

# Disease and Treatment Burden in Children and Adolescents with Growth Hormone Deficiency (GHD)

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## Background

- In both early and later childhood, GHD results in slow or flat rate of growth.
  - The child usually has normal body proportions, but often looks chubbier, shorter and younger for their age compared with most children of the same age and gender.<sup>1,2</sup>
- Children with GHD may experience psychological and behavioral issues related to their short stature, including social withdrawal, academic underachievement, anxiety, and shyness.<sup>3-9</sup>
- Treatment involves growth hormone injections, typically given once a day and continuing until the child reaches final height.
- With GH replacement treatment, many children with GHD can reach normal height.<sup>2</sup>
- Improvement in self-esteem, emotional well-being and mood in children with GHD has been shown after growth hormone treatment.<sup>10,11</sup>
- If left untreated, or if GHD develops late in childhood, the condition can contribute to shorter-than-average height and delayed puberty.<sup>12</sup>
- Unfortunately, no disease-specific measures exist to assess the impact of GHD and treatment on children and adolescents as well as the treatment burden for parents of these children.

## Objective

- To explore the burden of GHD and treatment for children, adolescents and parents and develop disease-specific models of the impact of GHD and treatment which can support the development of disease-specific outcome measures.

## Methods

- For concept elicitation, the literature regarding GHD was reviewed, and qualitative interviews with GHD clinical experts, children (ages 8 – <13) with confirmed GHD and parents of children (ages 4 – <13) with confirmed GHD were conducted.
- Interview transcripts were analyzed based on adapted Grounded Theory for major and minor themes and sub-concepts.
- Based on the qualitative analysis, theoretical models for the impact of GHD and GHD treatment were developed.
  - Themes were considered major if they were endorsed by more than 15% of either child or parent respondents. Minor themes were those for which endorsement fell below 15% of either child or parent respondents. Minor subthemes were reviewed and considered for item generation based on conceptual importance.
- Items were generated for major themes and were cognitively debriefed resulting in validation-ready versions of the measures.
- The study was reviewed and approved by an independent institutional review board (IRB).

## Results

- Eight clinical experts who treated, on average, 3.1 new cases of GHD per month were interviewed.
- A total of 70 respondents were interviewed regarding both the impact of GHD and GHD treatment.
  - Respondents were 39 children (ages 8 – 13) with GHD and 31 parents of children (ages 4 – <13) with GHD in the US (21 children, 18 parents), the UK (7 children, 5 parents) and Germany (11 children, 8 parents) (see Table 1).
- The cognitive debriefing sample included 13 GHD children ages 8 – <13 and 13 parents of children with GHD ages 4 – <13.
- Concept elicitation identified 4 disease burden (see Table 2), 3 child and 2 parent treatment burden domains (see Table 3).
- Based on the concept elicitation and cognitive debriefing findings, it was decided that children ages 9 – <13 are able to complete the measures on their own as a patient reported outcome (PRO).
- Children and parents reported consistent symptoms/impacts, although the severity of the impact sometimes differed with parents reporting greater severity than children.
- Based on Theoretical Models of disease and treatment burden (see Figures 1 and 2), Conceptual Models of 2 disease-specific measures were generated (see Figures 3 and 4):
  - Treatment Related Impact Measure – Child GHD (TRIM-CGHD), a measure of the impact of disease on children with GHD. There is a PRO version for children ages 9 – <13 and an Observer Reported Outcome (ObsRO) version, to be completed by parents, for children ages 4 – <9.
  - Treatment Burden – Child GHD (TB-CGHD), a measure of the burden of GHD treatment. There is a PRO version for children ages 9 – <13 and an ObsRO version, to be completed by parents, for children ages 4 – <9.
- The TB-CGHD also includes a Parent PRO section to assess the treatment burden on the parent.
- Responses did not differ substantially among countries.

