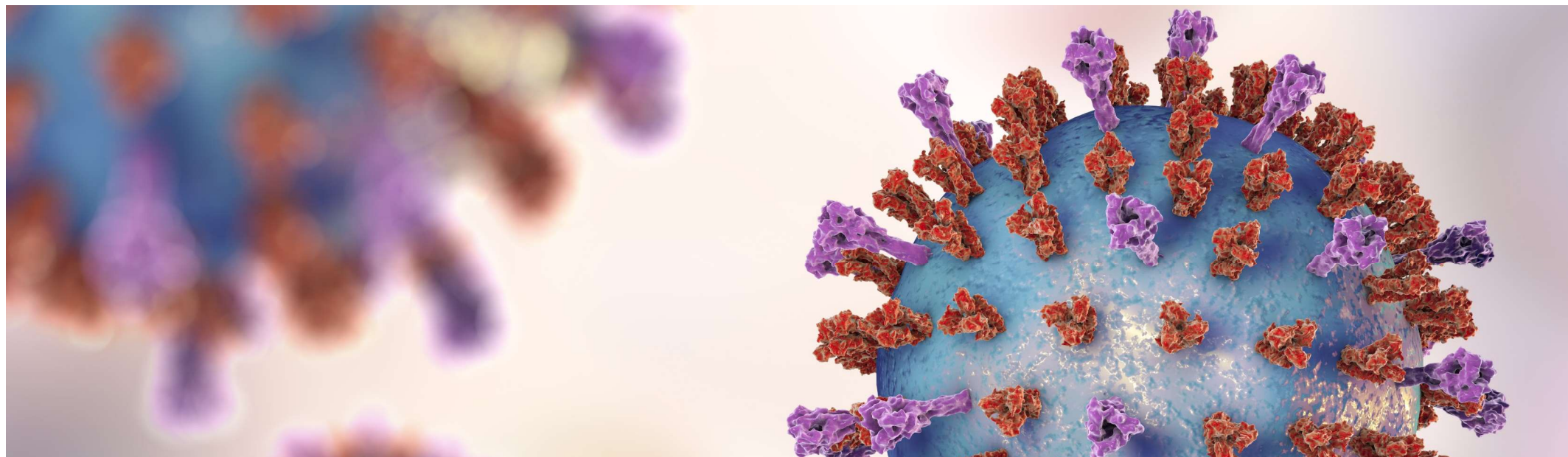




Exit interviews with Caregivers and Clinicians Confirm Content Validity and Feasibility of Completing the Pediatric Respiratory Syncytial Virus (RSV) Electronic Severity and Outcome Rating System (PRESORS) for Pediatric RSV Clinical Studies

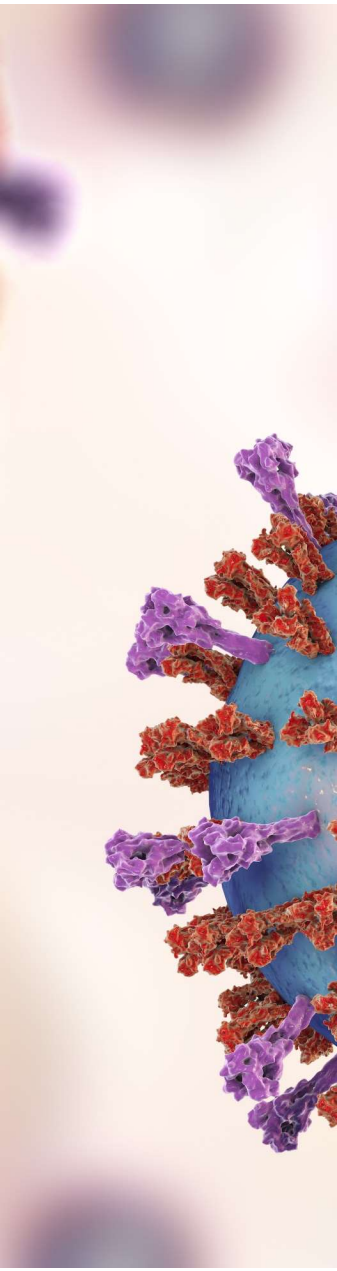
Presented at ISPOR US 2021- virtual, May 17-20

The structure of Respiratory Syncytial Virus (RSV)

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Conflict of interest

- Janssen sponsored this study
- Sophi Tatlock, Rebecca Grimes and Rob Arbuckle were employees of Adelphi Values, a health outcomes research consultancy paid by Janssen to complete the study.
- Elisha Santucci-Hutcheson, Rekha Sinha, James Witek and Jane Scott were paid Janssen employees at the time this study was conducted.
- Jane Scott holds stock in Johnson and Johnson, the parent company of the research sponsor

Overview of presentation

Background

- What is RSV?
- How is RSV treatment assessed?
- What is PRESORS and how was it developed?

Objectives and methodology

Results

Conclusions and key takeaways

Background

- What is RSV?
- How is RSV treatment assessed?
- What is PRESORS and how was it developed?

What is RSV?

