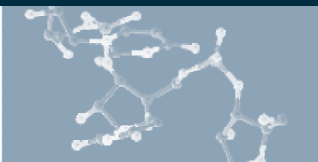


Challenges in Drug Development for Muscle Disease

Assessing Safety as an Endpoint

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Safety as an Endpoint

- “Reactive”, amorphous endpoint
 - Describes *unintended* consequences of drug use
 - May take many forms (eg, headache, rash, QT prolongation, transaminase elevations)
 - Unexpected events may occur at any time
 - Expected events may occur at unexpected times
- Consequences
 - Not strictly definable a priori
 - Usually has no treatment effect size of interest
 - Rarely considered in sample size calculation
 - Often not amenable to formal statistical analysis

Critical Questions in Addressing Safety during Clinical Development

- Functional
 - Are safety considerations adequately built into each study design?
- Strategic
 - Does the overall development plan define *benefit:risk* consistent with the disease severity and patient population?
 - Does the safety profile compare favorably against therapies in development or already approved?

Actively Addressing Safety is Critical in Trial Design

Safety Considerations Are Addressed in All Major Clinical Protocol Sections

- ✓ Background Information
- ✓ Objectives and Endpoints
- ✓ Patient Selection
- ✓ Study Treatment
- ✓ Schedule of Events
- ✓ Adverse Event Assessment
- ✓ Statistical Analysis
- ✓ Informed Consent

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Background Information – Provides Critical Safety Support for Trial Design Details

- Preclinical safety pharmacology and toxicology data
 - hERG assay for QT prolongation
 - Neurological, pulmonary, and cardiovascular testing
 - General toxicology testing (rodent, nonrodent) of sufficient duration
 - Genotoxicity (Ames, CHO, micronucleus)
- Clinical safety data
 - Adverse events and laboratory abnormalities
 - Subject population characteristics
 - Doses and duration of therapy
- Preclinical and clinical PK
 - Prior exposures (AUC, C_{max}) relative to projected patient exposures
- Class effects
 - Toxicity profiles of similar drugs or agents

Objectives and Endpoints – Establishes Clear Intent to Evaluate and Analyze Safety Profile

- Study objectives: evaluation of safety should always be listed as a study goal
 - *Example:* To characterize the safety profile of “study drug” in children with Duchenne muscular dystrophy
- Study endpoints: safety profile should always be listed as a study endpoint
 - *Example:* Safety profile characterized by type, frequency, severity, timing, relationship to study drug, outcome, and seriousness of any adverse events or test (eg, laboratory/ECG) abnormalities

Patient Selection – Limits Enrollment to Patients Who Can Safely Provide Interpretable Data

- In primary studies, both risk and potential benefit must be considered to achieve an acceptable balance
- To avoid risk, criteria should generally exclude patients with:
 - Medical or prior therapy that adversely affects safety or safety data analysis (eg, known allergy to medication class, patient with active viral hepatitis enrolled to study of a drug that might be hepatotoxic, pregnancy for potentially teratogenic drug)
 - Need for another drug likely to promote a severe drug-drug interaction
 - Inappropriate age (eg, based on available toxicology)
- To justify risk, criteria should generally exclude patients with:
 - An equivocal diagnosis of the target disease
 - No chance for efficacy because disease is too far advanced
 - Prior therapy or condition that would confound interpretation of efficacy results (eg, recent change in steroid dosing, gentamicin concurrent with PTC124 for nonsense suppression)

Study Treatment – Establishes Dosing Regimen with Appropriate Safeguards

- Dose regimen plan/dose escalation plan based on:
 - Preclinical efficacy data (establish target plasma concentrations)
 - Preclinical toxicity/TK data (to determine dose/exposure limits and therapy duration limits)
 - Clinical toxicity/PK data (to establish dose/exposure limits)
- Dose modification recommendations
 - Defines toxicities requiring changes in planned treatment
 - Stipulates plan for treatment interruption and resumption, dose modification, and make-up of missed doses
- Supportive care recommendations
 - Defines suggested/prohibited supportive care (eg, antiemetics, antidiarrheals) based on known drug toxicities/interactions
- Treatment cessation provisions
 - Defines toxicity criteria mandating permanent cessation of therapy

