

Patient- and Observer-Reported Measurement in Pediatrics: Development in Cystic Fibrosis

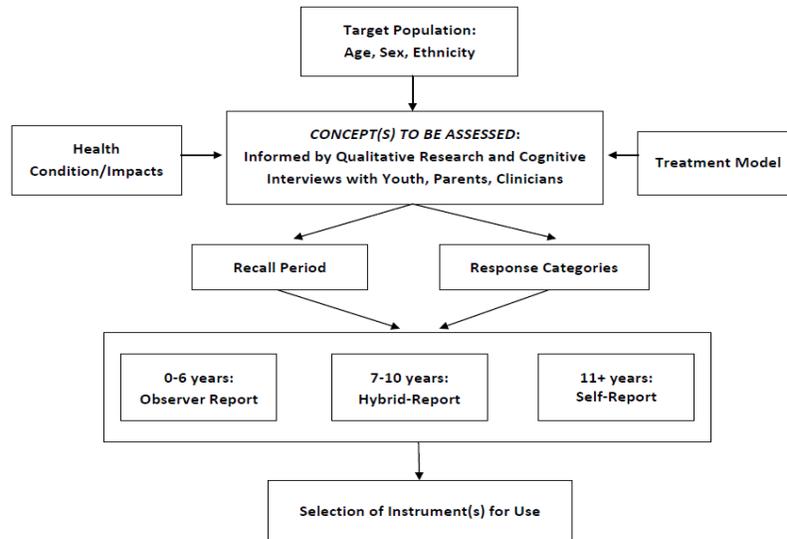
Measurement in Clinical Trials: Review and Qualification of
Clinical Outcome Assessments -- Public Workshop
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Principles and Challenges

- Rapidly changing and variable child development requires careful attention to context of measurement.
- Qualitative research and cognitive interviews with patients, parents, and clinicians indispensable.
- Self-report of symptoms and impacts whenever possible.
- Use **verifiable** report of observable concepts only when self-report not possible.

Context of Measurement in Pediatrics



Why is Self-Report Preferred in Pediatrics?

- Some treatment effects are known **only** to the youth themselves, e.g., pain, mood, perceived health, daily function
- Biomarkers and ObsROs do not often accurately reflect how youth feel and function
- Well-developed measures reported by youth are as reliable as observations reported by clinicians or parents

Cut-Off Age for Self-Report

- No established guidelines
- Affected by concreteness of reported concept
- Age 7 often cited as bottom of age range
- Mixed validity & reliability results below age 11
- Ages 7 to 11: Combination of self- and observer-report may be best
- Age 11+ generally acceptable psychometrically
- Age is generally not best criterion, assessment of comprehension & willingness/motivation to respond is better

Verifiable Observation

A sign or impact must be able to be detected by a sense or senses:

- Seen (*vision*)
- Heard (*auditory*)
- Smelled (*olfactory*), or
- Felt (*touch*)

| Self-Report Concept | Observer-Report Concept (Sense) |
|----------------------------------|--|
| Difficulty breathing | Gasping for breath? (see) |
| Feverish | Feverish (touch) |
| Tired | Lying down to rest more than usual (see) |
| Chills or sweats | Chills or sweats (see, touch) |
| Cough | Cough (see, hear) |
| Cough up mucous | Cough up mucous (see) |
| Tightness in chest | None |
| Wheeze | Wheeze (hear) |
| Difficulty sleeping | ? |
| Worried | ? |
| Irritable | Behaving fussy (see, hear) |
| Depressed | ? |
| Frustrated | Behaving fussy (see, hear) |
| Time spent sitting or lying down | Time spent sitting or lying down (see) |
| Reduce usual activities | Reduce usual activities (see) |
| Miss school or work | Miss school or work (see) |

Observable Signs: Examples in Ages 0-6

- **Labored breathing (hear):** Even as he's breathing at night, it'll sound like the breathing is more labored, it's harder for him to breathe, and it'll have that kind of crackle-pop kind of thing going on, as well. (#13)
- **Fussiness (see):** "Well, about a week and a half ago or so, he started just getting fussy, and he wouldn't finish all of his bottle which is not normal for him. And so his appetite was tapering off. He was getting fussier." (#2)

Reliability and Validity of Observation

- Inter-rater reliability is more appropriate than test-retest, although difficult to implement
- Test-retest is affected by consistency and frequency of observed phenomenon over time, as well as by measurement error
- **KEY POINT** -- Reliability not sufficient by itself: “How do we know we are measuring the right thing(s) for development, condition, and treatment context?”