**Table 1 Concept Elicitation Sample Characteristics**

| Sample Characteristic  | Total                                   |
|--|---|
| <b>Children N=39</b>   |   |
| Age group counts, years, n (%)   | 8–9: 7 (17.94)<br>10–<13: 32 (82.05)    |
| Gender, n (%)  | Female: 11 (28.20)<br>Male: 28 (71.79)  |
| Age at diagnosis, years, mean (range)  | 8.07 (3–12)                             |
| Age first started GHD medication (92.29% of children), years, mean (range)       | 8.57 (3–12)                             |
| <b>Parents N=31</b>  |   |
| Parent age, years, mean (range)  | 39.09 (23–47)                           |
| Relationship to child <sup>1</sup> , n (%)                                       | Mother: 30 (88.23)<br>Father: 4 (11.76) |
| Child's age at diagnosis, years, mean (range)                                    | 5.88 (3–12)                             |
| Age child first started GHD medication (85.29% of children), years, mean (range) | 6.24 (3–12)                             |

Interview countries were the US, UK and Germany.  
<sup>1</sup>3 parents described the experiences of 2 of their children.

**Table 2 Disease Burden**

The % of children and parents who endorsed each major domain subtheme

| Disease Burden Domains and Subthemes   | Total Sample (%) | Children (%) | Parents (%) |
|--|------------------|--------------|-------------|
| <b>Symptom Domain</b>  |                  |              |             |
| Poor appetite  | 48               | 33           | 65          |
| Reduced strength/poor muscle development   | 42               | 36           | 50          |
| Poor energy  | 38               | 33           | 44          |
| Reduced endurance  | 32               | 23           | 41          |
| Poor sleep   | 22               | 18           | 26          |
| Tiredness  | 18               | 8            | 29          |
| <b>Physical Impact Domain</b>  |                  |              |             |
| Reduced/limited performance in sports/activities or excluded from sports/physical activities | 58               | 54           | 62          |
| Hindered in reaching things  | 44               | 36           | 53          |
| <b>Social Well-being Domain</b>  |                  |              |             |
| Being mistaken for younger   | 58               | 44           | 74          |
| Teasing (name calling)   | 41               | 28           | 56          |
| Not fitting in/level of ease with peers  | 30               | 13           | 50          |
| Treated differently from peers by parents  | 25               | 10           | 41          |
| Choosing not to participate or holding back from participating in activities                 | 25               | 10           | 41          |
| Treated differently by other children  | 22               | 10           | 35          |
| Being left out/excluded from activities  | 14               | 5            | 24          |
| Bullying   | 12               | 10           | 15          |
| <b>Emotional Well-being Domain</b>   |                  |              |             |
| Worry (about size, how others treat you, if you will grow, being different)                  | 55               | 44           | 68          |
| Poor self confidence   | 41               | 23           | 62          |
| Feeling annoyed  | 25               | 15           | 35          |
| Feeling sad  | 25               | 26           | 24          |
| Being embarrassed  | 21               | 18           | 24          |
| Feeling angry  | 18               | 3            | 35          |
| Feeling upset  | 12               | 5            | 21          |
| Feeling nervous/anxious  | 7                | 0            | 15          |

## Selected Quotes About Disease Burden

- Symptom Domain**
- Child: *I'm eating more. I used to not be eating all of my plate, but now I'm eating most of it.*
  - Parent: *Her appetite has doubled, so now she takes seconds and thirds at dinner.*
- Physical Impact Domain**
- Child: *Like if we were playing tag ... I wouldn't run as fast as I really thought I wanted to ... I played, but it wasn't really all that enjoyable.*
  - Parent: *So this whole summer he took basketball lessons. But he still couldn't, like he could barely shoot the basketball ... And that made him not want to play.*
- Social Well-being Domain**
- Child: *Making friends is a little easier now because I know that they won't treat me like an 8-year-old or something like that.*
  - Parent: *She was constantly underestimated by her environment ... she was constantly confronted with the fact that people thought that she was younger.*
- Emotional Well-being Domain**
- Child: *I was always smaller than the other kids, but like last year I wasn't growing at all and I was getting kind of worried.*
  - Parent: *My son was already worried. He is 7 now, and during the last 6 months he was really worried why he didn't grow anymore.*

