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MARGOLIS CENTER
FOR HEALTH POLICY

Advancing Drug Development for the Prevention
and Treatment of Respiratory Syncytial Virus
Infections

5/2/2016

Advancing Drug Development for the Prevention and Treatment of Respiratory Syncytial Virus Infections

Opening Remarks
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RSV Drug Development

- Most active it has been in decades
- At present, no oral drugs approved: Only IM route for prophylaxis and inhalation for treatment
- Multiple drugs are in development for treatment and prevention including mAbs and small molecules
- Having a variety of new possibilities could change the RSV drug development paradigm
 - Learn from past RSV development, but don't limit to past designs
 - Also learn from influenza drug development which has several approved small molecules for use in children

Workshop Objectives

- Primary Focus: Clinical Endpoints for Treatment (and Prevention)
- Other Important Issues:
 - Defining pediatric trial population and baseline disease severity
 - Establishing prospect of benefit for initiating pediatric trials
 - Role of data in other populations in drug development

A Word on Endpoints

- Our Expectation is for Clinical Endpoints
 - Could include serious outcomes or other clinical outcomes
 - Or palliation of symptoms
- Surrogate (i.e., Virologic) Endpoints are not considered appropriate for phase 3 trials (for an accelerated approval) for respiratory viruses
 - Changes in clinical symptoms are common and should occur in the same time frame as virologic changes so there is no time (or sample size) advantage for using a viral surrogate
 - Effects on virus without any associated clinical effects would not be considered efficacy to balance any associated safety risks
- Clinical outcome scales may not be fully “validated” until after we have an active (approved) RSV drug

Facilitating Drug Development for Treatment of Respiratory Syncytial Virus (RSV) Infections

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May 2, 2016

Respiratory Syncytial Virus (RSV) Disease

- Causes mild upper respiratory disease in healthy older children and adults
- Young infants, immunosuppressed children/adults and the elderly can develop severe lower respiratory disease
- Other than aerosolized ribavirin which has limited efficacy, there is no approved anti-RSV product for treatment of acute RSV
- Currently one marketed anti-RSV immunoprophylactic product approved for the prevention of hospitalization due to RSV in at-risk infants and young children

Challenges in RSV Therapeutic Development

- Establishing definitions for respiratory syncytial virus (RSV) disease severity
- Defining populations suitable for clinical trials
- Identifying clinically meaningful efficacy endpoints

Challenges in RSV Therapeutic Development (cont.)

- Describing non-clinical and clinical development approaches for pediatric-focused products
- Exploring the types of supportive efficacy/proof-of-concept data needed to initiate clinical trials in infants and young children
- Facilitating RSV drug development for other populations, such as elderly and immunocompromised patients

Issues in RSV Treatment Trials

- Challenges in clinical trial design
- Lack of robust and reliable clinical endpoints
 - Severity scores
- Population issues
 - Disease severity and comorbidities

Issues in RSV Treatment Trials (cont.)

- Extrapolation of Efficacy- Bronchiolitis in infants has no direct adult correlate
- Pediatric Studies –prospect of clinical benefit / proof of concept
- Relevant outcomes

Theoretical Issues for Treatment of Acute RSV-LRTI

- For non-immunocompromised infants and young infants, RSV viral load generally peaks prior to severe clinical symptoms and usually is declining when an infant is hospitalized.
 - During the period of peak clinical symptoms, does a therapeutic intervention to accelerate the decline in viral load result in a more rapid resolution of symptoms?
 - In this acute phase, is one class of anti-RSV therapeutic more likely to be effective than another (e.g. RNA polymerase inhibitor vs. fusion inhibitor)?
 - In designing clinical trials of agents for the treatment of acute RSV, how are these issues taken into account in enrollment criteria and in study design including endpoints?

Issues in Selecting Clinical Trial Endpoints for Prophylaxis Studies

- RSV hospitalization: no longer appears to be viable endpoint due to a shift toward increased outpatient management
- Medically attended lower-respiratory illness (MALRI): requires clinicians to apply study definitions and make accurate and reliable diagnosis