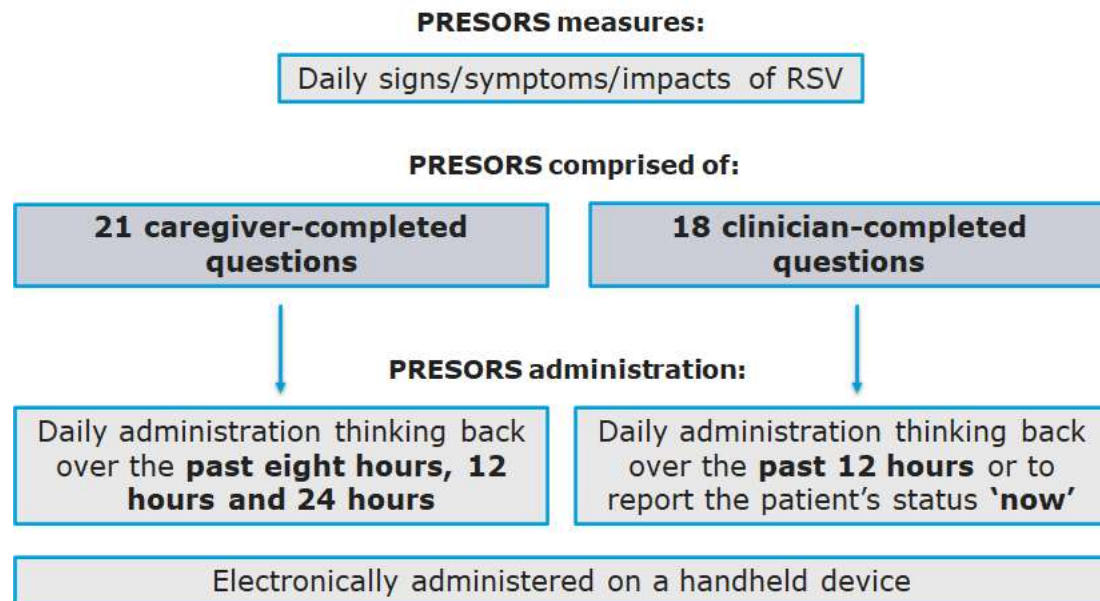
- While less widely recognised than influenza, **Respiratory Syncytial Virus** (RSV) is prevalent, highly contagious and a leading cause of bronchiolitis and pneumonia in children [1]
- Predominantly occurring in the **winter months**, RSV leads to more than 3 million hospitalizations and nearly 60,000 deaths in children under 5 years of age each year, nearly half of which occur in infants **under 6 months** old in temperate climates [2]



[1] Bawage S, et al. Recent Advances in Diagnosis, Prevention, and Treatment of Human Respiratory Syncytial Virus. *Advances in Virology*. 2013;2013:1-26.

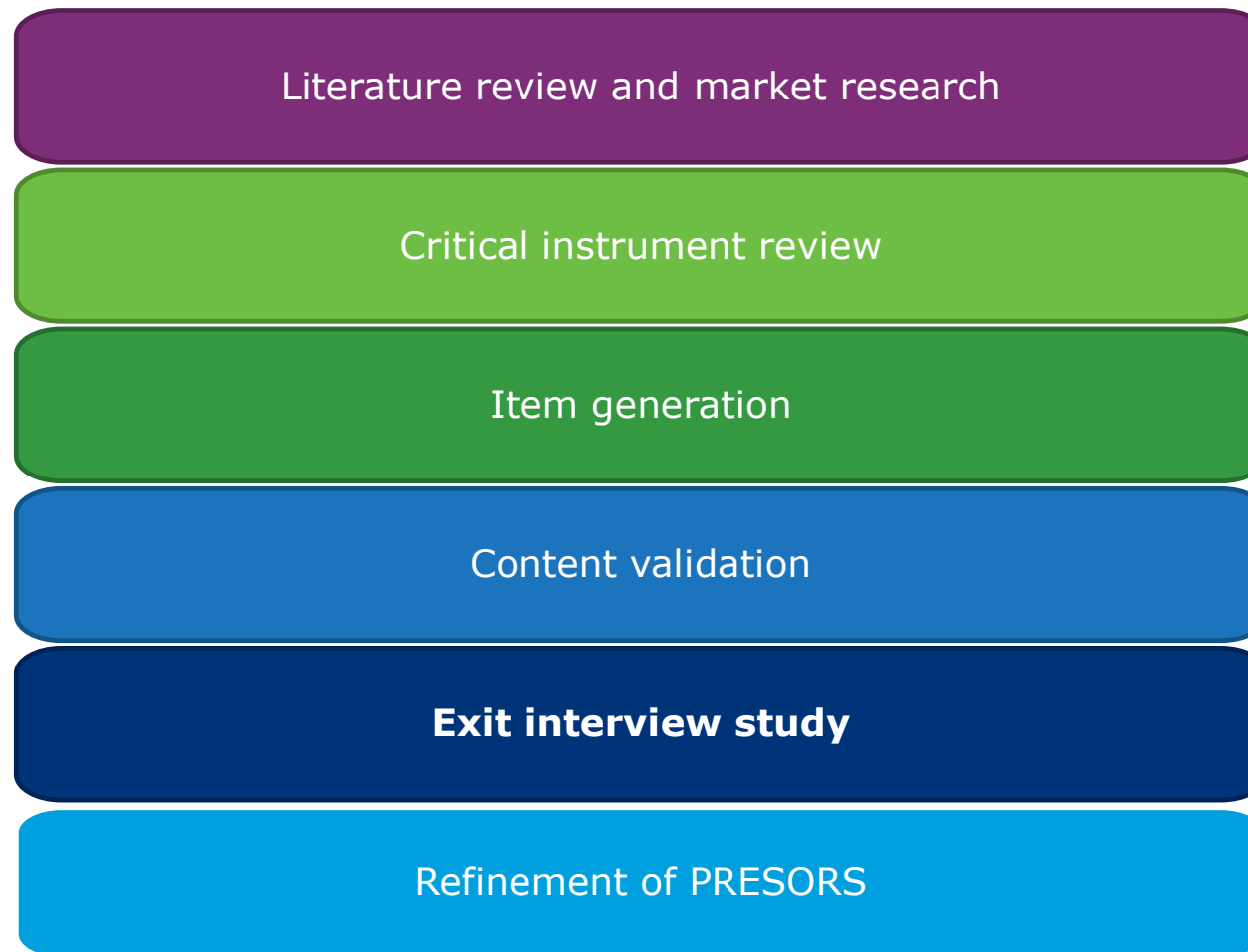
[2] Oxford Vaccines Group. Respiratory syncytial virus (RSV). Available at: <http://vk.ovg.ox.ac.uk/rsv>. Last accessed: September 2019.

What is the PRESORS and why was it developed?



