General Landscape of Extrapolation of Efficacy in Pediatric Drug Development

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FDA

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U.S. evidentiary standard for approval

- For approval, pediatric product development is held to same evidentiary standard as adult product development
- A product approved for children must:
  - Demonstrate **substantial evidence of effectiveness/clinical benefit** (21CFR 314.50)

Substantial evidence of effectiveness

"Evidence consisting of adequate and well -controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved"

– Section 505(d), Food, Drug & Cosmetic Act

Clinical benefits to support drug approval

Clinical outcomes

- Direct measure of how a patient feels, functions, or survives
- Improvement or delay in progression of clinically meaningful aspects of the disease

Surrogate endpoints

- A substitute for how a patient feels, functions, or survives
- **Established surrogates** (e.g. blood pressure, low density lipoprotein (LDL) in adults, forced expiratory volume in 1 sec (FEV_1) in asthma)
- Surrogates reasonably likely to predict clinical benefit
  - Accelerated approval
  - Requires additional studies post-marketing to confirm clinical benefit
  - For serious conditions that filled an unmet medical need

Pediatric extrapolation

"If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, [FDA] may conclude that **pediatric effectiveness** can be extrapolated from adequate and well - controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies." (21 CFR §355c)

Children should only be enrolled in clinical trials if the scientific objectives cannot be met by enrolling subjects who can provide informed consent (e.g. adults).

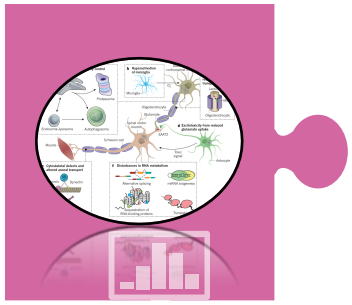
The foundation of pediatric extrapolation is degree of disease and response similarity

Goal: To predict how a drug/biologic will behave in children on the basis of data generated in adults

What evidence supports disease and response similarity?

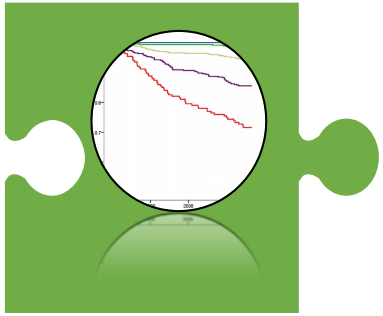
Disease similarity

Evidence of common pathophysiology, natural history* between adults and children

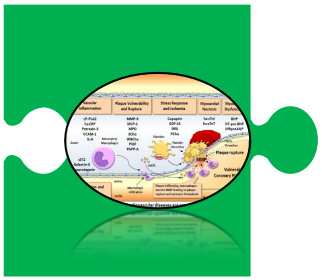


Response similarity

e.g. similar endpoints, mode of action, or biological pathway, ontogeny of biomarker expressions, experience with drugs in the same therapeutic class, similar placebo response rate, etc..

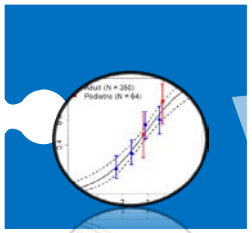


If disease/response are similar, what data are needed to support approval?



PD/Biomarker endpoint

Availability of a PD endpoint/biomarker that can be used to predict efficacy in children?



Similarity in E-R

Evidence of similar concentration or concentration-response relationship in each population

* FDA guidance for Industry, 1998

Techniques to make optimal use of available data: M&S, adaptive designs, Bayesian statistics, meta-analytic approaches, etc.

Extrapolation approaches in pediatric programs

Increasing level of **evidence required from pediatric studies**

Increasing level of **confidence in similarity of disease/response**

~60% Pediatric Programs
require at least 1 adequate, well-controlled efficacy trial (clinical or surrogate endpoint)

1 or more adequate-well controlled studies powered on a <u>clinically meaningful</u> endpoint
Bipolar disorder, systemic juvenile idiopathic arthritis, major depression, migraine, polyarticular JIA (pJIA), bronchopulmonary dysplasia, ADHD, nausea/vomiting, partial seizures (<4 y/o), respiratory syncytial virus, prophylaxis of venous thromboembolism, atopic dermatitis, etc.