Summary

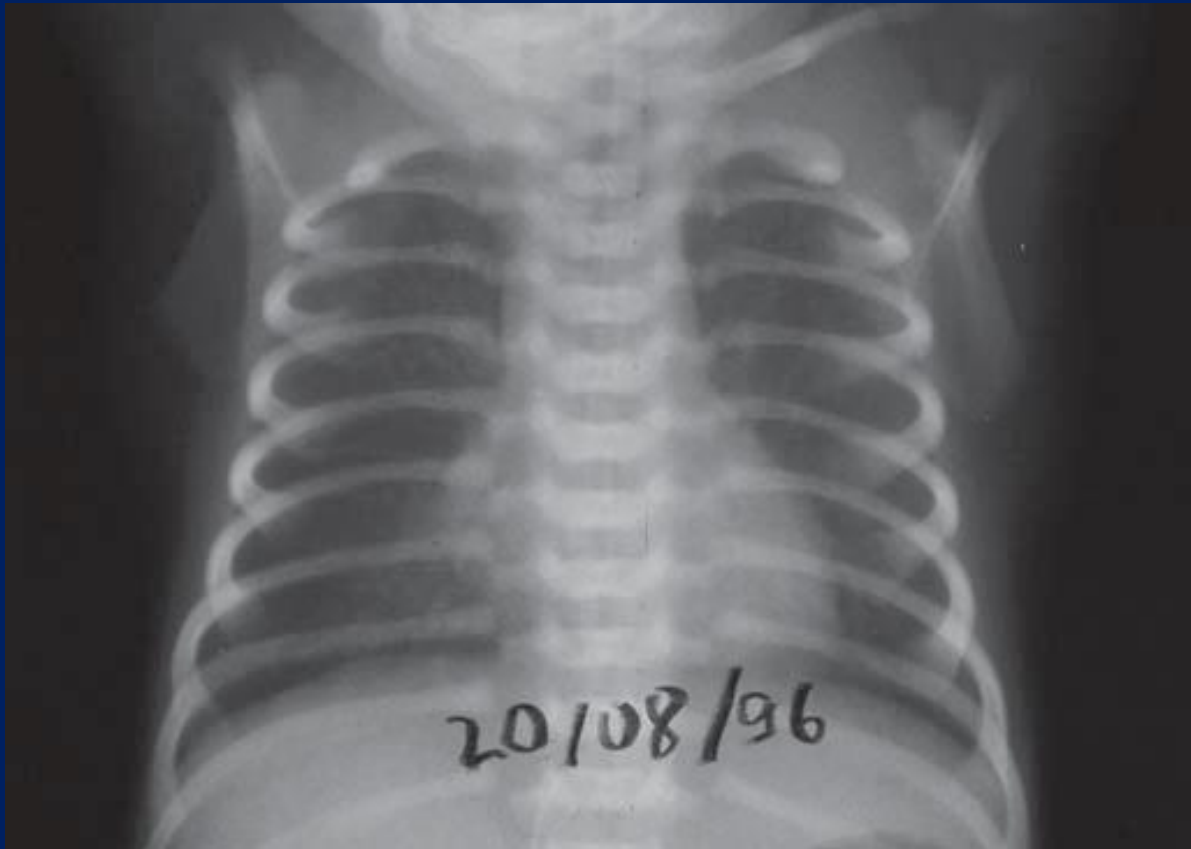
- RSV can cause severe lower respiratory disease in young infants, immunosuppressed children/adults and the elderly
- RSV product development has many challenges which include:
 - Developing definitions for RSV disease severity
 - Defining populations suitable for clinical trials
 - Selecting appropriate clinical trial designs and identifying clinically meaningful efficacy endpoints

RSV Treatment Trials: Establishing Definitions And Identifying Endpoints

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Chief, Pediatric Infectious Diseases
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Radiographic Appearance of Severe RSV Disease

