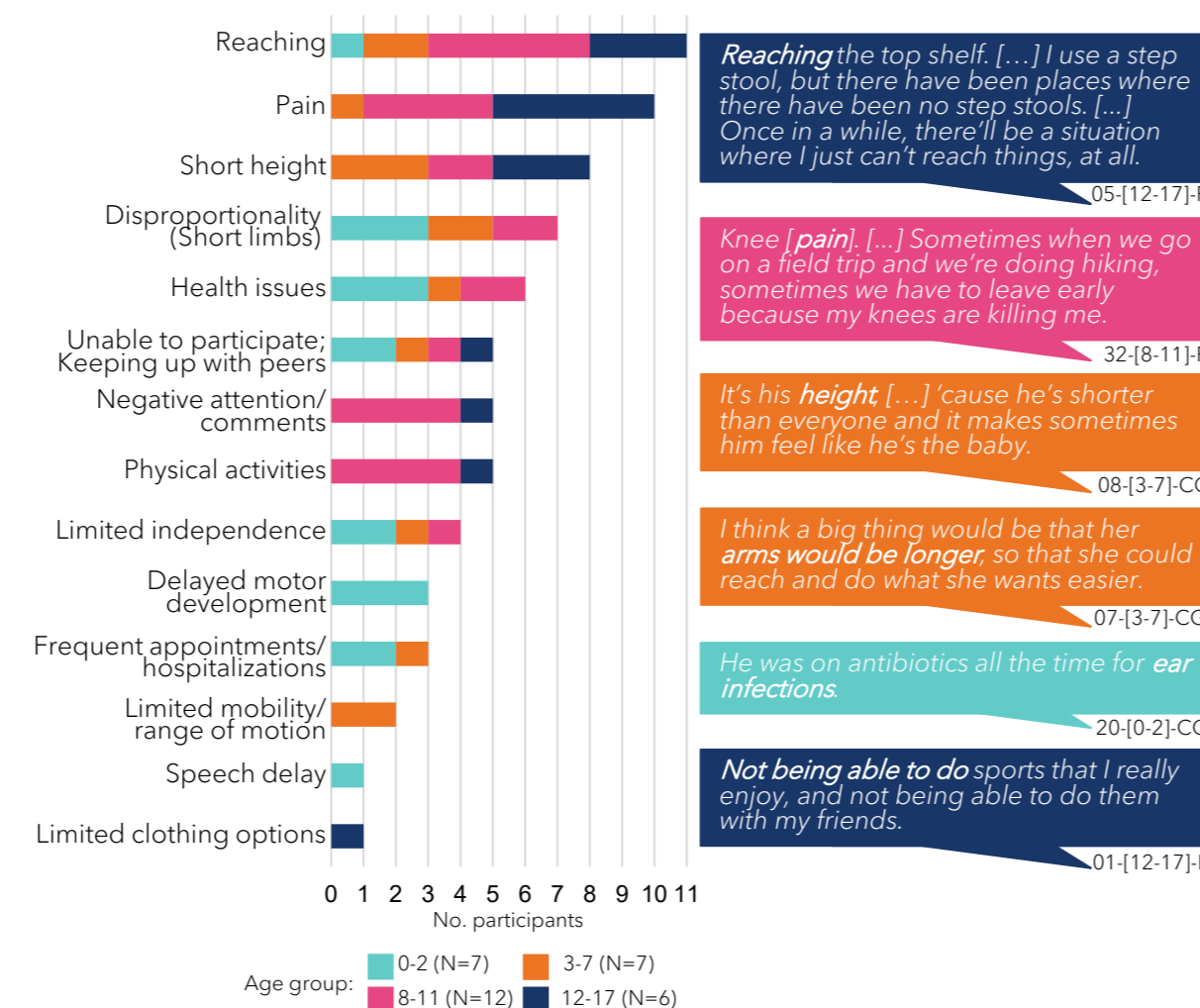


Abbreviated model presents domain names and example (most frequently reported) concepts only

## KEY MEASUREMENT CONCEPTS

- Participants were asked to name the three most bothersome aspects of achondroplasia (Figure 2)
  - Caregivers of CWA aged 0-7 years were asked to answer this on behalf of their child, while CWA aged 8-17 years were asked directly.
- Reaching, pain, short height, and short limbs were the most bothersome aspects of achondroplasia across the full sample.
- However, it should be noted that short limbs was not mentioned by CWA aged 12-17 years, and pain and short height were not reported by caregivers of children aged 0-2 years.
  - Amongst these youngest children, caregivers reported delayed motor development and health problems (e.g. sleep apnea, frequent ear infections) as areas of concern.