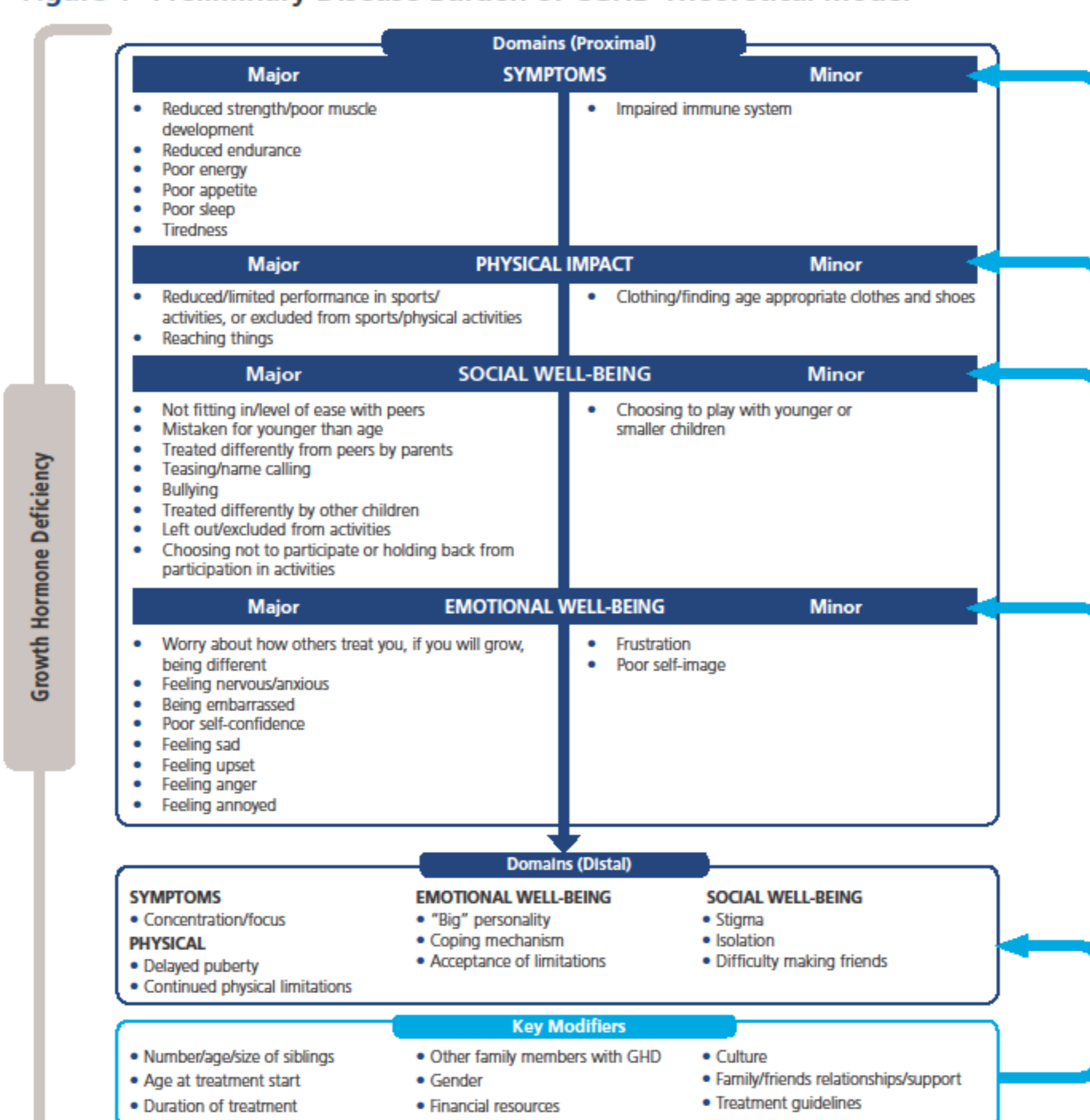
**Table 3 Treatment Burden — Children and Parents**  
The % of children and parents who endorsed each major domain subtheme

