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ENDPOINTS

PAH Workshop June 13, 2017

YOUR HEALTH AND SAFETY... OUR PRIORITY.

OUTLINE

- General overview
- Consideration of endpoints for pediatric pulmonary hypertension trials

CLINICALLY MEANINGFUL ENDPOINTS

- Endpoints that in themselves represent or characterize the clinical outcome of interest
- Directly measure
  - A benefit that is detectable by the patient
    - How a patient feels, functions or survives
  - A decrease in the risk of developing a complication that can occur as a result of having the condition/disease

SURROGATE ENDPOINTS

- Laboratory measurement or physical sign used as a substitute for a clinically meaningful endpoint
- Ideally the surrogate endpoint exists within the therapeutic pathway of the intervention' and therefore' expected to reflect the clinically meaningful endpoint
- Validation required
- Benefit of using surrogate endpoint
  - May not be feasible to use direct endpoint
    - Very low event rates
    - Ethical reasons
  - Faster and easier
  - Less expensive

ENDPOINTS

- PAH endpoints mainly validated for adults with IPAH
- Traditional endpoints used in adults can be difficult/ not appropriate to assess in children
- Need to define and measure endpoints that are clinically relevant to children

FUNCTIONAL ENDPOINTS

ENDPOINT	STRENGTH	WEAKNESS
Growth parameter (height, weight)	General predictors of child health Failure to grow is a sign of illness	Growth catch-up may not occur
New York Heart Association Functional Classification	Predictor of survival Convenience Ease of classification Widely used	Subjective patient self reporting Poor for inter-trial comparisons Poor detection of subtle changes Not child oriented
Panama Functional Classification	5 age groups with developmentally appropriate criteria	Validation Complexity Time to complete

HEMODYNAMIC ENDPOINTS

ENDPOINT	STRENGTH	WEAKNESS
Cardiac catheterization	Measurement of right ventricular structure/function Measurement of PAH	Invasive Specialized centres Sedation/anaesthetic risk
Echocardiogram	Non-invasive Widely available	Strict compliance to study protocol Not all information available in all patients with exception of septal position
Cardiac MRI	Measurement of cardiac structure and function	Strict compliance to study protocol Sedation/anaesthetic risk

EXERCISE ENDPOINTS:

ENDPOINT	STRENGTH	WEAKNESS
6 minute walk distance test (6MDT)	Simple Widely used	Lack of correlation with disease/ treatment outcomes; Influenced by physical characteristics of patient Ceiling effect Lack of validation for pediatric age, culture differences
Cardiopulmonary exercise test	Ability to evaluate physiological severity Reproducible	Need of technical expertise Takes time to perform and for interpretation Lack of appropriate equipment for use in children Age limitations
Ambulatory physiological monitoring	Simple device Real life data	Validation

LABORATORY ENDPOINTS:

ENDPOINT	STRENGTH	WEAKNESS
Brain natriuretic peptide (BNP/ NT-pro BNP)	Sensitive to cardiac volume overload and increased wall stress	Not specific to disease Standardization of assay Stability in transport??
Serum uric acid	Sensitive- impairment	Not specific for disease or degree of improvement
Renal function (serum creatinine, creatinine clearance)	Sensitive-impairment	Not specific for disease or improvement

ENDPOINTS: PROs

	Strength	weakness
PROs	Assess a patient's physical or emotional state Allow investigators to evaluate the effectiveness of a treatment and/or changes in the disease trajectory from a patient's point of view	Validation

FACTORS TO CONSIDER IN CHOICE OF ENDPOINT

- Will the endpoint be able to answer the study question?
- Is the endpoint appropriate for the phase of the trial?
- Is the endpoint appropriate for the population being studied?
  - age, culture, gender, etiology of PAH, degree of disability
- What is the degree of change in endpoint required to be clinically meaningful?