

Supplementary Materials

Supplementary Table 1. Summary of changes to health state vignettes based on initial review by research team.

Domain/Item/Issues	Original description from Hanbury et al. ¹	Example revised content
Context/Framing of health state <ul style="list-style-type: none"> Changed parent/carer perspective to child perspective Removed reference to 'your child' in the content of all health state vignettes 	In all health states	
	Imagine that you are a parent or caregiver of a child with a severe medical condition. This medical condition means that:	Imagine a 10-year old child with a severe medical condition. This medical condition means that:
Motor impairment <ul style="list-style-type: none"> Content of the original vignette was very symptom- focused and did not describe the implications/impact of the symptoms Added impact of being bedridden/immobile to the description 	E.g. Health state 1: Bedridden	
	Your child is bedridden and unable to move by themselves. This means that your child is unable to lift and control their head, crawl, sit, or stand.	They are bedridden and unable to move by themselves. This means that they are unable to lift and support their own head, crawl, sit, or stand. It is difficult for the child to be transferred from the bed to a wheelchair. They need to be moved regularly by parents/ carers to prevent bed sores.
Feeding/swallowing difficulties <ul style="list-style-type: none"> Added context to what causes feeding/swallowing difficulties 	E.g. Health state 1: Bedridden	
	They are unable to feed themselves and may need to be fed through a tube (a "nasogastric" tube).	Due to lack of head control, difficulty swallowing and risk of choking, they are unable to feed themselves and may need to be fed through a tube (a "nasogastric" tube).
Oculogyric crises <ul style="list-style-type: none"> Oculogyric crisis is a key symptom of AACDd. However, the terminology is very clinical/technical and it is not clear how much of the term is understood by participants Removed the term "oculogyric crises" and revised the description of the event and its implication to child to improve clarity. 	E.g. Health state 1: Bedridden	
	Your child experiences something called an oculogyric crisis. This is where their eyes rotate or roll in unusual ways, similar to an epileptic seizure. This may last for several hours, several times a day.	Their eyes rotate or roll in unusual ways, similar to an epileptic seizure. This occurs several times a day, spontaneously without any trigger, and may last for several hours. It is painful and uncomfortable for the child during an episode.
Irritability/Screaming <ul style="list-style-type: none"> It is not uncommon for a child to be irritable and screaming. Further context was added to describe the specific behavioral issue faced by a child with AACDd. According to medical experts, child is inconsolable, and crying/screaming is unprovoked. 	E.g. Health state 1: Bedridden	
	Your child screams constantly throughout the day and night. They will be extremely irritable and agitated.	They may scream or cry constantly without any trigger throughout the day and night. They are extremely irritable and agitated.
Sleep <ul style="list-style-type: none"> As it is not uncommon for a child to have sleep problems, further context was added to describe the specific sleep issues faced by a child with AACDd. According to medical experts, sleep problem is due to neurotransmitter imbalance and often manifests as trouble getting to sleep and interrupted sleep. 	E.g. Health state 1: Bedridden	
	Your child will have problems sleeping.	They have difficulty getting to sleep and experience disturbed sleep.
Quality of life domains	E.g. Health state 1: Bedridden	

Domain/Item/Issues	Original description from Hanbury et al. ¹	Example revised content
<ul style="list-style-type: none"> • Original vignette did not describe impact of disease on child's quality of life • Descriptions on how the condition impact a child's ability to do daily activities, leisure activities, their social interactions and pain/discomfort were added based on findings from the literature 	Not described in original vignette	<p>The child is unable to carry out their daily activities (e.g., self-care, washing, dressing) and is dependent on their parent/carer. Leisure activity (e.g., going out to the park, playing with toys) is severely limited.</p> <p>The child is unable to play or interact with other children. They experience pain and discomfort most of the time.</p>
<p>The original vignette assumed that a child who is able to walk with assistance (HS5) does not experience dystonia, oculogyric crises, or any other autonomic symptoms. However, the absence of symptoms was not described explicitly. Medical experts explained that AADCd symptoms are still present in individuals who are able to walk with assistance due to underlying residual neurotransmitter imbalance. Symptoms such as autonomic symptoms, dystonia and oculogyric crisis were added to HS5. The severity of these symptoms was updated based on medical expert opinion.</p>	<p>E.g. Health state 5: Walking with assistance</p> <p>Not described in original HS5</p>	<p>They very occasionally experience painful muscle spasms, and their arms and legs move involuntarily with sudden jerking or twisting. Their eyes rotate or roll in unusual ways, similar to an epileptic seizure. This happens very occasionally and spontaneously without any trigger. It is painful and uncomfortable for the child during an episode. They have very occasional abdominal problems, such as constipation or diarrhea. Other symptoms include the very occasional blocked nose (nasal congestion), drooling and sweating</p>
<p>Across all health states, some of the descriptions were poorly worded, ambiguous, inconsistent or not in line with best practice recommendations (e.g., use of future tenses, using relative descriptions). Descriptions were revised where relevant for consistency across health states and to improve clarity.</p>	<p>E.g. Health state 1: Bedridden and Health state 5: Walking with assistance</p> <p>Example in HS1:</p> <p>Your child will have severe abdominal problems, such as constipation or diarrhea. Other symptoms include severely blocked nose (nasal congestion), which may lead to serious chest infections, as well as excessive drooling, excessive sweating and extreme tiredness.</p> <p>Example in HS5, sleep domain:</p> <p>Your child will be more tired than usual</p>	<p>Example in HS1:</p> <p>They have severe abdominal problems, such as constipation or diarrhea. Other symptoms include severely blocked nose (nasal congestion), excessive drooling, excessive sweating and extreme tiredness.</p> <p>Example in HS5, sleep domain:</p> <p>They need more sleep than other children their age.</p>