- Measuring and monitoring **observable signs** of the infection is the only agreed means of assessing RSV severity in infants and therefore understanding efficacy of treatments.
- The **Pediatric RSV Electronic Severity and Outcomes Rating System (PRESORS)** was developed as an electronic daily diary (eCOA) to monitor the clinical course of pediatric RSV disease based on clinician (ClinRO) and parent/caregiver (ObsRO) ratings of the severity of RSV signs they observed.

Brief overview of activities conducted to develop and evaluate the PRESORS



PRESORS v6.0 implemented in Phase 0 study

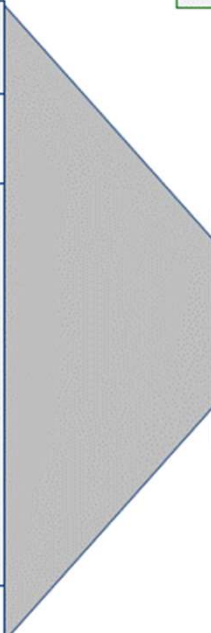
ObsRO

Caregiver PRESORS

ClinRO

Clinician PRESORS

Sub-concept	Concept	Measurement concept
Activity	Behavioral	Severity of pediatric RSV disease
Sleep		
Crying		
Nutrition	Feeding tolerance	
Dehydration		
Respiratory effort	Breathing difficulties	
Cyanosis		
Apnoea		
Breathing sounds		
Cough		
Nasal secretions (cold signs)		
General condition		
Time spent with child		
Caregiver impact		

Sub-concept	Concept	Measurement concept
Activity	Behavioral	 Severity of pediatric RSV disease
Sleep		
Nutrition	Feeding tolerance	
Dehydration		
Tachypnea	Breathing difficulties	
Respiratory effort		
Cyanosis		
Apnoea		
Cough		
Breathing sounds		
Nasal secretions		
General condition		

Objectives and methodology of exit interview sub-study

Objectives

To interview parents/caregivers of infants and investigators who participated in 64041575RSV0001 Phase 0 pediatric RSV study to evaluate the following during hospitalization and post discharge at home:

CONTENT VALIDITY of the PRESORS

Perform top-line **concept elicitation** and **cognitive debriefing** to further evaluate the content validity of the PRESORS and support refinement of the measures

FEASIBILITY of daily PRESORS completion

Identify any potential revisions to study procedures which may enhance feasibility of collecting valid and reliable data using the PRESORS

USABILITY of eCOA device

Identify any revisions to training procedures or issues caregivers encountered using the devices

Methodology: Phase 0 Study design

- The PRESORS was successfully implemented into **64041575RSV0001 Phase 0 study** across 16 sites:



8 sites in the US (Northern Hemisphere)



4 sites in Chile (Southern Hemisphere)



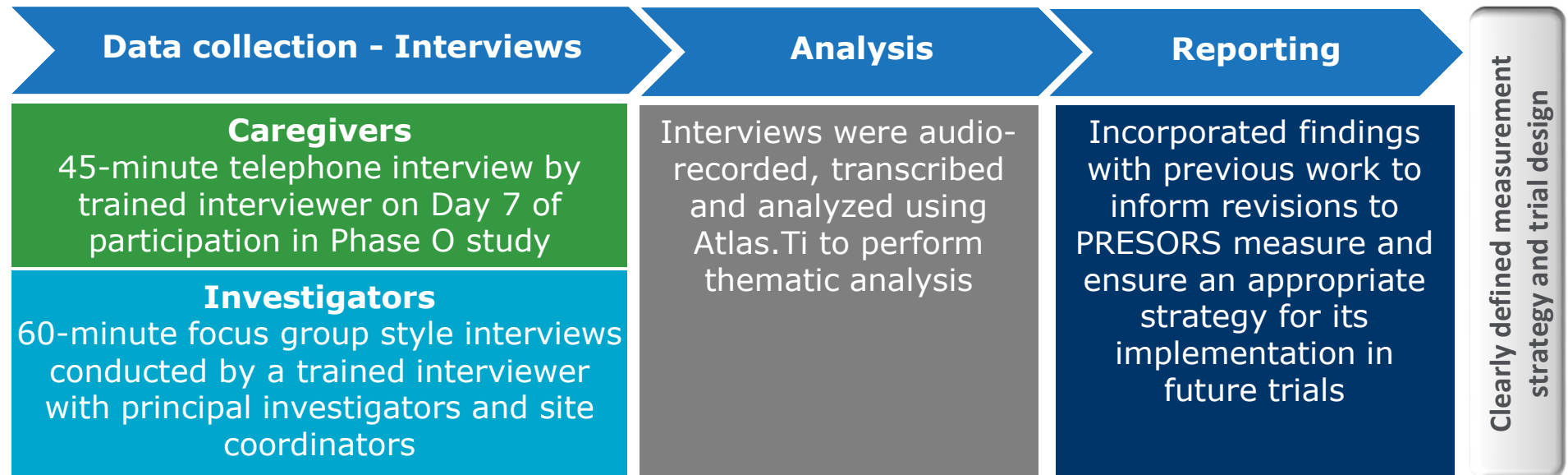
4 sites in Argentina (Southern Hemisphere)

- Patients (≤ 36 months of age), admitted to hospital with lab-confirmed RSV were enrolled in the study for 7 days
- Following daily completion of PRESORS, caregivers and investigators were invited to take part in an interview

	Caregivers	Investigators
PRESORS completion	Days 1-6: completed caregiver measure twice per day (continued at home post discharge) Day 7: completed once	Days 1-7: completed clinician measure once per day while child admitted
Interview	Took part in 45-minute telephone exit interview on Day 7 (+2 days)	Took part in 60-minute telephone interview following enrolment of approximately 4 patients

Methodology: exit interview study design

- The exit interview was included as an activity within the overall trial protocol