1 or more adequate-well controlled studies powered on a <u>surrogate</u> endpoint
Diabetes, anemia, idiopathic thrombocytopenia, treatment of venous thromboembolism, hypertension, hypercholesterolemia, asthma, etc.

Controlled study without formal statistical power
Community acquired pneumonia, nosocomial infections, skin and skin structure infections, etc.

Descriptive efficacy study without concurrent control
Plaque psoriasis, Neurogenic detrusor over-activity, pJIA (NSAIDs), etc.

Small dose-ranging studies (randomization to multiple dose levels)
Sedation, ulcerative colitis (infliximab), etc.

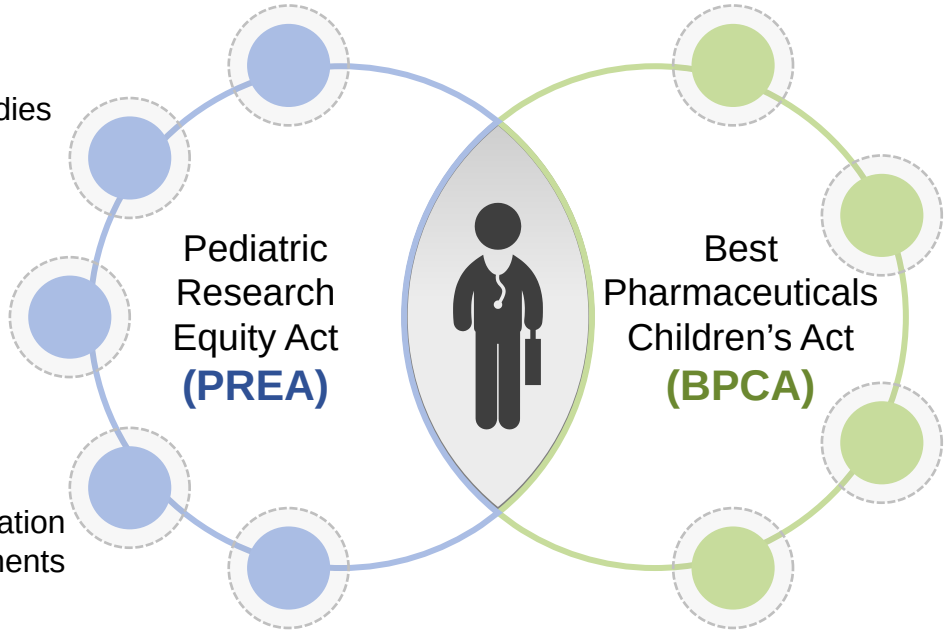
Small PK/PD studies (single dose level matching adult exposures)
HIV, erosive esophagitis (infants), anesthetics, pulmonary arterial hypertension,

PK/safety only (single dose level matching adult exposures)
Partial onset seizures (4 years and older), bacterial sinusitis, herpes simplex, analgesics/anesthetics (well known MOAs; over 2 y/o), imaging products, melanoma (adolescents)