| Treatment Burden Domains and Subthemes — Children   | Total Sample (%) | Children (%) | Parents (%) |
|---|------------------|--------------|-------------|
| <b>Child Physical Domain</b>  |                  |              |             |
| Pain  | 33               | 41           | 24          |
| Bruising  | 19               | 21           | 18          |
| Burning/stinging  | 8                | 10           | 6           |
| Soreness  | 8                | 15           | 0           |
| <b>Child Emotional Well-being Domain</b>  |                  |              |             |
| Worry about injections, worry about remembering   | 37               | 23           | 53          |
| Unhappiness about injection frequency   | 25               | 26           | 24          |
| Fear of injections  | 22               | 8            | 38          |
| Embarrassment about treatment   | 22               | 15           | 29          |
| Annoyance about injections  | 11               | 15           | 6           |
| Feeling different from other children   | 10               | 13           | 6           |
| <b>Child Interference Domain</b>  |                  |              |             |
| Interference with overnight or other activities   | 29               | 33           | 24          |
| Time needed emotionally to prepare for shot (avoiding or delaying the injections)                   | 23               | 8            | 41          |
| Needing to stop/interrupt what you are doing (daily routine)  | 19               | 21           | 18          |
| <b>Treatment Burden Domains and Subthemes — Parents</b>   |                  |              |             |
| N=31 %  |                  |              |             |
| <b>Parent Emotional Well-being Domain</b>   |                  |              |             |
| Worry or anxiety about treatment or treatment administration  | 18               | 58           |             |
| Worry about causing child pain  | 13               | 42           |             |
| Feeling guilt   | 7                | 23           |             |
| Feeling sadness   | 5                | 16           |             |
| Feeling frustration   | 3                | 10           |             |
| <b>Parent Interference Domain</b>   |                  |              |             |
| Interference/time needed to prepare/administer injection (logistics) OR prepare child for injection | 13               | 42           |             |
| Interfere with travel/vacations   | 13               | 42           |             |
| Scheduling time around daily/family routines  | 11               | 35           |             |
| Interfere with social life  | 5                | 16           |             |