Seattle CF Measurement -- Development Map

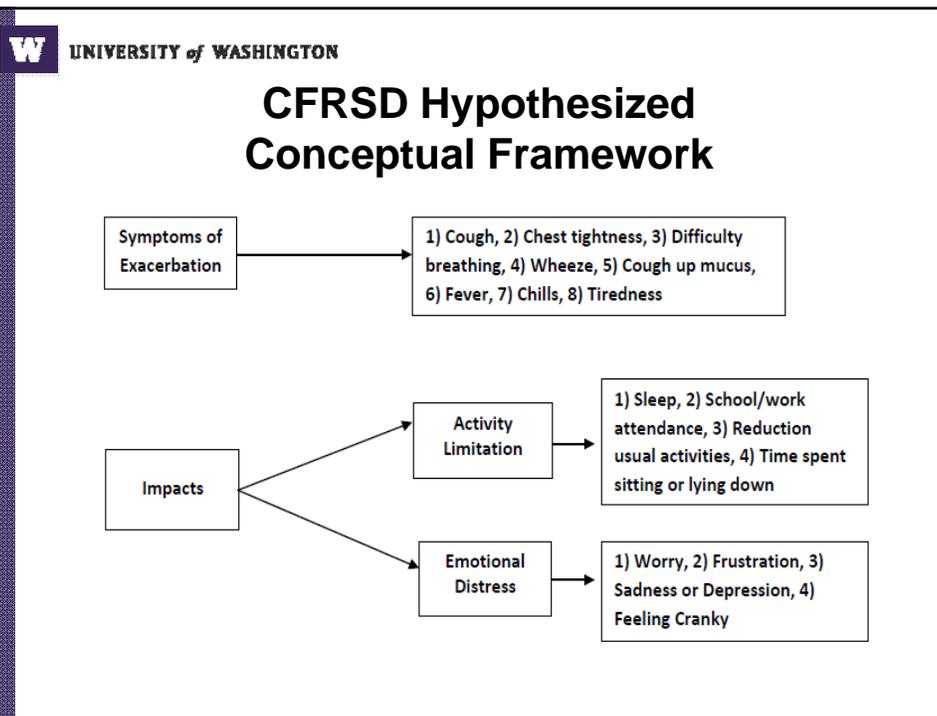
| Age | Instrument Type | Reporter | Concepts Measured | Instrument Name | Status | Funding Sources |
|-----------------------|------------------------------------|---------------|---|---|------------------------|---|
| Infancy through Age 6 | 24-hour Diary | Parent | Observable CF-related signs, emotional & activity impacts | Cystic Fibrosis Sign Diary (CFSignD 0-6) | In Phase I development | Cystic Fibrosis Foundation, NIH, Vertex Pharmaceuticals |
| 7 through 11 Years | 24-hour Diary | Self & Parent | Observable CF-related signs, emotional & activity impacts | Cystic Fibrosis Sign Diary (CFSignD 7-11) | In Phase I development | Cystic Fibrosis Foundation, NIH |
| 12 Years + | 24-hour Diary, 7-day Questionnaire | Self | CF-related symptoms, emotional & activity impacts | Cystic Fibrosis Respiratory Symptom Diary (CFRSD) | In Phase II testing | Cystic Fibrosis Foundation, NIH |

Cystic Fibrosis Respiratory Symptom Diary (CFRSD): Ages 12+

(Source: *Project Breathe – Goss CH, et al. J Cyst Fibros. 2009 Jul;8(4):245*)