List partially adapted from Dunne et al. *Pediatrics* 2011

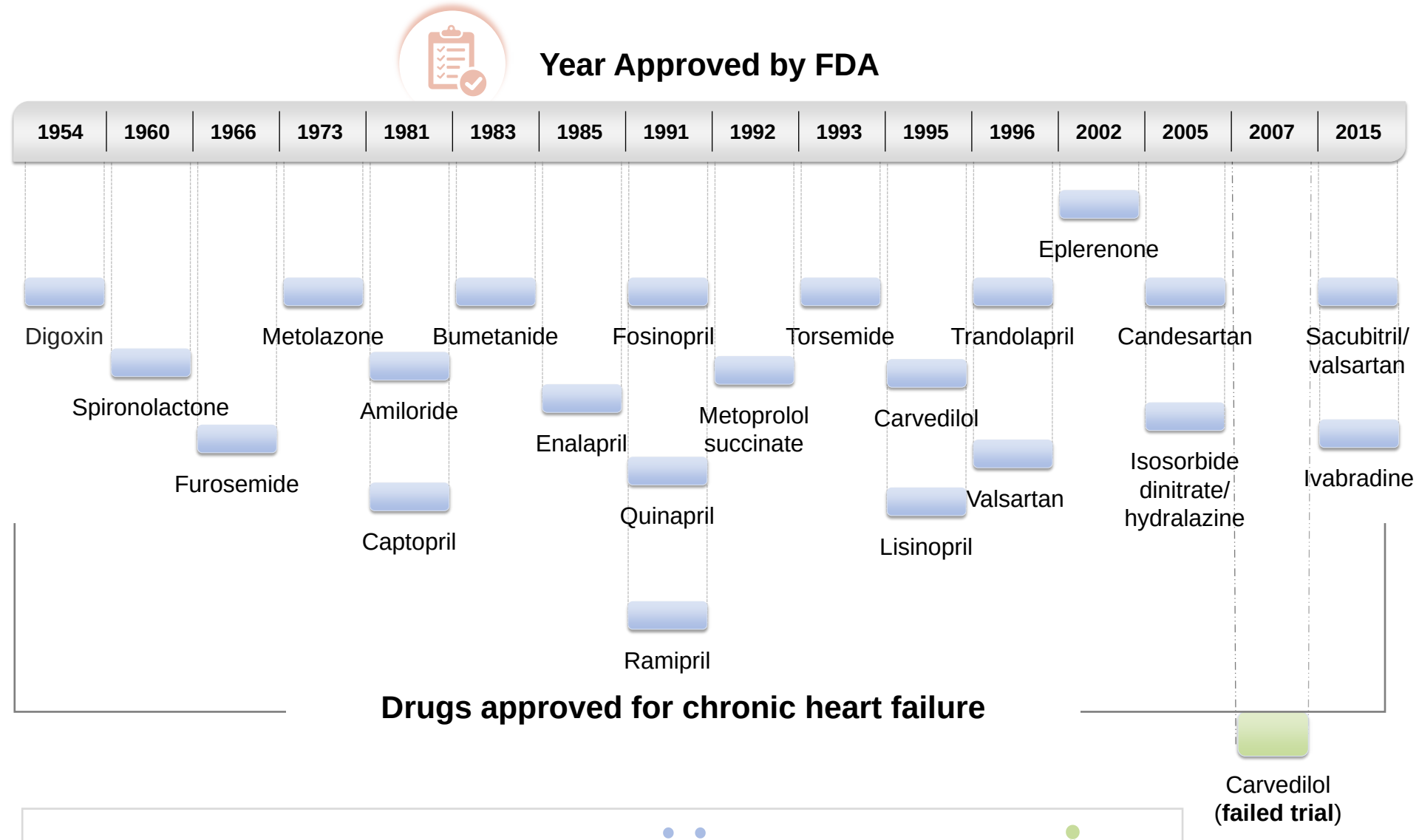
Drug development in pediatric heart failure: regulatory framework

The context is a drug/biological product developed for **adult heart failure, studied in adult patients** and then investigated for its potential use in children



To date, pediatric HF studies are not required under PREA but are encouraged under BPCA