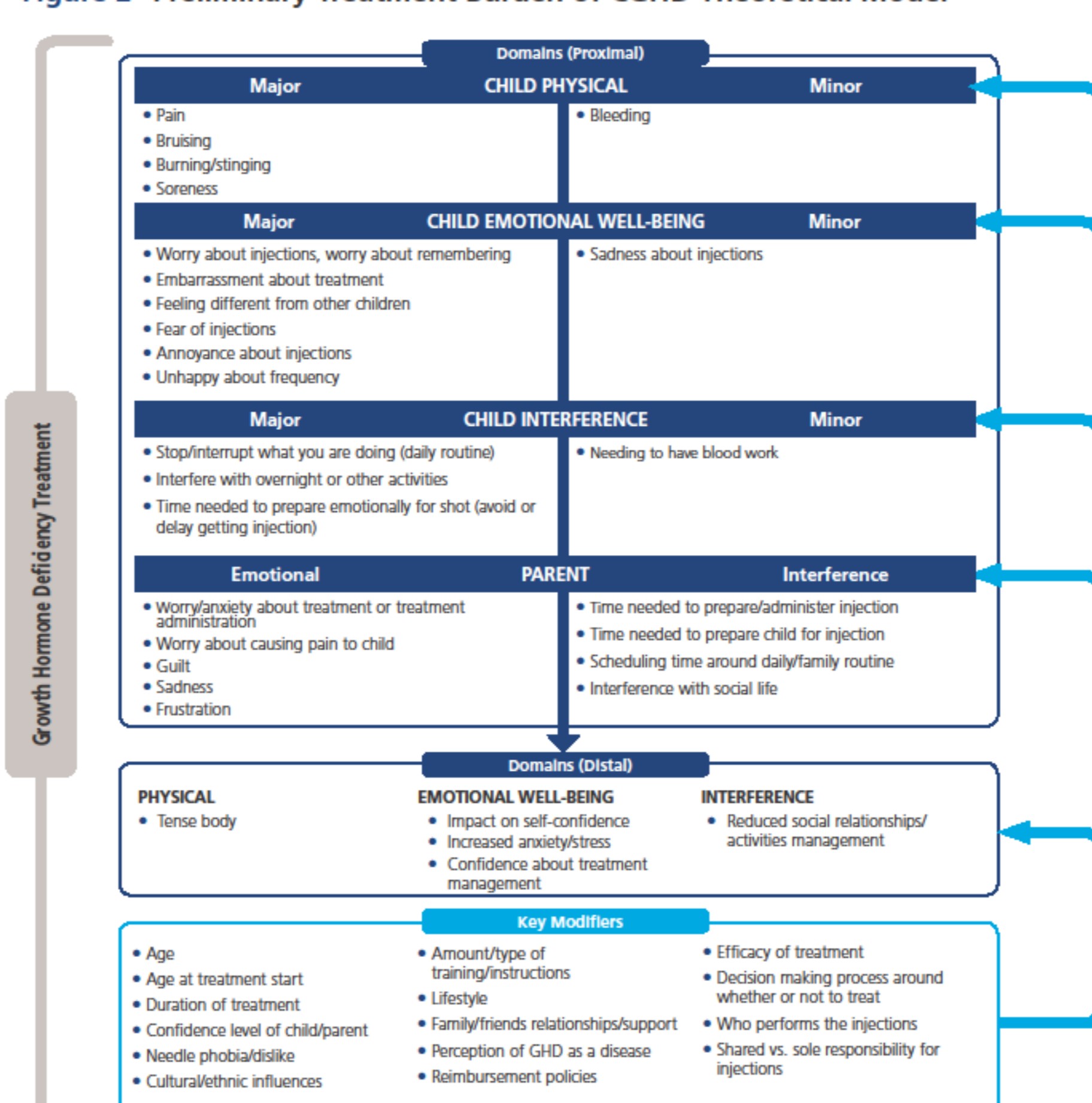
## Selected Quotes About Treatment Burden

- Child Physical Domain**
- Child: *Like it hurts all the time a little bit.*
  - Parent: *It hurts. Yes, I mean she screams. She cries, it hurts.*
- Child Emotional Well-being Domain**
- Child: *Well worry about like if I like to be able to get it on time, to do it like at a certain time. ... Because I worry about what happens if I forgot about it now ... That's what worries me.*
  - Parent: *He would bring it up. "Is it time for my shot?" "No, honey, it's not." "Or my medicine?" ... "Are you sure it's not time?" "Okay when?"*
- Child Interference Domain**
- Child: *That I sometimes simply don't want to do it ... I just run away somewhere.*
  - Parent: *Yeah. Definitely he — every night it's that 10 minutes of anger right before.*
- Parent Emotional Well-being Domain**
- I'm trying to not let him see that I'm freaking out because he needs to see me calm. Yeah, it's been hard too. I get worried too...*
  - I almost have to mentally prepare myself to give him the shot because it hurts me in my heart to know that I'm doing something to him he finds so unpleasant.*
- Parent Interference Domain**
- Even if, like, I were to be going out, I couldn't go out until later because I'd have to give him the shot.*
  - I feel like it ruins every single night...*