FIGURE 2. MOST BOTHERSOME CONCEPTS FOR CWA

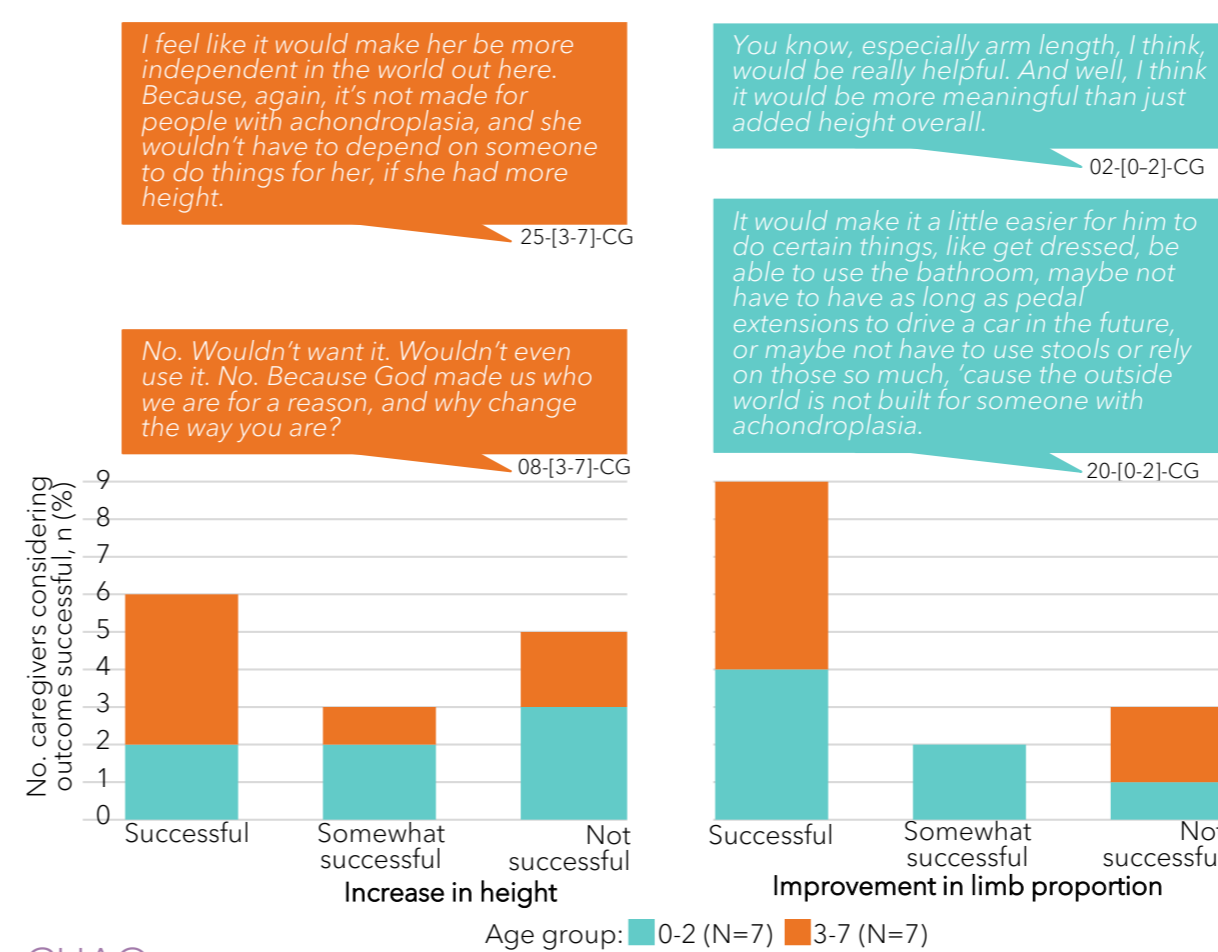


- Fourteen caregivers of children aged 0-7 years were asked whether an increase in height and/or an improvement in limb proportionality would be a meaningful treatment outcome (Figure 3).

- Nine caregivers (n=9/14, 64%) considered an increase in height a successful/somewhat successful treatment outcome.

- 11 caregivers (n=11/14, 71%) reported an improvement in limb proportionality would be considered a successful/somewhat successful treatment outcome.

