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RTI (h)(s) Health Solutions

Psychometric Evaluation of a Novel Observer-Reported Outcome Tool for the Assessment of Respiratory Syncytial Virus Infection Symptoms in Infants

Seth Toback,[1] Sandy Lewis,[2] Carla DeMuro,[2] Jason W. Chien,[1] Richard Schwartz,[3] Todd Wolynn,[4] Paul Wisman,[5] Stan Block,[6] Wilson Andrews,[7] Shelly Senders,[8] Nicole Williams,[2] Valerie Williams[2]

[1]Gilead Sciences, Inc., Foster City, CA; [2]RTI Health Solutions, Research Triangle Park, NC; [3]Advanced Pediatrics, Vienna, VA; [4]Kids Plus Pediatrics, Pittsburgh, PA; [5]Pediatric Associates of Charlottesville, VA; [6]Kentucky Pediatric/Adult Research, Bardstown, KY; [7]Pediatric and Adolescent Medicine, P.A., Marietta, GA; [8]Senders Pediatrics, South Euclid, OH

GILEAD

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
800-445-3252

Introduction

- Respiratory syncytial virus infection (RSV) is a common seasonal disease that infects most young children by age 2 years and is the leading cause of lower respiratory tract infection requiring hospitalization
- Novel antiviral medications are in development to improve the clinical outcome of RSV
  - However, no caregiver-reported clinical outcome assessments developed in alignment with the FDA patient-reported outcome guidance exist for RSV[1]
  - There is no widely accepted clinical endpoint for RSV clinical trials
- To address this need, the Gilead RSV Caregiver Diary (GRCD) was developed following a rigorous qualitative methodology
  - A literature review was conducted to identify potential constructs of interest and to evaluate the content of existing clinical outcome assessments, focusing on identification of observable symptoms and changes in these symptoms over time
  - 16 caregivers of RSV-infected infants were interviewed individually in the outpatient setting to elicit additional concepts of interest
  - Candidate questionnaire items were tested in 2 iterative rounds (n=7 and 8) of cognitive debriefing interviews
  - Further in-depth interviews with 8 caregivers of children hospitalized due to RSV were also conducted
  - Clinical pediatricians provided expert input throughout development
- The resulting GRCD comprised 19 questions specific to 12 directly observable RSV symptoms
  - To allow more accurate capture of symptom fluctuation and change, questions concerning day- and nighttime observations were included, each rated with a 5- to 7-point graded response scale

GRCD Item Example: Daytime Cough Frequency

How much did your child cough during the day?

- ☐ Did not cough at all
- ☐ Coughed a little
- ☐ Coughed several times
- ☐ Coughed frequently
- ☐ Coughed nearly all day

Objective

- To evaluate the psychometric properties of the draft GRCD

Methods

Study Design

- To assess the psychometric properties of the GRCD, data were collected in an outpatient, multicenter, prospective, 2-week, US-based observational study of young children with confirmed RSV
- Data were collected during a single RSV season: Oct 2014–Feb 2015
- No medical procedures or treatments were supplied as part of this study; physicians treated patients per usual practice
- ~105 adult caregivers were asked to participate and record their responses directly into the Web portal or on a paper-based version of the GRCD twice daily for 14 days

Key Inclusion Criteria

- Child aged <24 months at screening and ≥37-week gestational age at birth, with confirmed diagnosis of RSV (by rapid antigen diagnostic) documented within 24 hours of Visit 1
- Child being seen for first physician-diagnosed acute respiratory tract illness with duration of symptoms ≤5 days (or worsening of chronic symptoms, eg, runny nose) at Visit 1
- Parent/caregiver able to have direct daily contact (≥14 hours of observation/day during day and evening) with child for 14 consecutive days after enrollment

Key Exclusion Criteria

- Child
  - With known chronic illness
  - Received nonsteroidal immunosuppressive therapies within 12 months of screening or any systemic corticosteroids for >7 consecutive days within 4 weeks of screening
  - Hospitalized within 28 days of screening
  - With documented RSV in last 14 days before enrollment

Measures

- GRCD
- Clinician Global Impression of Severity (CGIS)[2]
- Midulla clinical severity score[3]
- Parent Global Impression of Severity (PGIS) and Parent Global Impression of Change (PGIC)[4]