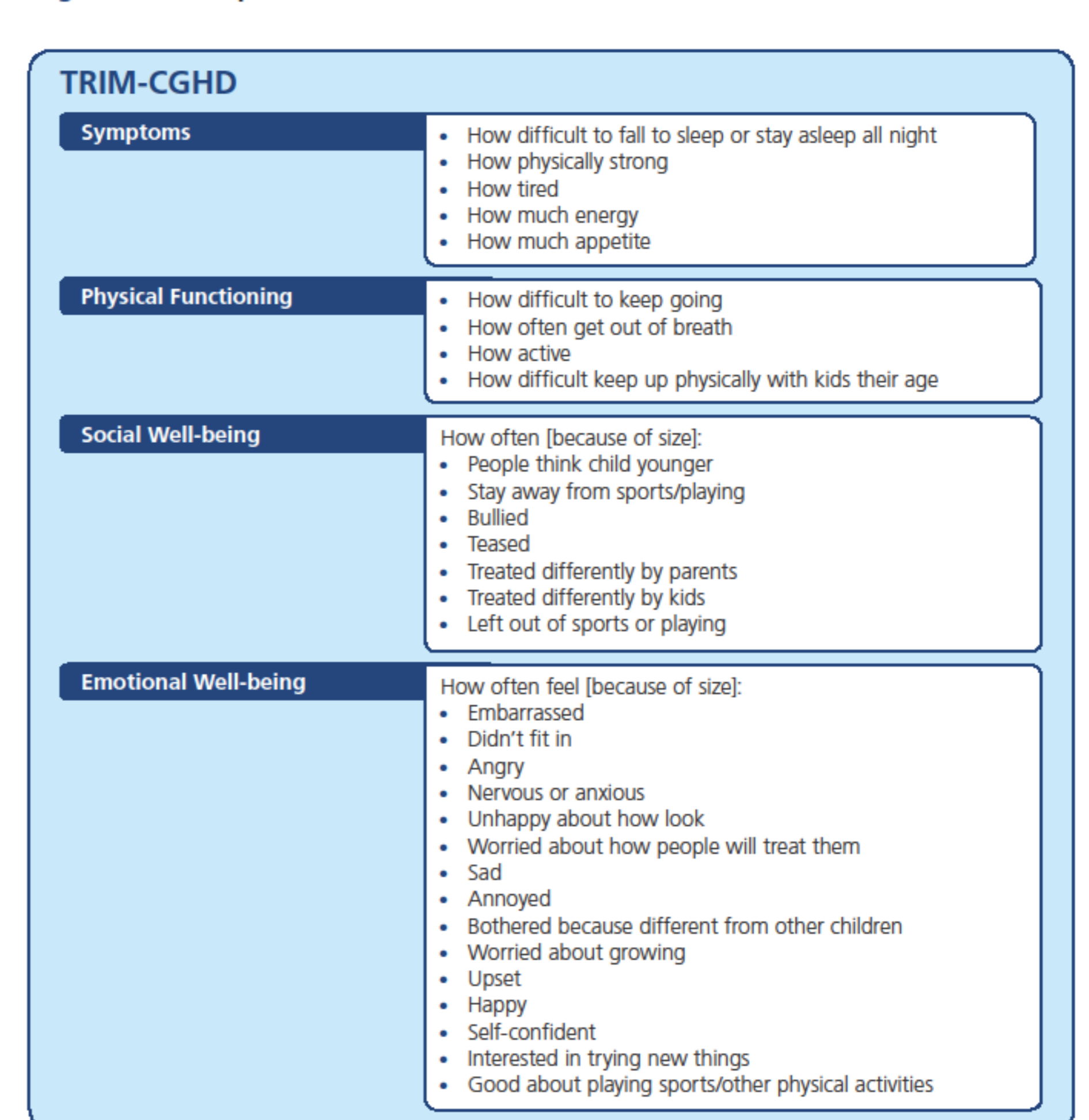
**Figure 1 Preliminary Disease Burden of CGHD Theoretical Model**