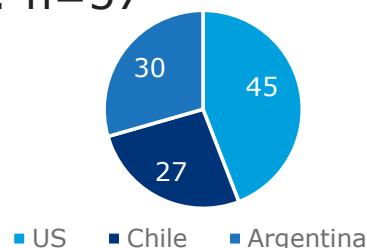
Results

Results: Sample

Final sample upon completion of recruitment (September 2019)

- A total of **102 caregivers of children** participated in a 45-minute exit interview

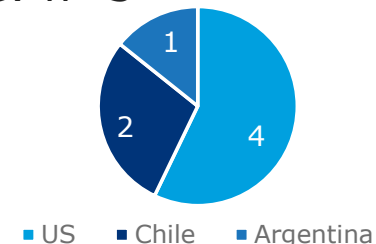
- > Northern hemisphere: n=45
- > Southern hemisphere: n=57



**Note. 105 patient subjects were enrolled but on three occasions, twins were enrolled, therefore pairs of combined exit interviews were conducted with caregivers.*

- > A total of **7 sites** participated in a 60-minute investigator interview

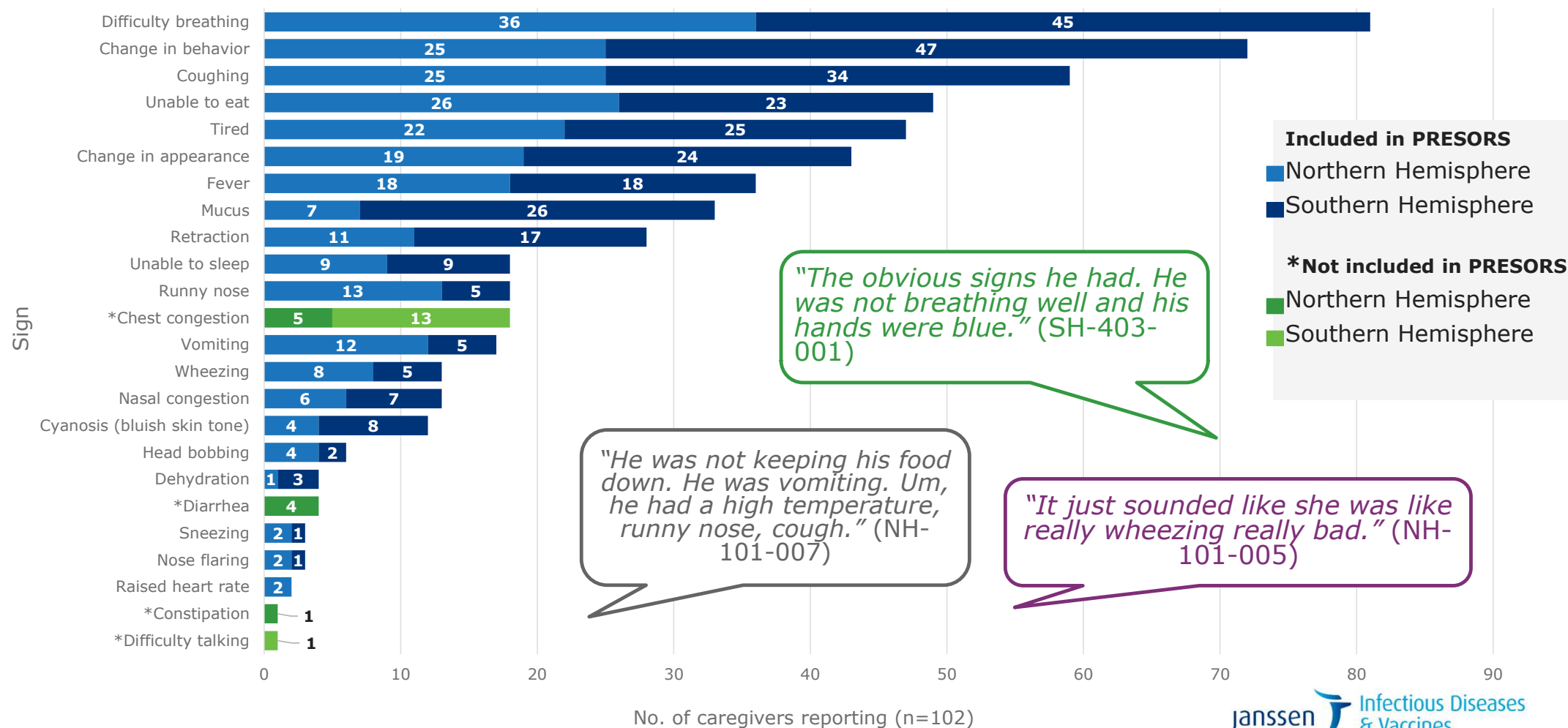
- > Northern hemisphere: n=4
- > Southern hemisphere: n=3