- n=25 concept elicitation interviews conducted at two centers
 - Seattle Children’s Hospital (n=13)
 - University of Washington Medical Center (n=12)

| N=25 | N or Mean | % or Range |
|--|-----------|-------------|
| Age Group | | |
| 6-11 yrs | 4 | 16% |
| 11-14 yrs | 4 | 16% |
| 15-18 yrs | 5 | 20% |
| 19-25 yrs | 6 | 24% |
| ≥ 26 | 6 | 24% |
| Gender | | |
| Female | 10 | 40% |
| Male | 15 | 60% |
| Children: Mean FEV ₁ % Pre. | 72.8% | 31%-109% |
| Adults: Mean FEV ₁ % Pre. | 58.4% | 23.7%-99.1% |



CFRSD Sample Screen Shot - Original

Cystic Fibrosis: Your Daily Experience

Instructions

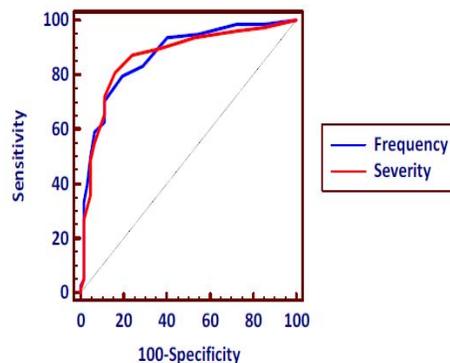
- Complete this diary between 5:00 P.M. and when you go to bed each evening.
- Think carefully about your experience with cystic fibrosis, specifically during the last 24 hours, before responding to each question. The "last 24 hours" is the amount of time that has passed since the same time the previous day.
- Please complete all of the questions in one sitting.

| | | | | | | | |
|--|--|---|---|---|---|---|---|
| Because of your cystic fibrosis, during the last 24 hours: | (Check one): <input type="checkbox"/> Yes | → | During the last 24 hours, when did you have difficulty breathing? | → | Overall during the last 24 hours, how difficult was it to breathe? | → | Overall during the last 24 hours, how often did you have difficulty breathing? |
| 1. Did you have difficulty breathing? | (Check one): <input type="checkbox"/> No | → | (Check one): <input type="checkbox"/> Night only <input type="checkbox"/> Day only <input type="checkbox"/> Both day & night | → | (Check one): <input type="checkbox"/> A little <input type="checkbox"/> Somewhat <input type="checkbox"/> A good deal <input type="checkbox"/> A great deal | → | (Check one): <input type="checkbox"/> A little bit of the time <input type="checkbox"/> Some of the time <input type="checkbox"/> Much of the time <input type="checkbox"/> All of the time |
| | | | If No, GO TO Question 2 ↓ | | | | |

Change in CFRSD Symptoms Alone -- Differentiate Well and Sick Periods

(Source: Biomarker Study)

- AUC
 - Frequency 0.871
 - Severity 0.867
- P=0.7



CFRSD Sample Screen Shot - *Revised*

Welcome to the Cystic Fibrosis Symptom Diary

Think carefully about your experiences **over the last 24 hours** before responding to each question.

Please complete all 16 questions in one session.

Click the right arrow to begin.

1. Overall during the last 24 hours, how often did you have **difficulty breathing**?

- None of the time
- A little of the time
- Some of the time
- Much of the time
- All of the time

Summary

- Content validity in context of use is paramount: Know ***what you're measuring and why it is important for treatment.***
- Content validity in pediatrics is key for ensuring ***developmental appropriateness*** of measurement.
- If possible, self-report is always preferred as ***direct*** evidence of treatment benefit.
- At best, verifiable observation of concepts provides ***indirect*** evidence of treatment benefit.
- ***Same rigor of measurement*** is expected for ObsRO and ClinRO as for self-reported PROs.



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Cystic Fibrosis Foundation
NIDDK
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