Normal Pediatric Lung

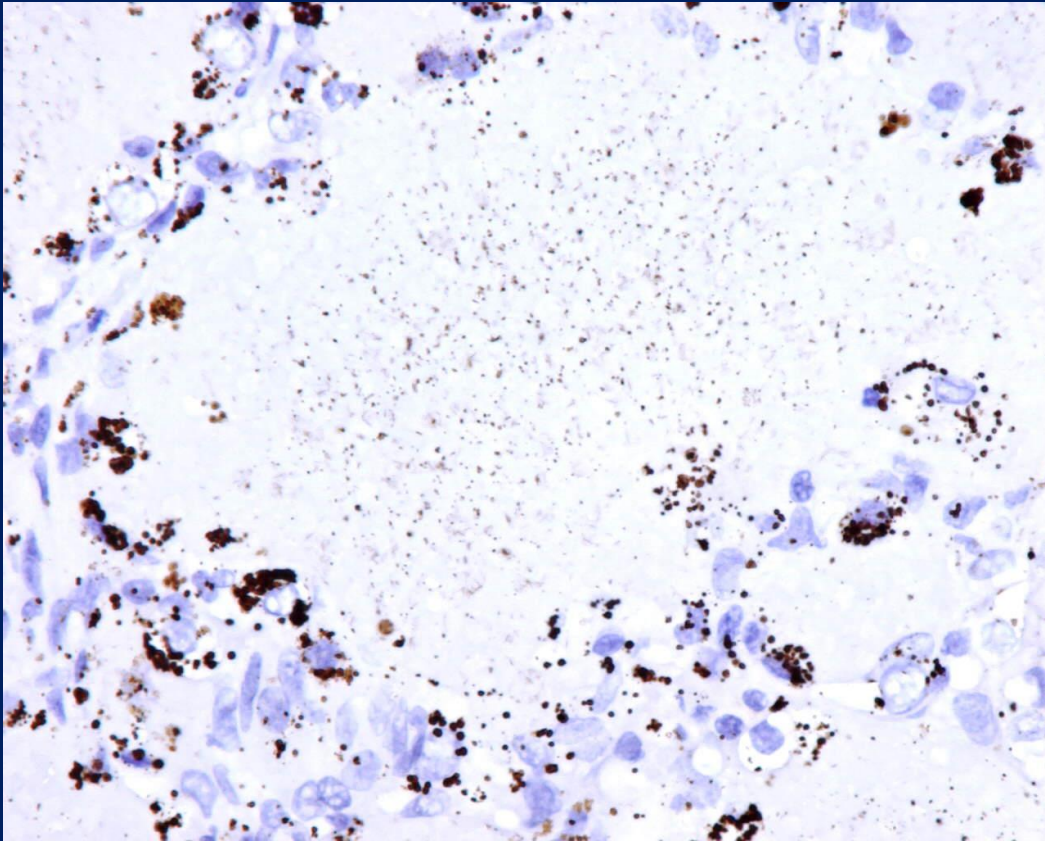


RSV Bronchiolitis

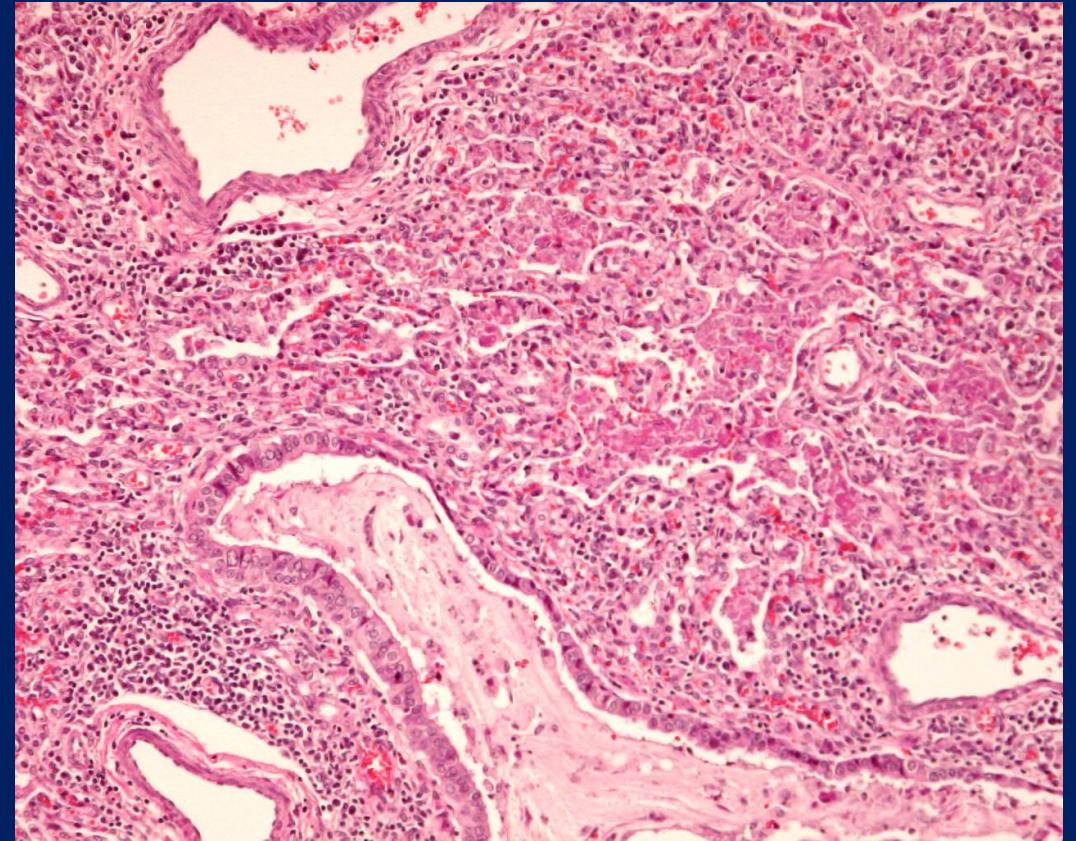


RSV Antigen in Lung and Lung Histopathology

Immunohistochemical stain for RSV antigen



H&E stain



Target Populations for Treatment Trials

I : Full Term, Otherwise Healthy, Infants

- Group most commonly hospitalized for RSV infection
- < 3 months of age at onset of RSV season (44% of hospitalizations, most deaths)
- Rapid breathing : > 60 bpm, > 70 suggests more severe disease
- Oxygen saturation : < 92%, < 88-90 suggests more severe disease
- Time to desaturation when oxygen removed