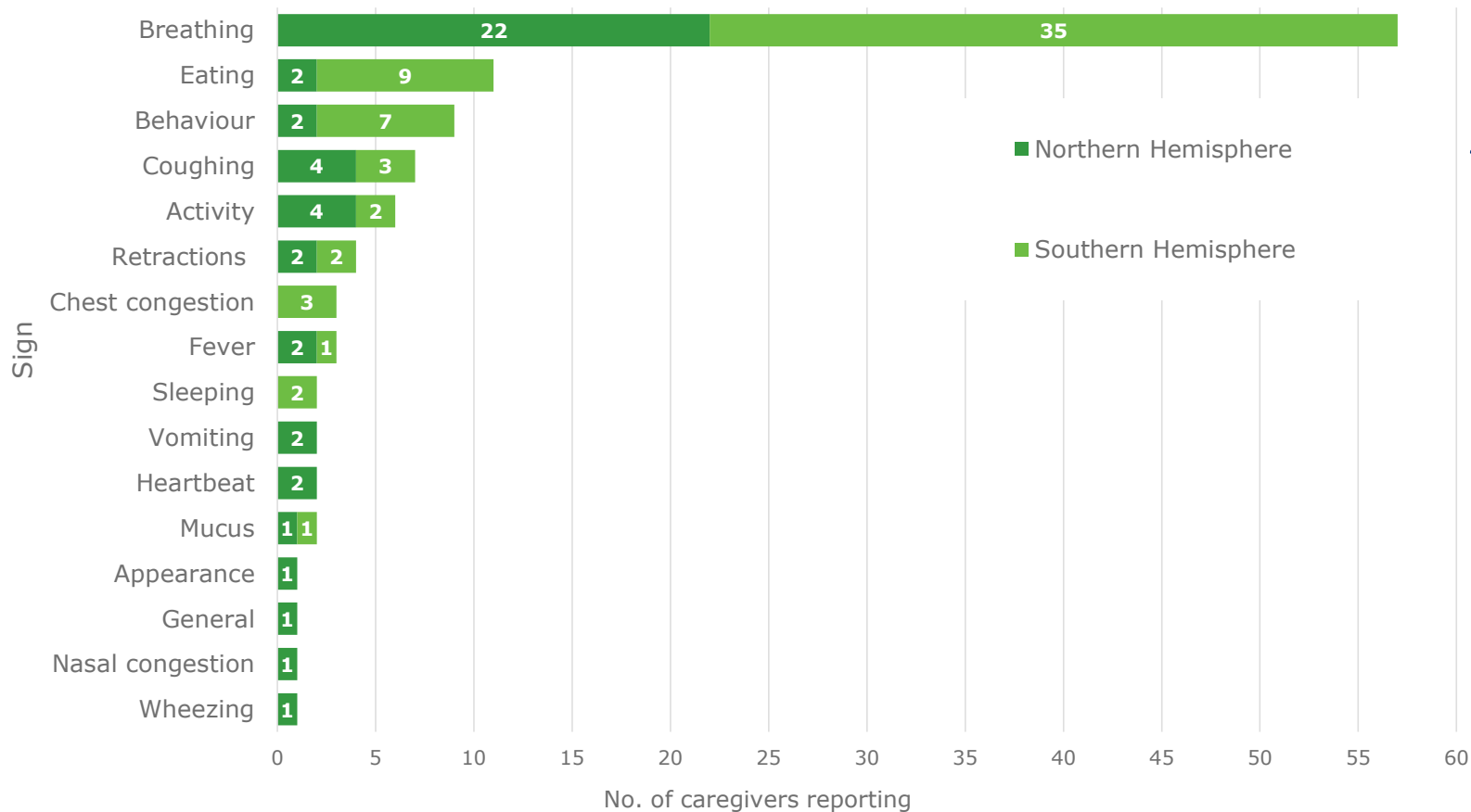
*It was not possible to collect background demographics information about the patients, caregivers or clinicians due to the restrictions in the Phase 0 protocol.

Results: caregiver interviews

20/24 signs reported by caregivers assessed in PRESORS



Signs considered most important to improve by caregivers



"Why would that be the most important thing you wished to see in your daughter?"....I mean, I wanted her to be able to breathe by herself, not needing any help." (SH-403-007)

"Um, and what was the most important thing that you wanted to see improve in your child's health?"....."Um, the cough. The cough was scary because, um, she would just cough and then whine right after. So it was like so tight and aggressive in the beginning." (NH-102-001)

PRESORS ObsRO: strong understanding of almost all item wording across both hemispheres

The majority of caregivers found the wording of all items in the PRESORS ObsRO to be clear.

- Item 18 ('hours spent with child') was the only item which was reported to lack clarity by a notable number of caregivers (n=15/102; 14.7%).

Item 18. How many hours did you spend with the child [recall period]?

_____ hours

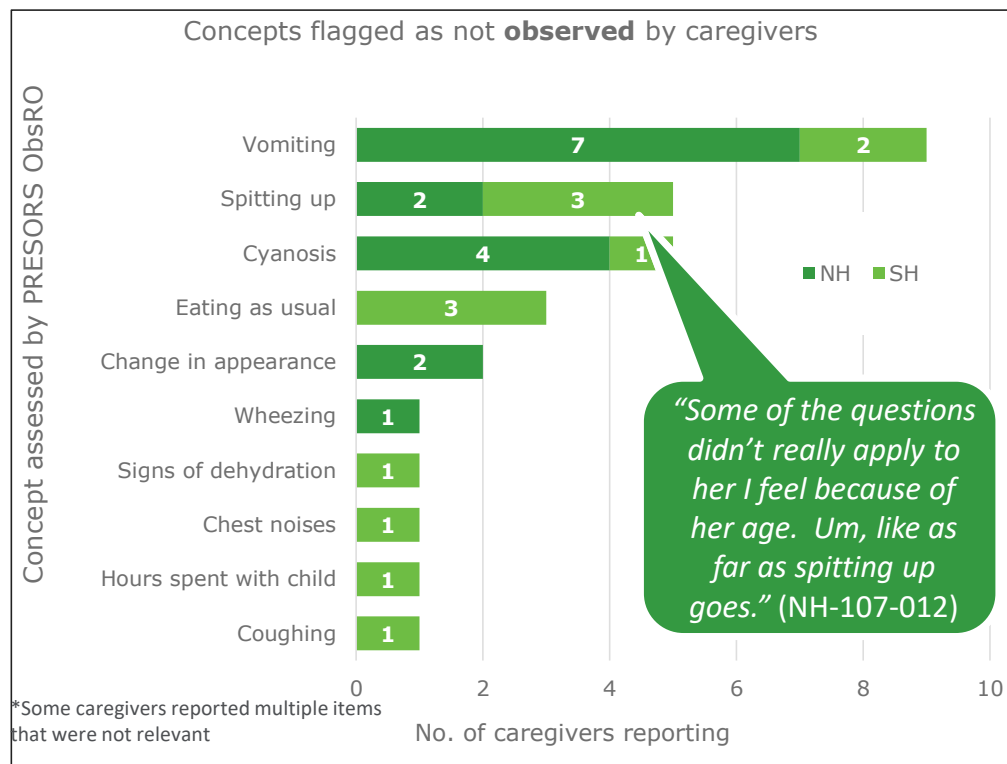
- Item 3a ('amount of sleep') (N=4/102; 3.9%) was the second item most frequently reported to lack clarity.