FIGURE 3. SUCCESSFUL TREATMENT OUTCOMES



## CHAQ

### RELEVANCE

- The CHAQ had good conceptual coverage of the physical limitations often experienced by CWA, and each item was reported as relevant by at least n=2 participants. Items evaluating difficulties with reach and difficulties with activities were particularly relevant.
- A domain importance exploration identified that the 'hygiene' and 'reach' domains were the domains that CWA would like to find less bothersome or to experience less frequently.
- The need for assistance using aids/devices or help from another person are factored into the CHAQ scoring. A list of aids/devices is presented, alongside a write-in response box for 'Other' items. 27 participants made use of the 'Other' option when completing the measure during the CD.
  - The most frequently reported aid/device in 'Other' was a step stool (n=22), followed by a light-switch extender (n=6) and devices for toileting (n=4).

### UNDERSTANDING

#### ITEM WORDING

- Many children in the aged 8-11 subgroup experienced difficulties reading and/or understanding words included in the measure.
- Caregivers and CWA aged 12-17 were overall able to complete the measure without difficulty but some experienced difficulties with some sections of the measure:
  - Instructions
    - Three caregivers noted that it may be difficult to know what 'most children at your child's age' are expected to do.
    - One caregiver reported that it may be difficult for them to think about whether their child's limitations are due to achondroplasia.
  - 'Arising' domain
    - Six caregivers misinterpreted 'arising' to mean waking up in the morning, rather than e.g. getting up out of a chair.
  - 'Aids and Devices' items
    - Five caregivers and one adolescent aged 12-17 were unfamiliar with one or more of the devices listed.
  - Participants often interpreted these items to ask about any aids or devices used due to achondroplasia, rather than those specific to the activities listed.
  - Global evaluation item
    - Three caregivers had difficulty understanding the term 'Global evaluation.'

#### RECALL PERIOD

- Overall, eight caregivers and six CWA were able to understand the recall period (past week) and were able to respond to all items appropriately.
- Two caregivers and three CWA had difficulty understanding the phrasing of the recall period: "averaged over an entire day, over the past week".
  - 14-[3-7]-CG: Err, so that was confusing. [...] Do you mean that things that he does every day, um, over the course of a week, or does that mean something else?
- Two caregivers and four CWA described an incorrect recall period when asked by the interviewer, e.g. the past few years (n=2), past year (n=2), past few months (n=1), past month (n=1), or the past day (n=1).
- It was unclear if the remaining participants interpreted the recall period correctly as they did not directly comment on it during their interview.

#### RESPONSE OPTIONS

- Likert scale: All caregivers were able to use the response options as written to select an answer to each item, but n=5 CWA struggled to understand the 'not applicable' response option.
- Pain/Global Evaluation 0-100 Visual Analogue Scale (VAS): All participants were able to use the scales as presented but n=6 felt they would be easier to interpret if the anchors appear to be reversed and n=4 found it difficult to choose where to place a mark.

#### PROPOSED AMENDMENTS AND RECOMMENDATIONS

- Due to difficulties experienced by children aged 8-11 it is recommended that self-completion is not appropriate for this age group and instead caregivers should complete the Observer-Reported (ObsRO) version of the measure on their behalf.
- Participant feedback suggested minor amendments to CHAQ wording (Table 2).

TABLE 2. RECOMMENDED EDITS FOR THE CHAQ

ELEMENT	EDIT	RATIONALE
INSTRUCTIONS	Shortened and simplified wording	To make them easier to understand.
RECALL PERIOD	Change to 'Over the past 7 days'	The instruction to 'average' difficulties experienced 'over an entire day' is not applicable to achondroplasia and several participants found the original description of the recall period to be confusing.
'ARISING'	Replacement of 'Arising' with 'Getting Up'	'Getting up' may better describe the applicable concepts
'AIDS AND DEVICES' ITEMS	Capitalization of "...any of the ABOVE activities."	May draw participants' attention that only aids/devices used during completion of the associated activities should be considered.
AIDS AND DEVICES ('HYGIENE,' 'REACH,' 'GRIPPING AND OPENING THINGS')	Addition of 'step stool' as a listed aid/device	To improve relevance of the measure to achondroplasia and reduce likelihood that participants fail to acknowledge use of this device.
'GLOBAL EVALUATION' ITEM	Removal of 'Global Evaluation' heading	To make the item easier to complete.
'PAIN' AND 'GLOBAL EVALUATION' RESPONSE SCALES	Replacement of 0-100 VAS with 0-10 NRS	A 0-10 NRS is easier to complete than a 0-100 VAS due to the clear numeric response options, and removes risk of inconsistencies in the length of the scale due to formatting/printing of pen and paper measures.
'PAIN' RESPONSE SCALE	Change anchors to 'No pain' and 'Worst pain imaginable'	These anchors are generally considered most appropriate for pain measurement.