Analytic Methods

- Item-level descriptive statistics and graphical techniques to examine symptom prevalence and change over time, and evaluate floor and ceiling effects
- Principal components analysis and exploratory factor analyses
- Reliability
  - Test-retest reliability: κ coefficients and intraclass correlation coefficients (ICCs) were computed using subset of patients assumed to be stable from Days 13 to 14 because caregivers responded exactly the same on PGIC on both days
  - ICCs >0.7 indicate acceptable reliability for group comparisons of multi-item scales
  - Internal consistency: Cronbach's coefficient α[5] and item-total correlations
  - Approximate range of optimal α 0.7–0.9, indicating set of strongly related items capable of supporting a unidimensional scoring structure, but not redundant
- Construct validity: correlations between GRCD scores and all available clinician-reported (CGIS and Midulla) and caregiver-reported (PGIS and PGIC) measures
- Discriminating ability: known-groups analyses of variance examined mean differences in GRCD scores between patients classified into groups on basis of CGIS and PGIS
- Responsiveness: effect sizes and standardized response means (SRMs) calculated
  - Effect sizes: ~0.2 = small; ~0.5 = moderate; >~0.8 = large

Results

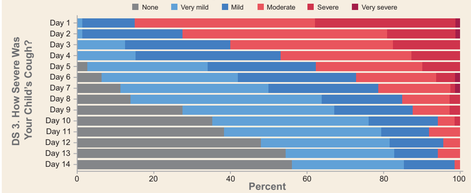
Participant Characteristics

Characteristic	Baseline (N=103)
Mean age, mo (SD)	7.4 (5.3)
Median (minimum–maximum)	7 (0–23)
0–6 mo, n (%)	51 (50)
7–12 mo, n (%)	35 (34)
13–24 mo, n (%)	17 (17)
Female, n (%)	43 (42)
Race, n (%)	
American Indian, Alaskan Native, Native Hawaiian, or Pacific Islander	0
Asian	6 (6)
Black or African descent	11 (11)
White	76 (74)
Other	2 (2)
Multiple	8 (8)
Daycare, n (%)	43 (42)
Mean caregiver age, y (SD)*	31.4 (5.5)
Median (minimum–maximum)	32 (19–46)
Female caregiver, n (%)	95 (93)
Caregiver race, n (%)	
American Indian, Alaskan Native, Native Hawaiian, or Pacific Islander	0
Asian	6 (6)
Black or African descent	11 (11)
White	80 (78)
Other	2 (2)
Multiple	4 (4)
Caregiver highest education level, n (%)*	
< high school	1 (1)
High school or GED*	13 (13)
Some college, technical training	19 (19)
College graduate	46 (45)
Advanced or professional degree	22 (22)

*n=101. GED, General Educational Development test; SD, standard deviation.

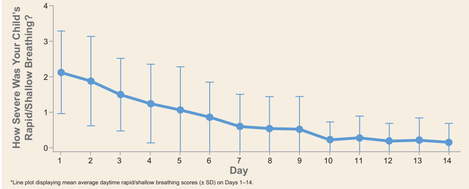
- Final analysis data set for psychometric evaluation included 103 patient-caregiver pairs
- All 103 pairs completed Visit 1; 102 caregivers (99%) completed end-of-study interview by telephone 15–18 days after Visit 1
  - 20 caregivers (19%) completed all 14 days of GRCD (overnight and daytime symptom diaries)
- Most children enrolled in Dec (26%), Jan (22%), Feb (42%)
- 11 caregivers (11%) completed paper-and-pencil GRCD forms and 92 (89%) completed electronic (Internet-based) questionnaires

Item-Level Example: Daytime Cough Severity*



*Stacked % plot displaying item-level response distributions for daytime cough severity at Days 1–14. DS, descriptive statistic.

Item-Level Example: Daytime Rapid/Shallow Breathing*



*Line plot displaying mean average daytime rapid/shallow breathing scores (± SD) on Days 1–14.

- All GRCD items showed substantial improvement in overnight and daytime symptoms over the course of the 2-week data collection

GRCD Composite Score Map

- The structure of the GRCD was explored using inter-item correlations and factor analysis
- Factor analyses were largely uninterpretable, but inter-item correlation matrices (data not shown) showed patterns of weak, moderate, and strong correlations among sets of items that were used to define separate composite scores for respiratory symptoms, RSV symptoms, behavior impact, and cough

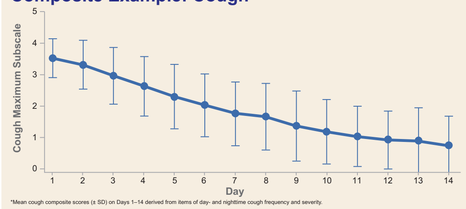
GRCD Composite Scores: Reliability and Responsiveness