"Maybe the one about sleeping. It was more difficult to answer as she was sedated.....Of course, since she is very little she was always sleeping"
(SH-403-007)

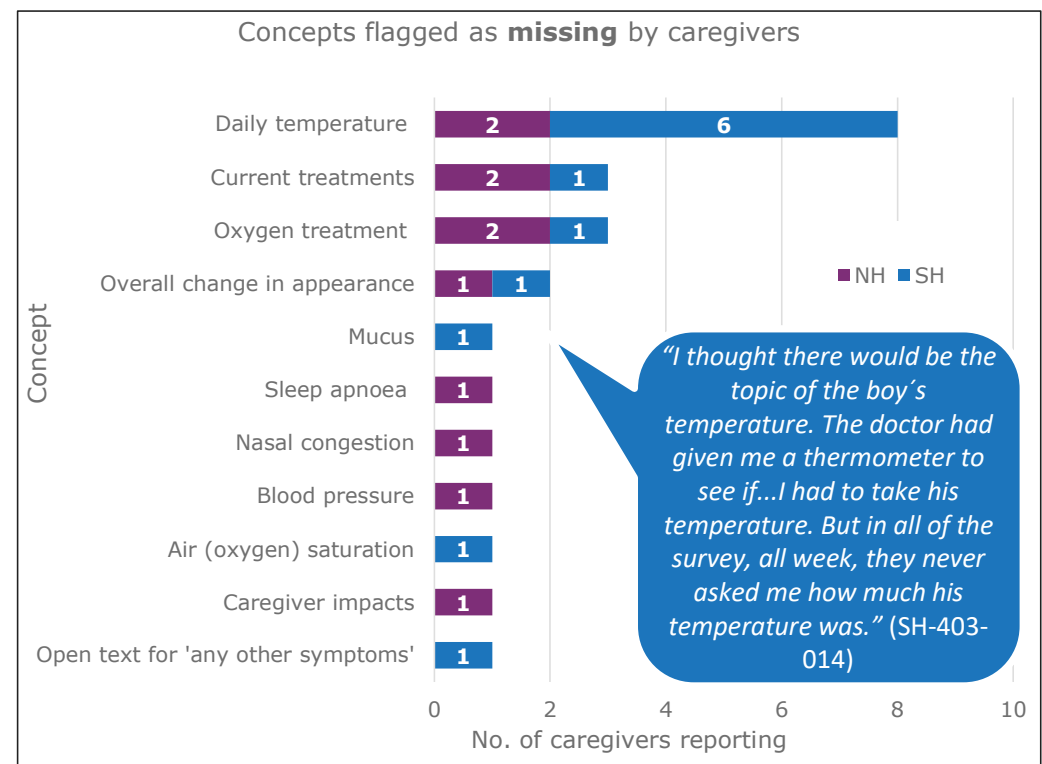
"...there were some questions that asked how much time I had spent with my son, for example, in the morning when he woke up, and since it's practically at the same time as the hospital schedule, I would count the hours, but I didn't understand if it meant when I was there all day long or on the hospital's schedule, and so it confused me a little" (SH-403-009)

PRESORS ObsRO: 76.4% of caregivers found all items in the PRESORS relevant

- **78** caregivers observed all the signs in the PRESORS in their child (n=78/102; 76.4%)
- **24** caregivers did not observe one or more signs in their child (n=24/102; 23.6%)*



- **80** caregivers felt that the PRESORS had **no missing concepts** (n=80/102; 78.4%)
- **22** caregivers identified concepts that were **missing** from the PRESORS diary (n=22/102; 21.6%)



PRESORS ObsRO: Majority of caregivers found response options to be balanced and sufficiently granular to capture the range of severity observed

- 11/102 (10.8%) caregivers felt that **extra response options were needed to increase sensitivity** for some items (n=1 NH, n=10 SH). These items were:

- Frequency of urination (n=5)
- Coughing and wheezing (n=1)
- Eating (n=1)
- Unspecified items (n=4)

INTERVIEWER: *"So, what option would you change, for example?"*
"That one (question), about pee, there is the same or less. And my daughter was peeing much more than usual." (303-018-SH)

INTERVIEWER: *"Is there any answer option that you would change?"* *"The one regarding eating as I mentioned before. To add the matter of the feeding tubes"* (403-011-SH)

"It's just like another option. Like if it says like coughing or wheezing, you can put like rattle." (102-001-NH)

PRESORS ObsRO: Diary completion



Recall period

- All caregivers understood the 12-hour recall period.
- 86/102 (84.3%) caregivers found the recall period **appropriate** and did not report any issues adhering to it.



Usability of eCOA device

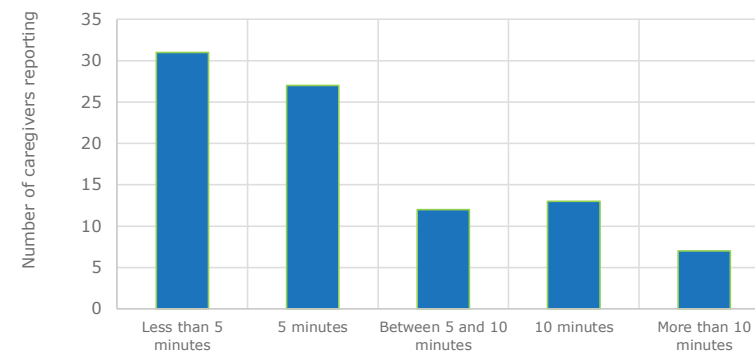
- All 92/92 (100.0%) reported that the device was easy to use

"The device is really easy to use. Um, the fact that they set an alarm helped remind me, um, every time I needed to do it. So, um, that was great."
(NH-101-006)



No caregivers reported any issues with time required to complete the PRESORS ObsRO