Heart failure treatment options

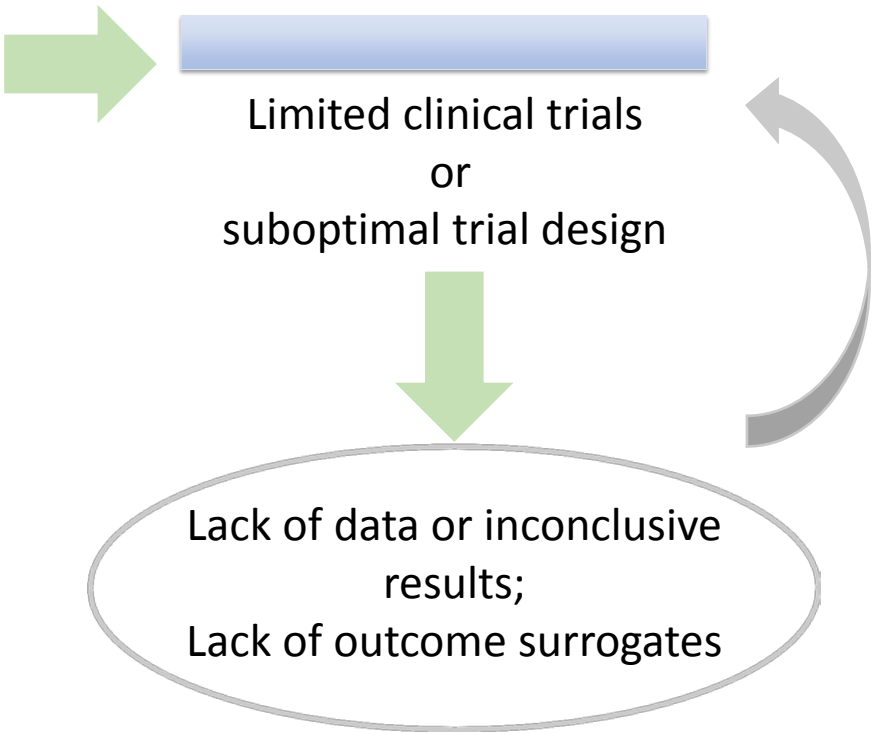


Adult clinical trials in heart failure

Product	Trial Design	Endpoint	Sample Size	Population
Candesartan	Placebo-controlled	Time to either cardiovascular **mortality or hospitalization** for heart failure	2,028	Heart failure with **reduced ejection fraction**.
Isosorbide dinitrate/ hydralazine		Reduction in **mortality**	642	Treatment of heart failure as an adjunct therapy to standard therapy in self-identified black patients to improve survival, prolong time to hospitalization for heart failure and to improve patient-reported functional status.
			804	
		Composite score consisting of all-cause **mortality**, **first hospitalization** for heart failure, and responses to the Minnesota Living with Heart Failure questionnaire.	1,050	
		Composite of the first occurrence of either **hospitalization** for worsening heart failure or **cardiovascular death**.	6,558	
Ivabradine		Composite of time to first **cardiovascular death**, **hospitalization** for acute myocardial infarction, or hospitalization for new-onset or worsening heart failure.	10,917	Heart failure with **reduced ejection fraction**.
		Composite of the first occurrence of either cardiovascular death or myocardial infarction.	19,102	
Sacubitril/ valsartan	Active control trial	Composite of reducing the risk of **cardiovascular death or hospitalization** for heart failure.	8,442	Heart failure with **reduced ejection fraction**.

Multiple challenges associated with conducting pediatric HF trials

- Small population
- Heterogeneous disease
- Low rates of clinical events used in adult studies i.e. mortality/hospitalization
- Lack of acceptable surrogate endpoints



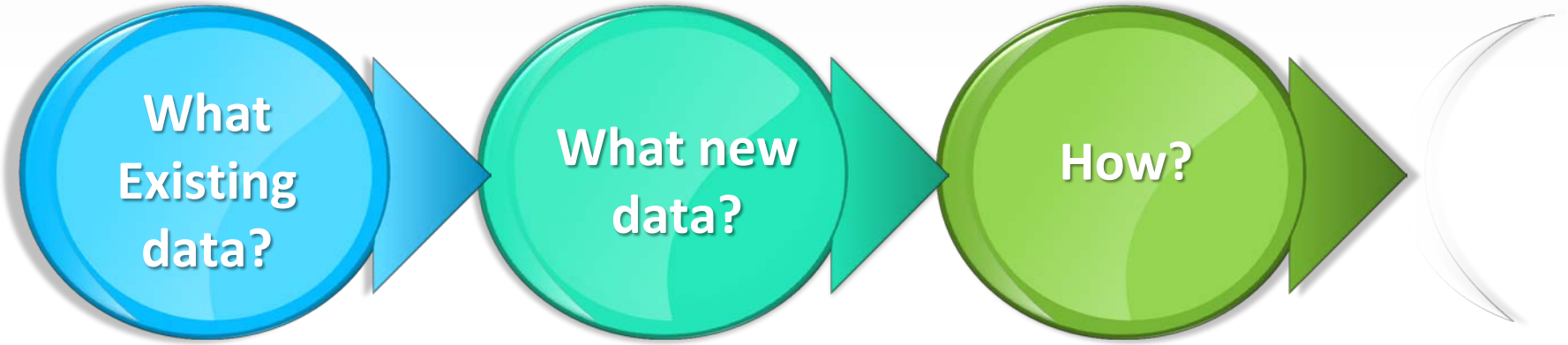
Drug Development in Pediatric Heart Failure