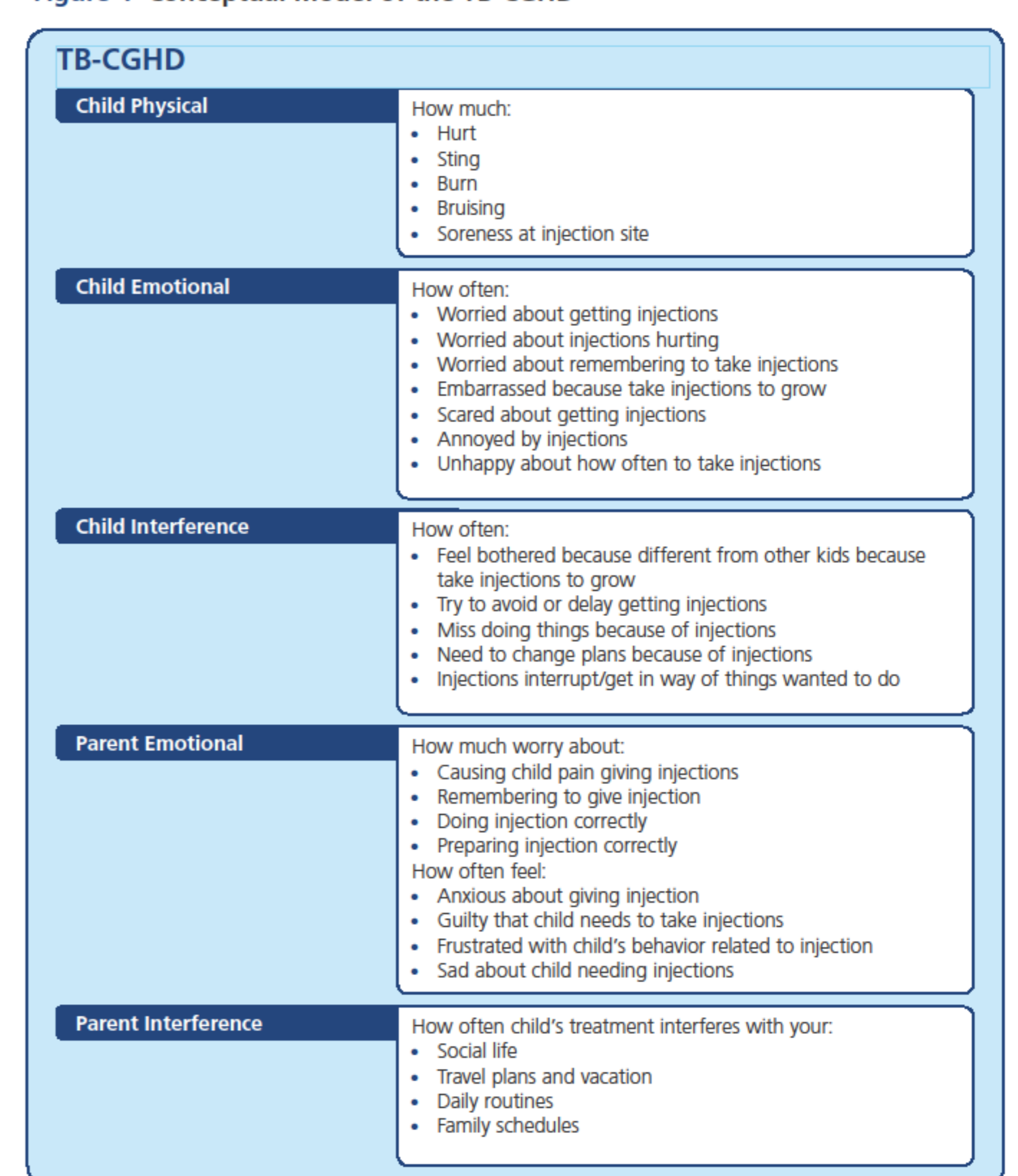
**Figure 2 Preliminary Treatment Burden of CGHD Theoretical Model**



**Figure 3 Conceptual Model of the TRIM-CGHD**



**Figure 4 Conceptual Model of the TB-CGHD**



## References

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## Conclusions

- The overall burden of GHD in children and adolescents is considerable and not limited to short stature.
- The burden of GHD includes other symptoms such as poor energy, as well as physical limitations and social and/or emotional impacts.
- There are modifiers to the experienced severity of both disease and treatment burden that may be amenable to interventions such as early identification and treatment.
- The conceptual models developed in this study have adequate conceptual validity to support item generation for new disease specific measures of the impact of GHD and treatment.
- Accurate and reliable assessment of symptoms and impacts, on both children and parents, may help clinicians to better address the burden of disease, assess treatment effect, and may improve the quality of doctor–patient communications.
- Interviews were designed to examine the impacts of childhood GHD. Future research should confirm that these impacts are disease-specific.