Diary completion time reported by caregivers



Completion rates

- Completion rates were high; only 15 caregivers described occasions where they **missed diary entries** (n=15/102; 14.7%)
- Majority of caregivers found it **easy to remember** to complete the diary (n=79/82; 96.3%)

PRESORS ObsRO completion setting: hospital vs. home

59 caregivers were asked about the differences between completing the diary at home and in the hospital (n=59/102; 57.8%)



Easier to complete at hospital
(n=17/102; 16.7%)

No difference
n=29/102; 28.4%



Easier to complete at home
(n=13/102; 12.7%)

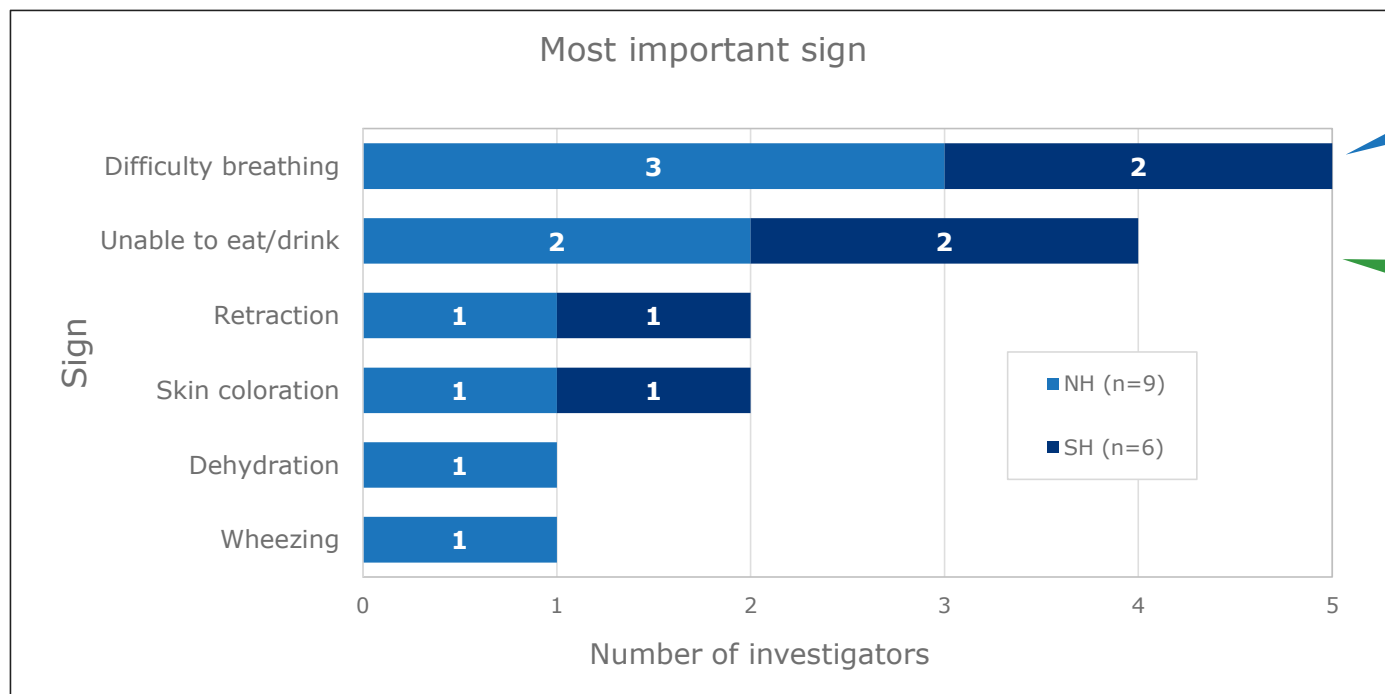
- They were not as **distracted** by daily living activities (n=14/17; 82.4%)
- They were **more focussed** on their child's symptoms (n=1/17; 5.9%)
- Completing the diary **killed time** (n=1/17; 5.9%)
- They felt **less anxious** that their child was receiving care (n=1/17; 5.9%)

- Caregivers felt more **relaxed** (n=5/13; 38.5%)
- Other **family members** could help with childcare (n=3/13; 23.1%)
- They felt more **anxious** in hospital (n=3/13; 23.1%)
- Being back in a **routine** (n=1/13; 7.7%)
- There was more opportunity to **observe** the child (n=1/13; 7.7%)

Results: Investigator interviews

Key RSV signs reported by investigators: all captured in PRESORS ClinRO

- Investigators were asked what signs they believed were most important in characterising and assessing the severity of RSV. All signs mentioned were captured in PRESORS.



"Um, I would say the signs of breathing problems, Question 6 was very important. Um, and then the, the eating, drinking, nursing" (NH-101-INV)

"Signs of respiratory difficulty, changes in coloration, rejection for food, as well." (SH-403-INV)

Note* Some investigators reported multiple signs

Investigator feedback on PRESORS ClinRO

RELEVANCE

"So older children are going to have a cold, pneumonia. But they're usually not going to have bronchiolitis that puts them in a hospital, unless they already have, uh, um, respiratory disease underlying like, you know, reactive airway disease or asthma."
(NH-106-INV)

The investigators were asked whether they believed the ClinRO assessed clinically **relevant concepts**:

- 6/7 investigators believed the ClinRO was relevant for all stages of development
- 1/7 suggested that for an older child around the age of five, unless they had an underlying respiratory condition such as asthma, some breathing items would not be relevant.