Domain/Item/Issues	Original description from Hanbury et al. ¹	Example revised content
The description of each health state is lengthy and complex due to the nature of the condition. To help with participant information processing, the description of the symptoms and impacts of the condition was re-ordered; More impactful descriptions were presented first. This is to help paint a good narrative of the description in each health state.	In all health states	
	NA	Reordered descriptions/domain in vignette to: motor impairment, motor disorders, oculogyric crises, feeding, pain/discomfort, mental impairment, behavior, sleep, other autonomic symptoms, impact on quality of life.

Supplementary Table 2. Summary of changes to health state vignettes based on healthcare provider (HCP) and caregiver feedback.

Domain/Item/Issue	Example of revised content by research team	Example of revised content based on HCP and caregiver feedback
<p>Hypotonia</p> <ul style="list-style-type: none"> Based on HCPs feedback that key difference in motor ability between the more severe and less severe health states were lack/presence of autonomous/voluntary movements. 	<p>E.g., Health state 1: Bedridden and Health state 3: Able to sit unaided</p> <p>Health state 1 They have very poorly developed muscle tone meaning their body, arms and legs are very floppy. This means they are unable to grasp or hold onto things.</p> <p>Health state 3 The muscles in their body, arms and legs are floppy. They are able to reach out and or hold onto things.</p>	<p>Health state 1 They have very poorly developed muscle tone meaning their body, arms and legs are very floppy. This means they are unable to grasp or hold onto things. They are unable to move voluntarily.</p> <p>Health state 3 The muscles in their body, arms and legs are floppy but have some voluntary movements. They are able to reach out and or hold onto things.</p>
<p>Feeding/swallowing difficulties</p> <ul style="list-style-type: none"> HCPs commented that patients in HS1 and HS2 used gastric tube rather than naso-gastric tube. Caregiver commented that their children in HS4 and HS5 were able to take solid food compared to pureed or soft food 	<p>E.g. Health state 1: Bedridden, Health state 3: Able to sit unaided, and Health state 5: Walking with assistance</p> <p>Health state 1 Due to lack of head control, difficulty swallowing and risk of choking, they are unable to feed themselves and may need to be fed through a tube (a "naso-gastric" tube).</p> <p>Health state 3 They are able to feed themselves a little bit, and do not need to be fed through a tube (a "naso-gastric" tube).</p> <p>Health state 5 They are able to feed themselves</p>	<p>Health state 1 Due to lack of head control, difficulty swallowing and risk of choking, they are unable to feed themselves and need to be fed through a tube (a "gastric" tube which is inserted through their tummy).</p> <p>Health state 3 They are able to feed themselves a little bit, but may need to be fed by a caregiver using pureed or soft foods.</p> <p>Health state 5 They are able to feed themselves and are able to eat solid foods.</p>
<p>Oculogyric crises</p> <ul style="list-style-type: none"> HCPs and caregivers commented that descriptions of oculogyric crisis and its frequency were inaccurate. 	<p>E.g. Health state 1: Bedridden</p> <p>Their eyes rotate or roll in unusual ways, similar to an epileptic seizure. This occurs several times a day, spontaneously without any trigger, and may last for several hours. It is painful and uncomfortable for the child during an episode.</p>	<p>Their eyes roll upwards, similar to an epileptic seizure. This occurs several times a week, spontaneously without any trigger, and may last for several hours. It is painful and uncomfortable for the child during an episode.</p>