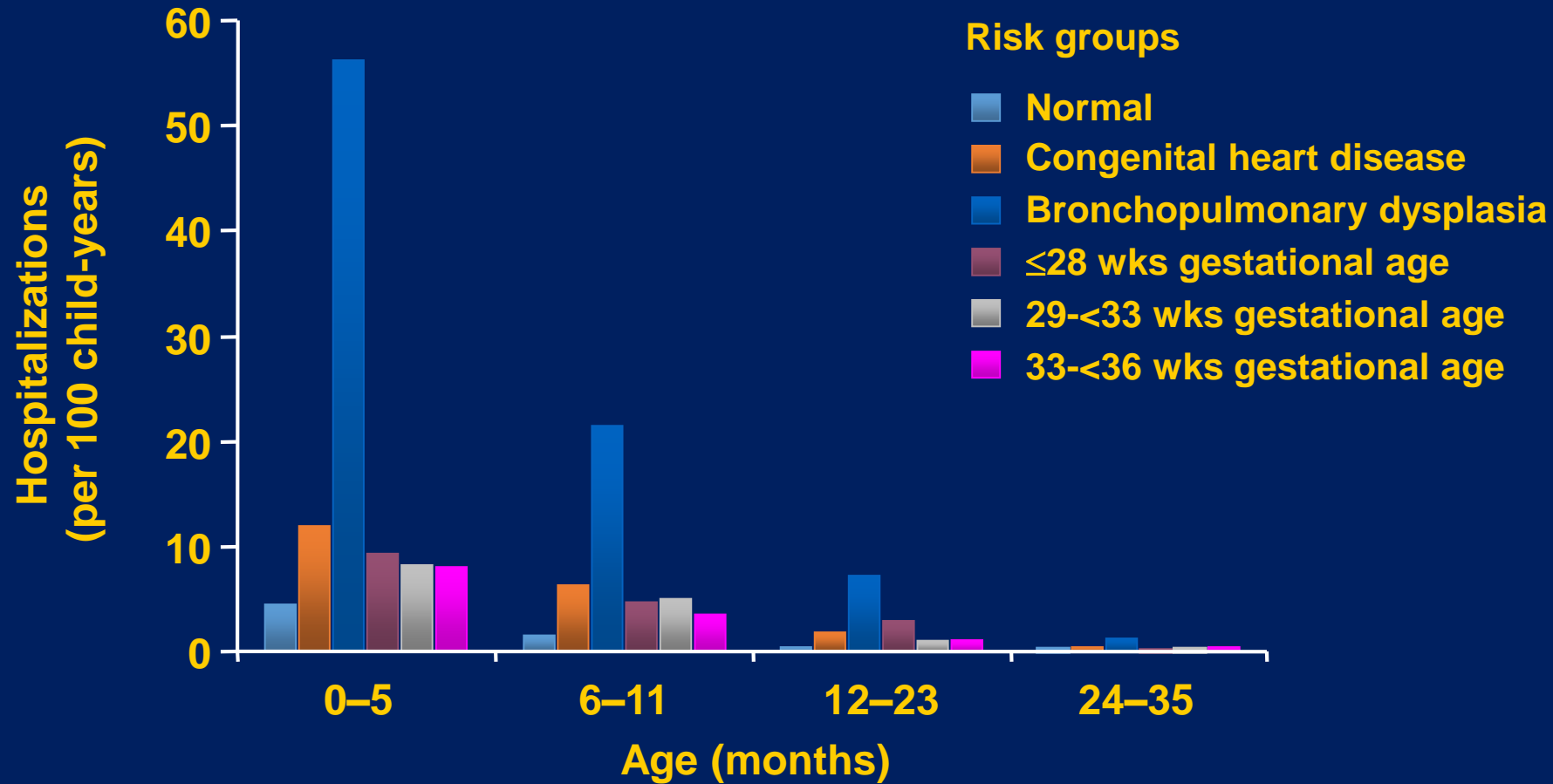
Subjective Measures of Illness

- Chest wall retractions : used by W.H.O., agreement difficult to obtain
- Reduced oral intake : < 50-75 % of normal volume for age
- RACS, RDAI scores don't correlate well with length of stay
- Clinical signs of pneumonia, bronchiolitis
 - Labored breathing, nasal flaring
 - Retractions
 - Crackles
 - Wheezing

II: High-Risk Infants

- Premature birth: < 37 weeks, with progressively shorter gestations carrying similar risk
- Bronchopulmonary dysplasia : especially if still on oxygen at the onset of RSV season
- Congenital heart disease : cyanotic or on cardiac medications

RSV Hospitalizations, Age, and Risk Group



Other High-Risk Infants

- Anatomic airway anomalies : T-E fistula, bronchomalacia
- Neurologic problems, especially leading to weak coughing or limited respiratory drive
- Immune deficiencies (HIV, reduced anti-viral immunity)
- Down syndrome
- Small for gestational age (weight at birth)

III : Elderly (≥ 65)

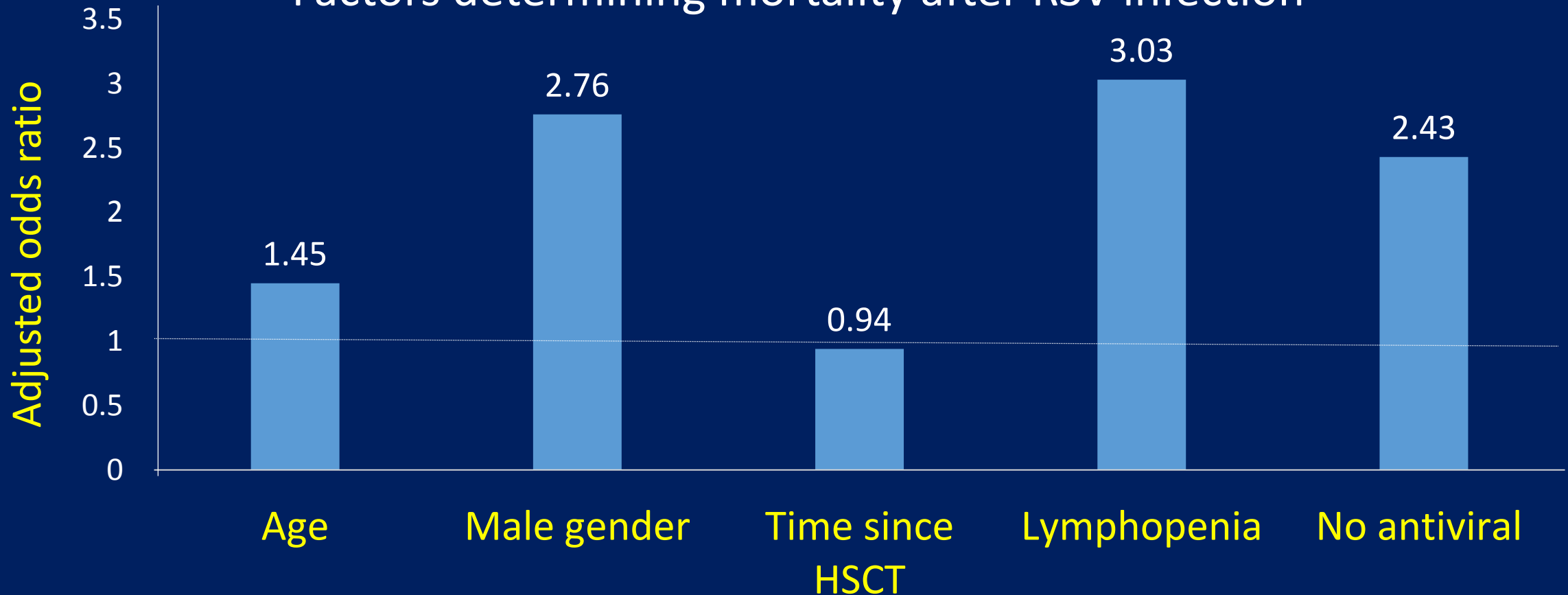
- 11% of hospitalizations for pneumonia
- 11% of hospitalizations for COPD
- 5% of hospitalizations for congestive heart failure
- 7% of hospitalizations for asthma
- Estimated 11,000 annual deaths
- \$680 million in hospital costs (1999 dollars)