Existing data?

- What adult data, if any, could be leveraged and to which pediatric HF population/subgroup does it apply

How?

- What is the optimal trial design to obtain the necessary data

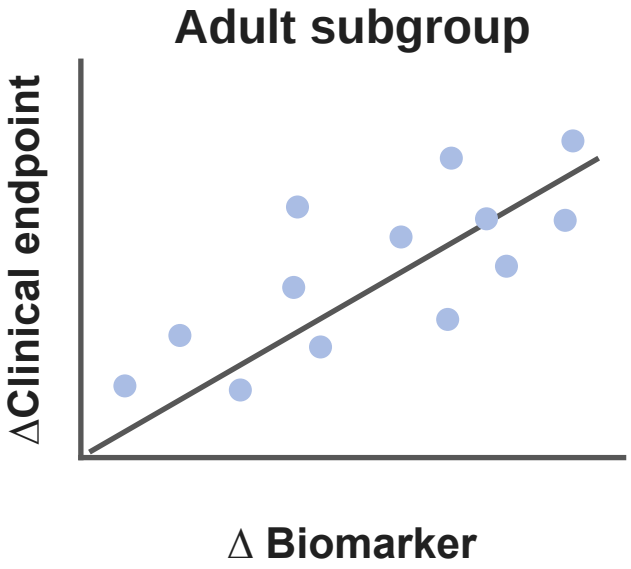


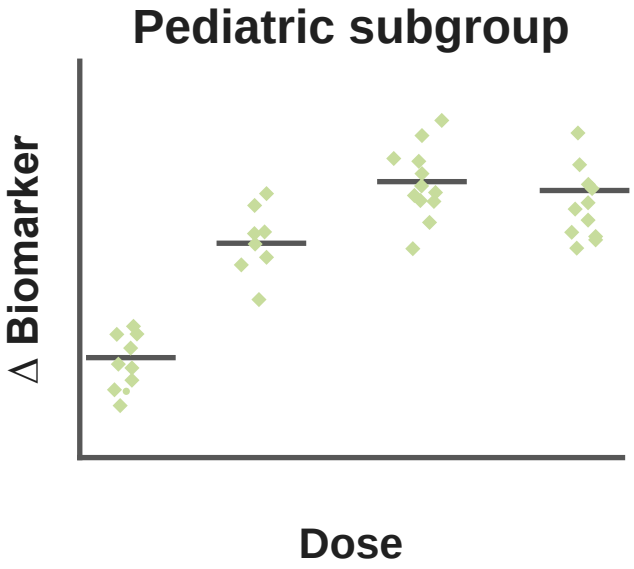
What new data?

- What additional data are needed in the target pediatric HF population?

If extrapolation is acceptable, what biomarker or clinical endpoint can be used to enable extrapolation of adult data ?

Adult and pediatric HF subgroups with **“similar” disease**





Adults

Establish a relationship between Δoutcome of interest & Δbiomarker to specify target for pediatric study