GRCD Composite Score (n=39)	Days 13–14 ICC (95% CI)	α 1st Day	α Last Day	Effect Size 1st–7th Day	Effect Size 1st–Last Day	SRM 1st–7th Day	SRM 1st–Last Day
Cough	0.77 (0.61, 0.87)	0.58	0.94	−2.73	−4.14	−1.69	−3.17
Respiratory symptoms	0.81 (0.68, 0.90)	0.67	0.78	−2.67	−4.16	−1.65	−3.16
RSV symptoms	0.94 (0.89, 0.97)	0.73	0.84	−2.75	−4.22	−1.48	−2.86
Behavior impact	0.43 (0.13, 0.66)	0.53	0.84	−2.83	−4.40	−1.53	−2.72
Global	0.90 (0.82, 0.95)	0.75	0.84	−2.72	−3.91	−1.96	−3.49

CI, confidence interval.

- Item-level k's (data not shown) ranged in strength from poor (overnight and daytime fever, daytime activity level, daytime eating, and daytime fussiness) to almost perfect agreement, with most indicating at least moderate agreement
- All test-retest ICCs for the composite were highly satisfactory, except for behavior impact subscale scores
- Internal consistency Cronbach α's were highly satisfactory, although values for respiratory symptoms, cough, and behavior impact subscales were <0.7 at Day 1
- Item-level effect size estimates of change were large, ranging from –0.86 to –3.55; SRMs were also large, ranging from –0.79 to –2.54 (data not shown)
- Effect size estimates for subscale and global score changes from the 1st to 7th day and to the last day were large

Composite Example: Cough*



*Mean cough composite scores (± SD) on Days 1–14 derived from items of day- and nighttime cough frequency and severity.

- All subscale and global scores showed substantial symptom improvement over the course of the 2-week data collection

Construct Validity Correlations at Visit 1 (n=49–78)

GRCD Composite Score	CGIS	Temperature	Respiratory Rate	Heart Rate	Oxygen Saturation	Midulla Score	PGIS	PGIC 7th Day	PGIC Last Day
Cough	0.04	-0.03	-0.03	0.02	−0.02	−0.09	0.56*	0.66*	0.63*
Respiratory symptoms	0.08	0.06	0.03	0.07	−0.14	0.11	0.66*	0.68*	0.50*
RSV symptoms	0.14	0.09	0.06	0.00	−0.14	0.10	0.70*	0.67*	0.63*
Behavior impact	0.12	0.06	0.15	0.15	0.10	0.12	0.45*	0.43*	0.36
Global	0.12	0.06	0.10	0.08	−0.03	0.12	0.68*	0.67*	0.62*

*P <0.01.

- Construct validity correlations supported the validity of GRCD subscale and global scores
  - Strongest correlations were between GRCD scores and the other parent-reported measures (PGIS and PGIC)
    - All subscale and global scores, except behavior impact subscale, achieved consistently strong correlations with PGIS at Day 1, and PGIC at Days 7 and 14
  - Correlations between GRCD scores and clinician-reported CGIS and Midulla scores were weak–moderate
- Discriminating ability: analysis of variance demonstrated that GRCD subscale and global scores differed across subgroups of patients rated as less or more ill on PGIS, but not on CGIS

Conclusions

- Based on the results of the psychometric analyses, 5 items were deleted from the GRCD
  - Overnight fever and daytime fever due to poor reliability, responsiveness, and construct validity correlations
  - 3 overnight symptoms (runny nose, congestion, and fussiness); however, matching daytime symptoms were retained, thereby reducing caregiver burden without impairing GRCD content validity
- The results of the psychometric evaluation build on qualitative research evidence for the GCRD, and strongly support its reliability, validity, and responsiveness for assessing RSV symptoms in young children
- The novel GRCD captures standardized parent/caregiver information not traditionally obtained in clinical practice or clinical trials
  - With additional validation in therapeutic studies, the GCRD will capture clinically meaningful symptoms useful in defining clinical endpoints in RSV trials

References

1. FDA. December 2009. http://www.fda.gov/downloads/Drugs/GuidanceCompliance RegulatoryInformation/Guidances/UCM193282.pdf; **2.** Guy W. US Dept of Health, Education, and Welfare Publication No. 76-338. Rockville, MD: National Institute of Mental Health; 1976:217-22; **3.** Midulla F, et al. Arch Dis Child 2010;95:35-41; **4.** Jaeschke R, et al. Control Clin Trials 1989;10:407-15; **5.** Cronbach L. Psychometrika 1951;16:294-334.

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