RSV Mortality per 100,000 Person-Years

Health Status	Age (years)	Mortality rate
Healthy	1-64	≤ 0.5
Healthy	≥ 65	7.2
Heart or lung disease	1-64	≤ 4.7
Heart or lung disease	≥ 65	26.5

IV. Immune Deficiency

Factors determining mortality after RSV infection



Overall, 29 % developed RSV pneumonia, and all-cause mortality was 16%

Definitions of Moderate and Severe RSV Illness

- Hospitalization
- Intensive care unit transfer
- Respiratory failure, with criteria defined previously, not apnea
- Respiratory rate > 60 (70) in infants
- Respiratory rate > 25 (30) in adults
- Oxygen saturation < 92 (< 88), varying with altitude
- Oxygen saturation reduced by 5% from baseline (i.e., 85% from 90%)
- pCO₂ > 50 mmHg, or increase from baseline
- Time to desaturation < 1 minute after oxygen removed

Summary

- Full term infants, premature infants, very elderly, heart/lung disease patients, HIV, transplant recipient (stem cell, lung, bone marrow) constitute target groups
- Age < 3 months, > 75 years are important target groups
- Underlying heart and lung disease enhances risk (infants and adults)
- Clinical features (RR, O₂ saturation, pCO₂, time to desaturation, retractions) indicate severity
- Elevated RR, marked retraction, wheezing and *reduced oxygenation* indicate LRI

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Identifying Appropriate Endpoints for RSV Treatment Trials: An Overview

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May 2, 2016

Disclaimers/Disclosures

H. Cody Meissner, M.D.

- I have no financial relationship with the manufacturer(s) of any commercial product(s) discussed in this activity
- I may discuss the use of certain medications or vaccines in a manner not consistent with the Package Insert, but all recommendations are in accordance with recommendations from the ACIP and AAP.

Signs & Symptoms to Capture RSV Disease Severity

More useful:

- Reduction in number of outpatient RSV MARI
- Reduction in progression to RSV LRI
- Difference in disease severity between groups
 - Clinical scoring
 - Difference in duration of illness

Signs & Symptoms to Capture RSV Disease Severity

More useful: (continued)

– Suggested scoring scale

- No RSV illness
- URI symptoms only
- Mild LRI
- Moderate LRI
- Mechanical ventilation

– Scoring factors

- Cough, tachypnea, wheezing, increased work of breathing (retractions, flaring, grunting, accessory muscle), fever

Signs & Symptoms to Capture RSV Disease Severity

Possibly useful

- Reduction in RSV hospitalization rates

<u>Age</u>	<u>Rate/1000</u>
<1 year	15 - 40
1 to 2 years	2 - 10
2 to <5 years	1 - 2

- Reduction in all-cause respiratory hospitalization

Signs & Symptoms to Capture RSV Disease Severity

Possibly useful (continued)

- Reduction in otitis media
 - Reduction in antibiotic use
- Reduction in viral load
 - May reflect genetic or anatomic predisposition
- Parent reported wheezing
- Biological markers

Signs & Symptoms to Capture RSV Disease Severity

Less useful:

- Radiographic changes
- Oxygen saturation measured by pulse oximetry
 - Lowest oxygen saturation
- Effect on apnea
- Mortality rates
- Subsequent episodes of asthma

Potential Confounding Variables

- Host factors
 - Chronologic age, gestational age, CHD, CLD, genetics, passively acquired maternal antibody, malnutrition, race or ethnicity
- Viral factors
 - Poorly understood virulence factors
 - Seasonal and geographic variation
- Duration of symptoms before treatment
- Co-infections

Economic Considerations

- The economic benefit will come from reduced RSV hospitalization rates, reduced outpatient MARI and reduced income loss by caregivers
- Endpoints should enable calculation of cost saved by disease avoidance



Regulatory Approach to Clinical Outcome Assessment Development

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Disclaimer

The views expressed in this presentation are those of the speaker, and do not necessarily represent an official FDA position.