## QOLISSY-BRIEF

### RELEVANCE

- The QoLISSY-Brief has good conceptual coverage of the impacts on well-being often experienced by CWA, and each item of the QoLISSY-Brief was reported as relevant by at least n=12 (33%) participants.
- Items evaluating reaching, height bother, being treated differently, and height preventing from doing things others could be most relevant.

### UNDERSTANDING

#### ITEM WORDING

- Many children in the ages 8-11 subgroup experienced difficulties reading and/or understanding words included in the measure, but caregivers and most adolescents aged 12-17 were able to complete the measure without difficulty.

#### RECALL PERIOD

- No recall period is included in the QoLISSY-Brief and therefore the time periods that respondents considered when reporting were varied and inconsistent (Table 2) ranging from the past week to several years.

TABLE 3. RECALL PERIODS USED BY PARTICIPANTS WHILE COMPLETING THE QOLISSY-BRIEF

RECALL PERIOD USED	N (%) (N=27)	EXAMPLE QUOTE
NON-SPECIFIC	6 (22)	13-[12-17]-P: Recently, but also, kind of, the general picture because, again, not having much experience with the general public right now.
RIGHT NOW/TODAY	5 (21)	20-[0-2]-CG: Um, I was trying to kind of think about him and his reactions and how he - his personality and how he acts today.
PAST WEEK	1 (4)	201-[0-2]-CG: Just in the past, like the past week.
PAST TWO WEEKS	2 (7)	18-[8-11]-P: I was thinking about a couple of weeks ago, I think.
PAST MONTH	2 (7)	19-[8-11]-P: Like, a little bit far back. [...] Um, a month ago or something like that. Like, a long time ago, not, like, a week, a long time ago.
PAST FEW MONTHS	5 (21)	38-[8-11]-CG: In just the last, you know, for a while. I mean, um, say few months or something like that. In the, in the, in the present or, or near-term past. Yeah.
PAST YEAR	1 (4)	15-[12-17]-P: Probably within the last year.
PAST 1-2 YEARS	3 (11)	01-[12-17]-P: Mostly in the past, like, year or two.
ENTIRE LIFE	2 (7)	05-[3-7]-CG: I was thinking about, like, his entire life here, when I answered the questions.

#### RESPONSE OPTIONS

- All participants were able to use the response options without difficulty.

#### PROPOSED AMENDMENTS AND RECOMMENDATIONS

- Due to difficulties experienced by children aged 8-11 it is recommended that self-completion is not appropriate for this age group and instead caregivers should complete the ObsRO version of the measure on their behalf.
- The addition of a 7-day recall period to the QoLISSY-Brief could improve the usability and suitability of the measures for CWA. This will standardize the time period that respondents think about, and is important for longitudinal data collection in clinical trials to facilitate the potential of the measure to be responsive to change. It is generally recommended that a PRO should include a recall period of 7 days to evaluate impact concepts.

## CONCLUSIONS

- The CHAQ and QoLISSY-Brief are relevant and appropriate measures of physical function and emotional/social well-being in pediatric achondroplasia.
- Minor edits to wording of the CHAQ and the addition of a 7-day recall period to the QoLISSY-Brief are recommended to improve understanding and standardize reporting.
- The developer of the CHAQ has granted permission to make these changes and form the 'CHAQ (adapted for achondroplasia),' and the sponsor of this work holds the copyright to the QoLISSY-Brief.
- Self-report is recommended for CWA aged 12-17 years and caregiver-report is recommended for ages 0-11 years.

## REFERENCES

- Horton WA et al. Lancet. 2007;370(9582):162-72.
- Pauli RM et al. Orphanet J Rare Dis. 2019; 14(1):1.
- Hunter A et al. J Med Genet. 1998;35(9):705-12.
- Pfeiffer KM et al. ESPE; September 19-21 2019; Austria, Vienna.

#### FUNDING AND COMPETING INTERESTS

This study was funded by Pfizer Inc. NVJA, HK, CJ, CM, and HP are employees and stockholders of Clarivate, a health economic and outcomes research consultancy that consults with various pharmaceutical companies. Pfizer funded Clarivate to undertake this research. SC, CLB and KB are employees and shareholders at Pfizer Inc. SP and KWW were employees at Pfizer Inc when this research was conducted, and are shareholders at Pfizer Inc. CC has no conflicts of interest to declare. NVJA and HK of DRG Abacus (Part of Clarivate) provided medical writing support that was funded by Pfizer Inc.