RESPONSE OPTIONS

6 investigators were asked whether they believed **response options** were appropriate:

- 5 investigators asked felt that the response options were appropriate (2 NH, 3 SH).
- 1 investigator believed that the ClinRO lacked precision (n=1 NH)

"There's a lot of difference between a severity of a kid between restless and disturbed most of the time and then comatose. So one of the intervening categories should be lethargic or difficult to—more difficult to arose." (NH-104-INV)

PRESORS ClinRO: Item feedback

There were
suggested
revisions to **5**
items

Concept assessed by item	Feedback on item
 Signs of breathing difficulties	Define all types of retraction in the same way that tachypnea is defined
 Nasal signs	Ask if nasal secretions have increased rather than if they are present
 Signs of cyanosis	Ask whether the infant has oxygen treatment within the cyanosis item
 Wheezing	Include <i>crackling</i> as a breathing sound
 Sleeping	Quality of sleep not relevant – remove from assessment

PRESORS ClinRO: Item feedback

6 concepts were flagged as missing by investigators:



Oxygen (n=2)

"...although it is in the clinical history, it is not in the PRESORS" (SH-303-INV)

"..they don't ever delineate whether or not this child is [already] being NG fed..." (NH-104-INV)



Eating/drinking – use of nasogastric tube (n=1)



Mechanical ventilation (n=1)

"...the PRESORS does not give you an alternative to evaluate him while intubated" (SH-403-INV)

"It has, uh, retractions, uh, in the way that the baby looks now and in the last 12 hours, but you don't have to put a number for respiratory rate" (NH-106-INV)



Respiratory rate (n=1)



Diarrhea (n=1)

"Um, the device also is not asking for example for other signs the baby might be having. And we had a couple of cases where the baby had diarrhea" (NH-106-INV)



X-ray (n=1)

"So far it's not even asking whether an x-ray was done" (NH-106-INV)

PRESORS ClinRO: Completion

DETERMINING RESPONSES

The clinicians were asked how they **completed** the PRESORS:

- Looking at notes (n=4; 2 NH, 2 SH)
- Asking nurses and other staff (n=1 NH)
- Through direct observation only (n=1 SH)
- Ask the caregiver (n=1 NH)

"The physical exam findings, I would get in observing the, the patient. There were some questions about in the past 12 hours identify symptoms, and, and I would ask the caregiver about that." (NH-101-INV)

EASE OF USE

INTERVIEWER *"What was your experience using the electronic device to complete the questionnaire?".... "It was easy, once I learned to use it." (SH-404-INV)*

All 7 clinicians confirmed that the diary was easy to complete (n=7; 4 NH, 3 SH)

Investigator feedback on PRESORS ObsRO

- All investigators believed that the caregiver PRESORS items were appropriate for caregivers to complete

RELEVANCE

- **5** investigators reported **all caregiver PRESORS items to be relevant** (4 NH, 3 SH)
- **2** investigators described items that they did **not believe were relevant**:
 - **Child spent sleeping** (1 NH)
 - **'time spent caring for the child'** only relevant once the infant had been discharged (1 SH)

MISSING ITEMS

- > **5** investigators did **not believe any concepts were missing** from the ObsRO PRESORS (3 NH, 2 SH).
- > The remaining 2 investigators did not comment on this

DIFFICULT ITEMS

- > Investigators believed that the following items were difficult for a caregiver to answer:
 - Number of hours spent with the child (n=1 NH)
 - Respiratory rate (n=1 NH)
 - Heart rate (n=1 NH)
 - Sleep quality (n=1 SH)

"That, that stumped every single one of them because it's like there's 168 hours in a week and how many, how many hours. And people had to like really stop and think." (NH-101-INV)

Conclusions and key takeaways

Summary of findings: PRESORS ObsRO

Finding

Impact on PRESORS ObsRO

- Majority of caregivers found all items in PRESORS ObsRO **relevant** and **easy to understand**

- Confirmed content validity**

- Most **frequently reported signs** were difficulty breathing, changes in behaviour and not eating

- Informed endpoints** and **scoring algorithm** for PRESORS ObsRO

- Temperature** most commonly reported as missing concept (n=8/102)

- Temperature captured in eCRF; no change needed

- Vomiting** reported as not observed (n=9/102)

- Standalone vomiting item **removed**

- Cyanosis** reported as not observed (n=5/102)

- Deemed clinically relevant for severe RSV; **retained**

- Item assessing **hours spent caring for child** difficult to complete

- Item not proximal to assessment of RSV severity; **removed**

- No caregivers reported any issues** with the time taken to complete or using the device

- Usability and feasibility confirmed** in both inpatient and outpatient settings

Summary of findings: PRESORS ClinRO

Finding

- Investigators confirmed that the PRESORS was **clinically relevant**
- **Key signs reported** to indicate RSV severity: difficulty breathing and being unable to eat/drink
- Use of **nasogastric tube** flagged as a missing concept
- **Oxygen administration and mechanical ventilation** were reported as missing concepts
- **X-ray** was reported as a missing concept
- **Diarrhea** was reported as a missing concept
- **Respiratory rate** was reported as a missing concept
- **Inclusion of 'crackles'** in the breathing sounds item
- **Increase in nasal secretions** to be assessed

Impact on PRESORS ClinRO

- **Content validity** of PRESORS ClinRO **confirmed**
- **Informed endpoints** and **scoring algorithm** for PRESORS ClinRO
- Nasogastric feeding **included in response options**
- Not relevant for outpatient setting and captured in the eCRF/ medical records for inpatients; **no change**
- Used to diagnosis, not assessing severity; **no change**
- Not deemed clinically relevant; **no change**
- Recorded in eCRF; **not deemed necessary to include**
- **Item added**
- **Item revised**

Conclusions and key takeaways

Reports from caregiver and clinician interviews from a large multinational study of pediatric patients treated for RSV disease in hospitals confirmed the PRESORS is well-understood, conceptually comprehensive and easy to complete electronically.

Demonstration of psychometric properties of and confirmation of scoring algorithm is required to ensure the PRESORS is fit for purpose:

ST4	Psychometric Evaluation of the Pediatric RSV Severity and Outcomes Rating System Version 6 (PRESORSV6), Caregiver Observer-Reported [ObsRO] and Clinician-Reported [ClinRO] Questionnaires in Children Aged 1 to 36 Months Hospitalized with Respiratory Syncytial VIRUS (RSV) Infection
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