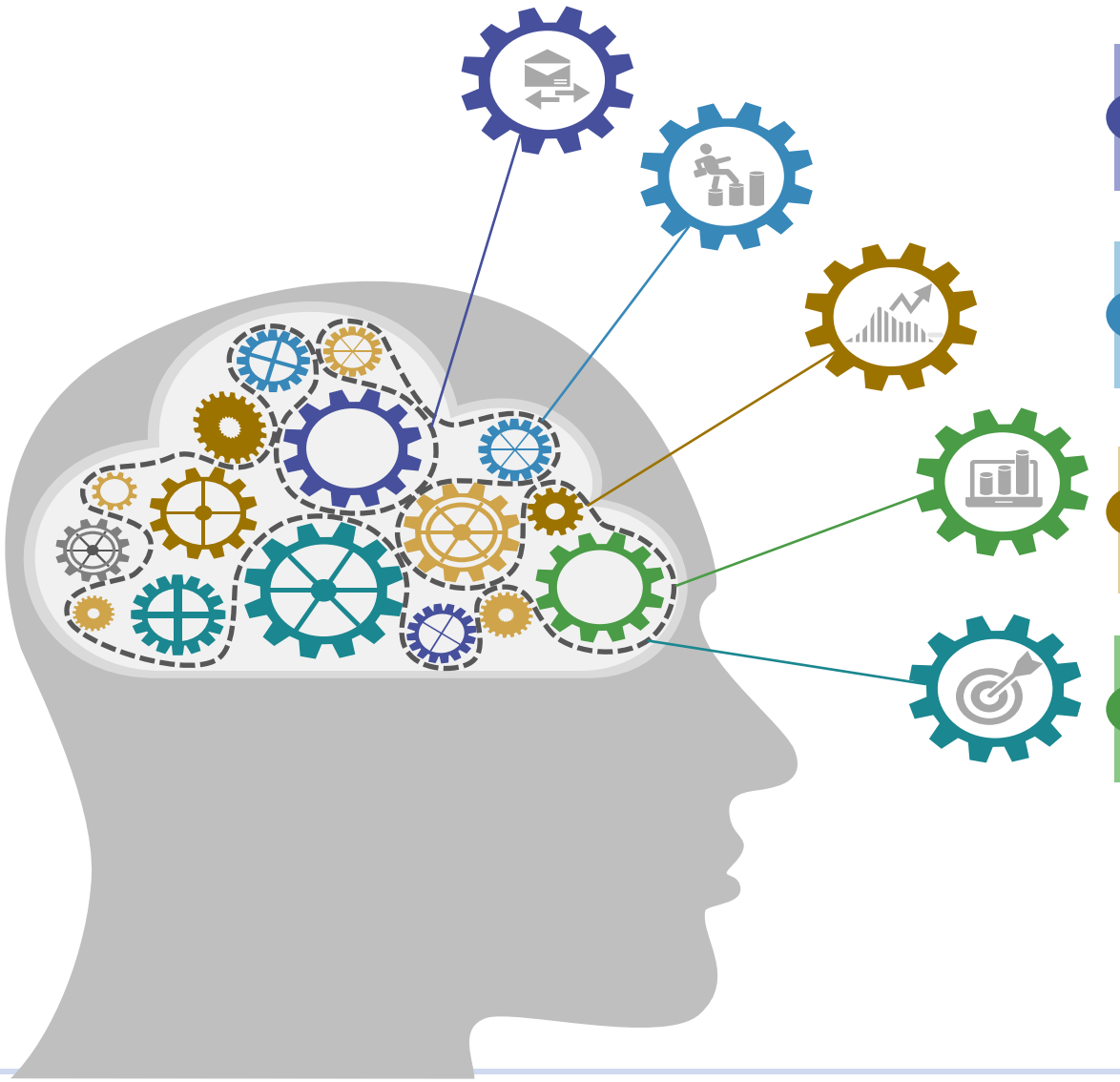
Pediatric study

Dose ranging study to achieve different degrees of biomarker response or target biomarker response

Adapted from Brar, S. Advisory Committee presentation July 29, 2010

Advancing drug development in pediatric heart failure

Focus for workshop presentations/discussions



1. What adult and pediatric HF subgroups have similar disease? How can different components of pediatric HF be integrated to facilitate drug development?

2. What evidence is needed to support reliance on a PD endpoint or biomarker to enable extrapolation of adult efficacy data?

3. What innovative trial design, statistical methodology, and quantitative tools can be used to assess the efficacy of HF products in children?

4. If extrapolation is NOT acceptable, what evidence is necessary from pediatric trials? How should such trials be designed?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