Purpose of an Outcome Assessment

- To determine whether or not a drug has been shown to provide clinical benefit to patients
 - **Clinical benefit**: A positive clinically meaningful effect of an intervention on how an individual *feels, functions, or survives*
- A conclusion of clinical benefit is described in labeling in terms of the concept of interest (outcome) measured
- One of the most important aspects of drug development is how that benefit is measured

Types of Outcome Assessments

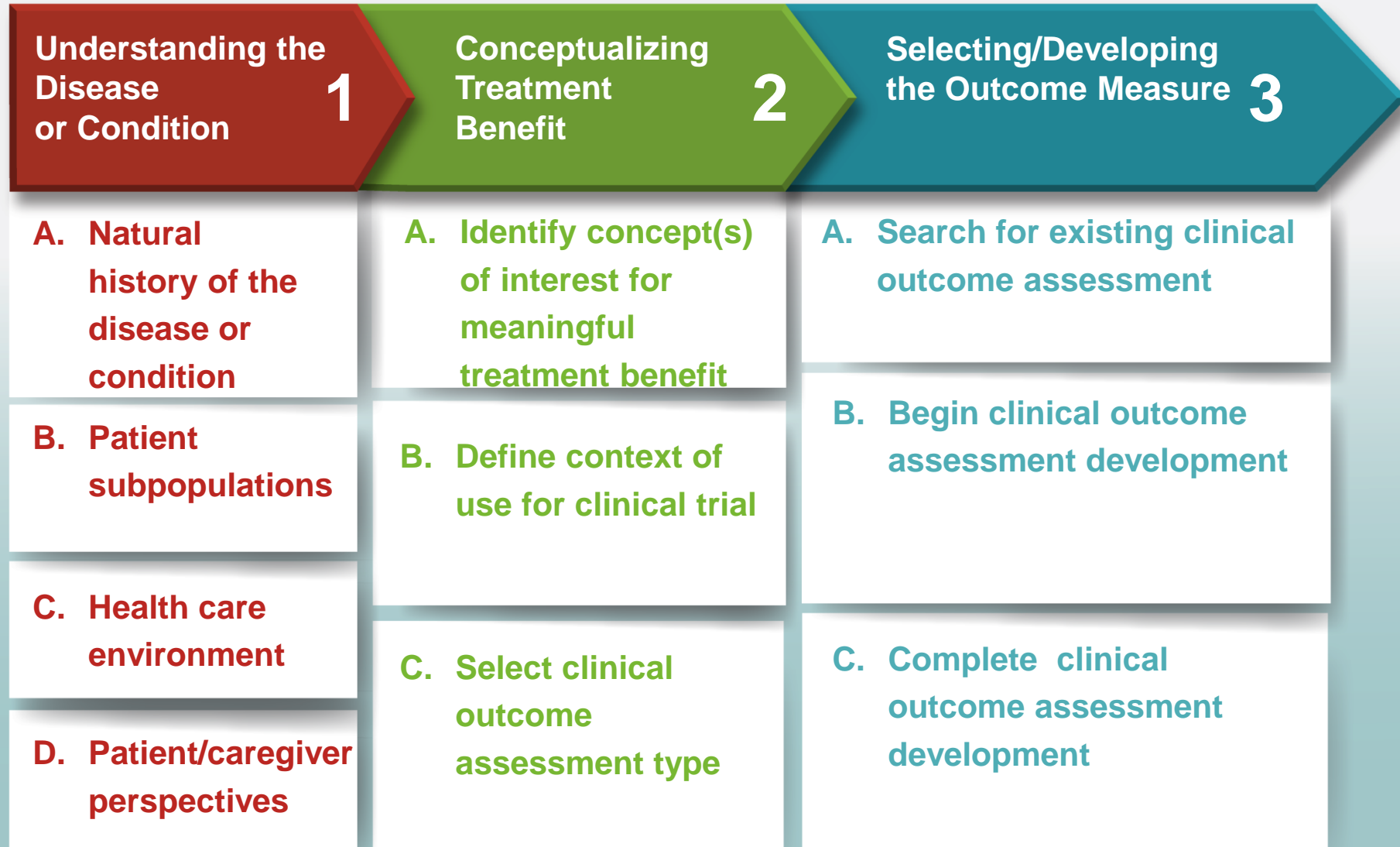
Clinical Outcome Assessments (COAs)

- Performance Outcomes (PerfOs)
- Clinician-reported Outcomes (ClinROs; includes overall survival)
- Observer-reported Outcomes (ObsROs)
- Patient-reported Outcomes (PROs)

Surrogates

- Often a biomarker* that is intended as a substitute for how a patient feels, functions, or survives