Domain/Item/Issue	Example of revised content by research team	Example of revised content based on HCP and caregiver feedback
<u>Irritability/Screaming</u> <ul style="list-style-type: none"> • According to HCPs and caregivers, irritability, screaming and crying are improved in the less severe health states but children still experience some impairment in emotion and mood regulations 	E.g. Health state 5: Walking with assistance Their mood is mostly the same as that of a child their own age, but they may become irritable or cry without a trigger.	Their mood is mostly the same as that of a child their own age. They occasionally react disproportionately and experience emotional outbursts

Supplementary Table 3. Final health state vignettes.

Health state	Description
HS1: Bedridden	<p>Imagine a 10-year-old child with a severe medical condition. This medical condition means that:</p> <ul style="list-style-type: none"> • They are bedridden and unable to move by themselves. This means that they are unable to lift and support their own head, crawl, sit, or stand. It is difficult for the child to be transferred from the bed to a wheelchair. They need to be moved regularly by parents/carers to prevent bed sores. • They have very poorly developed muscle tone meaning their body, arms and legs are very floppy. This means they are unable to grasp or hold onto things. They are unable to move voluntarily. • They also frequently experience painful muscle spasms, and their arms and legs may move involuntarily with sudden jerking or twisting. • Their eyes roll upwards, similar to an epileptic seizure. This occurs several times a week, spontaneously without any trigger, and may last for several hours. It is painful and uncomfortable for the child during an episode. • Due to lack of head control, difficulty swallowing and risk of choking, they are unable to feed themselves and need to be fed through a tube (a “gastric” tube which is inserted through their tummy). • They experience pain and discomfort most of the time. • They are unable to follow objects with their eyes. They are able to recognize faces but are unable to interact with people. They can understand simple words but are not able to speak. They do not reach any of the developmental milestones as other children their age. • They may scream or cry constantly without any trigger throughout the day and night. They are extremely irritable and agitated. • They have extreme difficulty getting to sleep and experience very disturbed sleep. • They have severe abdominal problems, such as constipation or diarrhea. Other symptoms include severely blocked nose (nasal congestion), excessive drooling, excessive sweating and extreme tiredness. • The child is unable to carry out their daily activities (e.g., self-care, washing, dressing) and is dependent on their parent/carer. • Leisure activity (e.g., going out to the park, playing with toys) is severely limited. • The child is unable to play or interact with other children.
HS2: Full head control	<p>Imagine a 10-year-old child with a severe medical condition. This medical condition means that:</p> <ul style="list-style-type: none"> • They are bedridden and unable to move by themselves. This means that they are unable to crawl, sit, or stand. However, they are able to support their own head. It is difficult for the child to be transferred from the bed to a wheelchair. They need to be moved regularly by parents/carers to prevent bed sores. • They have very poorly developed muscle tone meaning their body, arms and legs are very floppy. This means they are unable to grasp or hold onto things. They have very few voluntary movements. • They often experience painful muscle spasms, and their arms and legs may move involuntarily with sudden jerking or twisting. • Their eyes roll upwards, similar to an epileptic seizure. This occurs several times a week, spontaneously without any trigger, and may last an hour or longer. It is painful and uncomfortable for the child during an episode.