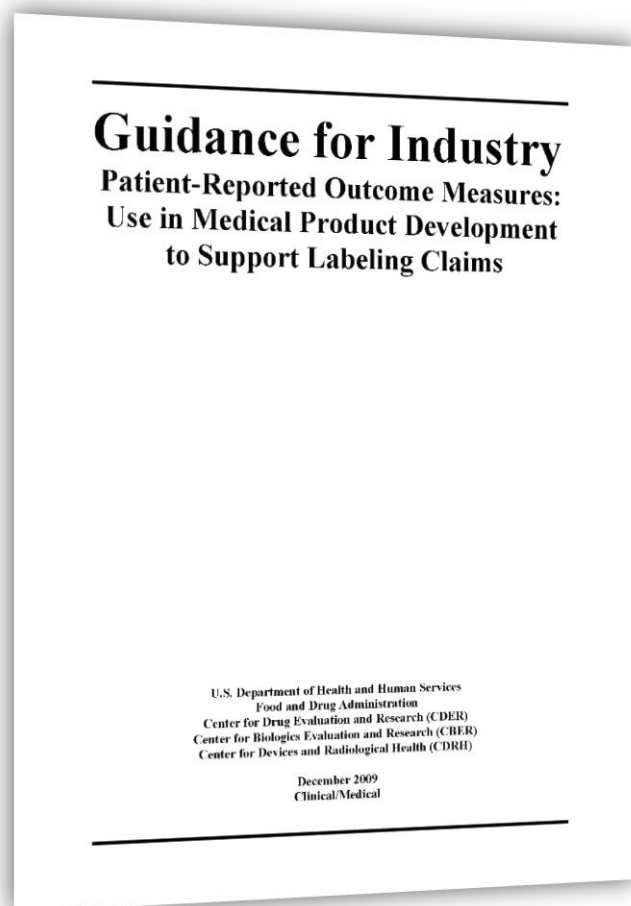
Roadmap to **PATIENT-FOCUSED OUTCOME MEASUREMENT** in Clinical Trials