Health state	Description
	<ul style="list-style-type: none"> • Due to poor head control, difficulty swallowing and risk of choking, they are unable to feed themselves and need to be fed through a tube (a “gastric” tube which is inserted through their tummy). • They experience pain and discomfort most of the time. • They are able to follow objects with their eyes and recognize and smile at people. They can understand simple words but are not able to speak. They do not reach any of the developmental milestones as other children their age. • They may scream or cry frequently without any trigger throughout the day and night. They are very irritable and agitated. • They have difficulty getting to sleep and experience disturbed sleep. • They have abdominal problems, such as constipation or diarrhea. Other symptoms include a blocked nose (nasal congestion), frequent drooling, frequent sweating and tiredness. • The child is unable to carry out their daily activities (e.g., self-care, washing, dressing) and is dependent on their parent/carer. • Leisure activity (e.g., going out to the park, playing with toys) is severely limited. • The child is unable to play or interact with other children.
HS3: Ability to sit unaided	<p>Imagine a 10-year-old child with a severe medical condition. This medical condition means that:</p> <ul style="list-style-type: none"> • They can sit without help, although they are not able to crawl or stand. They are unable to walk, but can be transferred to a wheelchair. They can support their own head. • The muscles in their body, arms and legs are floppy but have some voluntary movement. They are able to reach out and hold onto things. • They occasionally experience painful muscle spasms, and their arms and legs may move involuntarily with sudden jerking or twisting. • Their eyes roll upwards, similar to an epileptic seizure. This happens occasionally and spontaneously without any trigger. It is uncomfortable for the child during an episode. • They are able to feed themselves a little bit, but may need to be fed by a caregiver using pureed or soft foods. • They experience pain and discomfort some of the time. • They are able to follow objects with their eyes and recognize and smile at people. They can understand simple words and babble a little. They reach a few of the developmental milestones as other children their age. • They may scream or cry occasionally throughout the day and night. They may occasionally react disproportionately and become irritable and agitated. • They have difficulty getting to sleep and experience disturbed sleep. • They have occasional abdominal problems, such as constipation or diarrhea. Other symptoms include the occasional blocked nose (nasal congestion), drooling and sweating. • The child has severe problems carrying out their daily activities (e.g., self-care, washing, dressing) and requires assistance from a parent/caregiver. • Leisure activity (e.g., going out to the park, playing with toys) is somewhat limited. • The child has severe difficulties playing or interacting with other children.

Health state	Description
HS4: Standing with support	<p>Imagine a 10-year-old child with a severe medical condition. This medical condition means that:</p> <ul style="list-style-type: none"> • They can lift and support their own head and are able to sit without help. They can stand with support from a walking frame or another person. • The muscles in their body, arms and legs are a bit floppy but they have voluntary movement. They can reach out their hands and hold onto things. • They occasionally experience muscle spasms, and their arms and legs sometimes move involuntarily with sudden jerking or twisting. • Their eyes roll upwards, similar to an epileptic seizure. This happens very occasionally and spontaneously without any trigger. It is uncomfortable for the child during an episode. • They are able to feed themselves more or less on their own. They are able to eat soft, solid food. • They experience pain and discomfort a little bit of the time. • They are able to follow objects with their eyes and recognize and smile at people. They can understand simple sentences and are able to say a few words. They reach a few of the developmental milestones as other children their age. • They may scream or cry occasionally. They may occasionally react disproportionately and become irritable and agitated. • They need more sleep than other children their age. • They have very occasional abdominal problems, such as constipation or diarrhea. Other symptoms include the very occasional blocked nose (nasal congestion), drooling and sweating. • The child has some problems carrying out their daily activities (e.g., self-care, washing, dressing) and requires assistance from a parent/caregiver. • Leisure activity (e.g., going out to the park, playing with toys) is somewhat limited. • The child has some difficulties playing or interacting with other children.
HS5: Walking with assistance	<p>Imagine a 10-year-old child with a severe medical condition. This medical condition means that:</p> <ul style="list-style-type: none"> • They can lift and support their own head and are able to sit without help. They can stand without any help, and walk as well, although they may occasionally need support from a walking frame or person to do so. • The muscle in their body, arms and legs are a bit limper than normal, but they have voluntary movement. They can reach out and hold onto things. • They very occasionally experience muscle spasms, and their arms and legs move involuntarily with sudden jerking or twisting. • Their eyes roll upwards, similar to an epileptic seizure. This happens very occasionally and spontaneously without any trigger. It is uncomfortable for the child during an episode. • They are able to feed themselves and are able to eat solid foods. • They experience pain and discomfort a little bit of the time. • They are able to follow objects with their eyes and recognize and smile at people. They can understand complex sentences and can speak simple sentences. They meet some of the developmental milestones as other children of the same age. • Their mood is mostly the same as that of a child their own age. They occasionally react disproportionately and experience emotional outbursts. • They need more sleep than other children their age.

Health state	Description
	<ul style="list-style-type: none"> • They have very occasional abdominal problems, such as constipation or diarrhea. Other symptoms include the very occasional blocked nose (nasal congestion), drooling and sweating. • The child has slight problems carrying out their daily activities (e.g., self-care, washing, dressing) and may require assistance from a parent/caregiver at times. • Leisure activity (e.g., going out to the park, playing with toys) is slightly limited. • The child has slight difficulties playing or interacting with other children.

References

1. Hanbury A, Smith AB, Buesch K. Deriving vignettes for the rare disease AADC deficiency using parent, caregiver and clinician interviews to evaluate the impact on health-related quality of life. *Patient Related Outcome Measures*. 2021:1-12.