Choosing Clinical Outcome Assessments

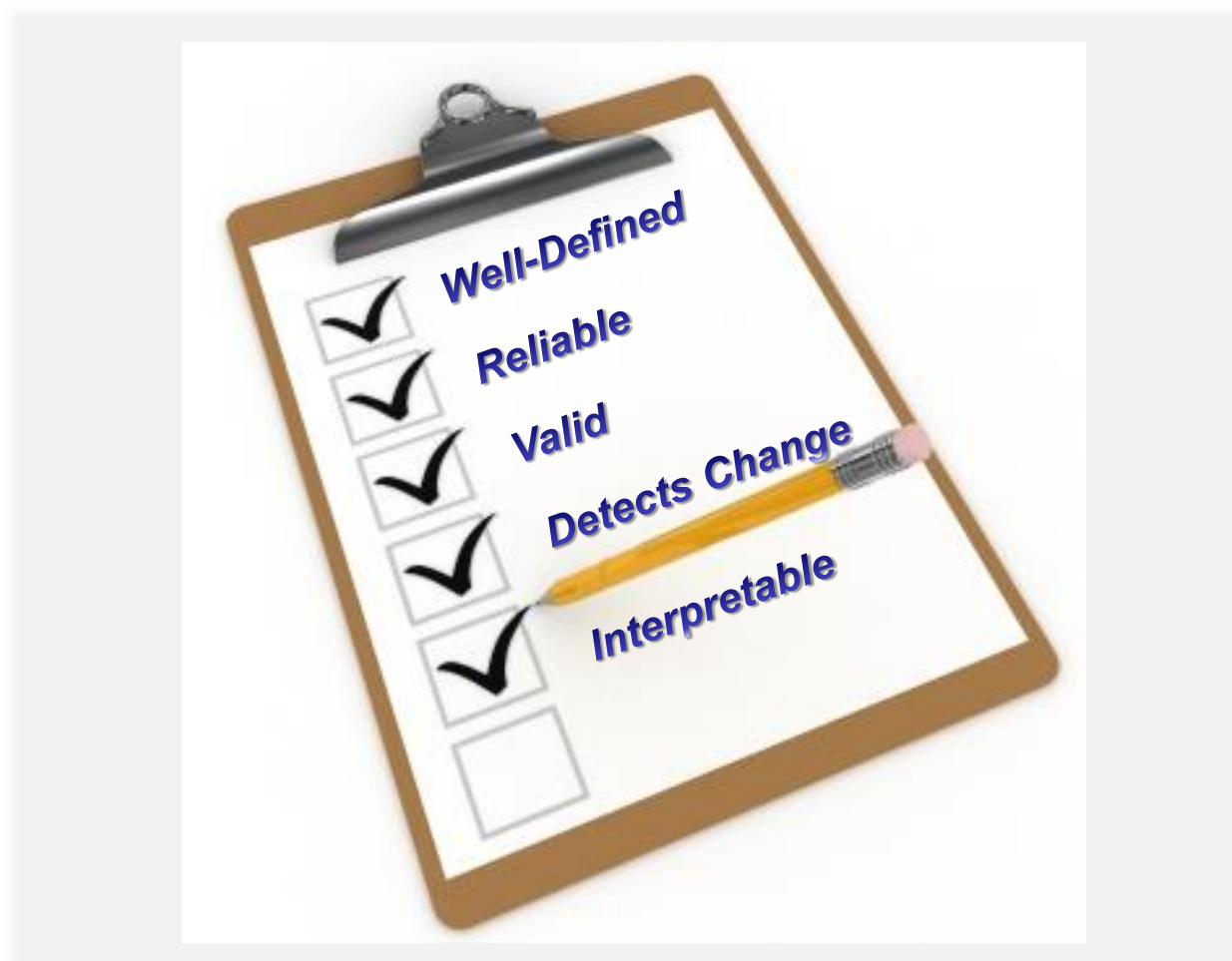


Good Measurement Principles

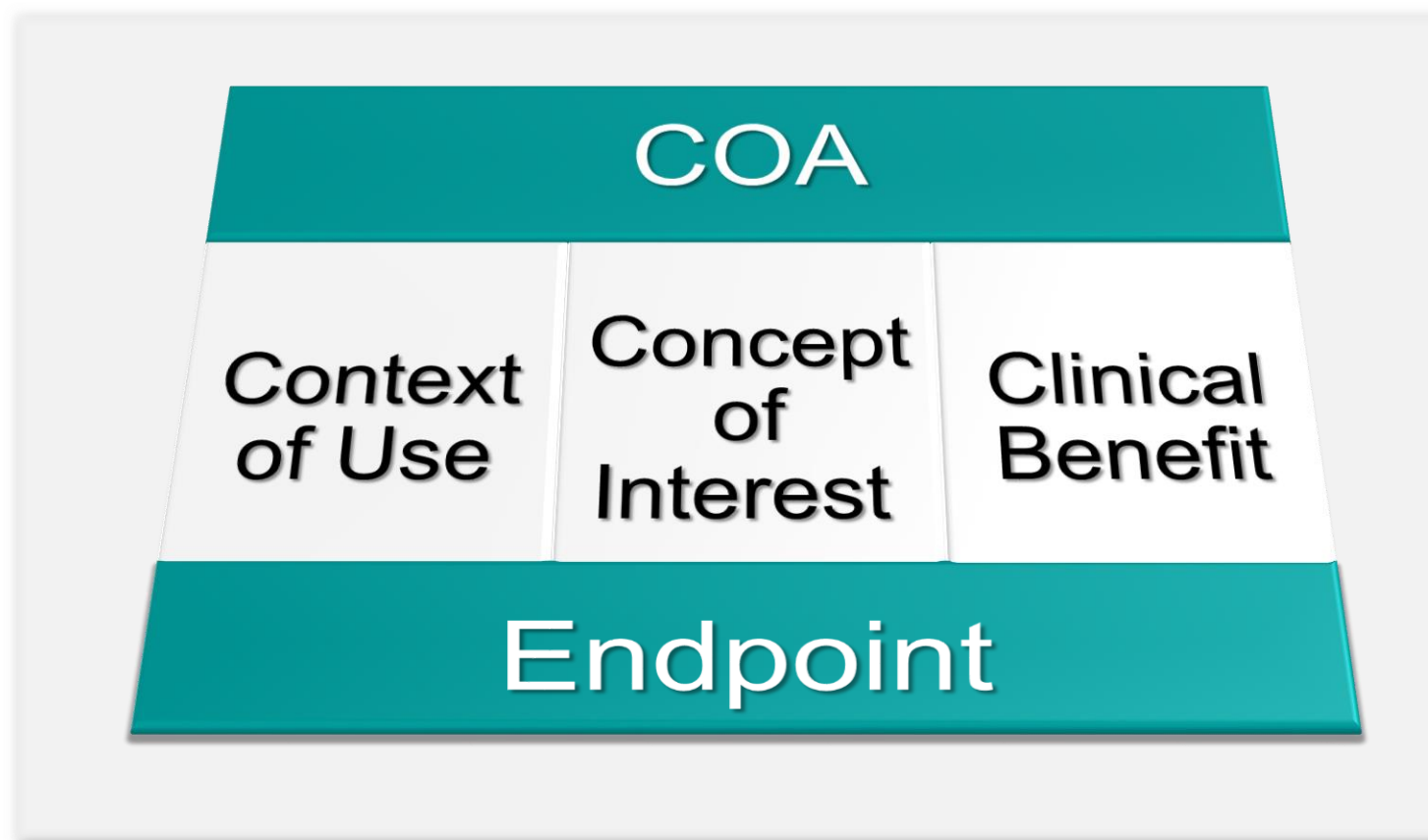


- Defines good measurement principles to consider for “well-defined and reliable” (21 CFR 314.126) PRO measures intended to provide evidence of clinical benefit
- All COAs can benefit from the good measurement principles described within the guidance
- Provides optimal approach to PRO development; flexibility and judgment needed to meet practical demands

Good Measurement Principles



From COA Development to Study Endpoint



Case Example

- Symptomatic RSV infection in adults
- Assessment of observable signs of disease and symptoms

Context of Use

Adults ($\geq 18y$) with symptomatic RSV

Clinical Benefit

Resolution of clinical signs and symptoms

Concept of Interest

Severity of RSV Signs and Symptoms

Clinical Outcome Assessment

Signs: Clinician-reported rating

Symptoms: Patient-reported symptom tool

Endpoint

Sign: Score change from baseline

Symptom: Score change from baseline

Potential Challenges in Using Clinical Outcome Assessments in RSV

- Measuring symptom improvement
 - Enriching for symptomatic patients in trial
- Using multiple types of assessments to form an endpoint
 - PRO and ObsRO assessments

Two Pathways for FDA COA Review & Advice

1

Within an individual drug development program

- Investigational New Drug (IND) submissions to FDA
- Potential to result in labeling claims

2

Within the Drug Development Tool (DDT) qualification program; outside of an individual drug development program

- Potential to result in qualification*