Schedule of Events – Specifies Type and Timing of Safety Evaluations

- Selection of parameters to be monitored
 - Necessary tests to confirm patient eligibility
 - Tests to monitor known preclinical or clinical toxicities
 - Tests to monitor for occult clinically significant toxicities
- Selection of timing
 - Baseline and end of treatment
 - Timepoints consistent with expected onset and duration of toxicities
 - Timepoints relevant to planned dose modifications
- Rigor of testing must be specified in context of:
 - Known toxicity profile
 - Phase of development, eg,
 - ◆ Phase 1-2: Expansive, frequent monitoring
 - ◆ Phase 3-4: Focused, less frequent monitoring
 - Patient/staff inconvenience, practicality, availability, and expense

Adverse Event Assessment – Defines Adverse Events

- Adverse Event – any untoward medical occurrence:
 - Untoward medical occurrence due to study drug or other drug
 - New illness or worsening of a preexisting illness
 - Injury or accident
 - Abnormalities of physical examination or laboratory/physiological testing that require clinical intervention or further investigation
- Serious Adverse Event – adverse event resulting in:
 - Death
 - Life-threatening adverse experience (carries immediate risk of death)
 - Inpatient hospitalization or prolongation of hospitalization
 - Persistent or significant disability/incapacity
 - Congenital anomaly/birth defect
 - Need for medical or surgical intervention to prevent a serious outcome
- Unexpected Adverse Event
 - Specificity/severity is not consistent with labeling, IB, or protocol

Adverse Event Assessment – Describes Interviewing and Recording Requirements

- Questioning to elicit adverse events
 - Open-ended questioning usually recommended, eg, *“Has your child had any new health problems?”*
- Recording requirements for each event
 - Date and time of last dose prior to onset of event
 - Onset date and time
 - Resolution date and time
 - Serious versus nonserious
 - Action taken
 - Outcome
 - Severity
 - Relationship to study drug

Adverse Event Assessment – Codifies Severity Assessment

Grade	Adjective	Description
1	Mild	No effect on overall well being, does not interfere with function, and does not require intervention
2	Moderate	Interferes with usual activity or affects clinical status, and may require intervention
3	Severe	Sign or symptom is incapacitating or affects clinical status and requires intervention and/or close follow-up
4	Life-threatening	Results in potential threat to life

Adverse Event Assessment – Codifies Severity Assessment – Potential Advantages of CTCAE

Grade	Adjective	Weight Gain	Pancreatitis	ALT/AST
1	Mild	5 – <10% of baseline	Asymptomatic, enzyme elevation and/or radiographic findings	>ULN–2.5xULN
2	Moderate	10 – <20% of baseline	Symptomatic, medical intervention indicated	>2.5–5.0xULN
3	Severe	=20% of baseline	Symptomatic, interventional radiology or surgery indicated	>5.0–20.0xULN
4	Life-threatening	--	Life-threatening (eg, due to circulatory failure, sepsis, hemorrhage)	>20.0 x ULN

*Common Terminology Criteria for Adverse Events v3.0

Adverse Event Assessment – Indicates Basis for Relatedness Assessment

Assessment	Nuanced Approach	FDA Causality Assignment
<ul style="list-style-type: none"> ■ Consistency with known effects ■ Temporal relationship to study drug ■ Potential alternative explanations ■ Improvement on drug withdrawal ■ Reappearance on rechallenge 	Definitely	<p style="text-align: center;">Related (suspected adverse drug reaction*)</p>
	Probably	
	Possibly	
	Unlikely	
		Unrelated
<p>* Reasonable possibility that the drug caused the response, ie, the relationship cannot be ruled out</p>		

Adverse Event Assessment – Dictates Reporting Requirements

Event Type	Investigator Report to IRB and/or Sponsor		Sponsor Report to FDA (Other Investigators)	
	Time	Type	Time	Type
<ul style="list-style-type: none"> • Fatal or life-threatening • Unexpected • Related 	24 hours	Telephone/Fax	7 days	Telephone/Fax FDA Form 3500A
	5 days	Source documents		
	Routine	CRFs	Annual	IND Report
<ul style="list-style-type: none"> • Nonfatal, serious • Unexpected • Related 	24 hours	Telephone/Fax	15 days	Written FDA Form 3500A
	5 days	Source documents		
	Routine	CRFs	Annual	IND Report
<ul style="list-style-type: none"> • Serious, expected • Serious, unrelated 	5 days	Source documents	Annual	IND Report
	Routine	CRFs		
<ul style="list-style-type: none"> • Nonserious 	Routine	CRFs	Annual	IND Report

Statistical Analysis Plan – Indicates Method for Adverse Event Classification – MedDRA

- Medical Dictionary for Regulatory Activities
 - International nomenclature system for adverse event coding, analysis, and reporting
 - Developed under the International Conference on Harmonization (ICH)
 - Owned by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)

- *Example:*
 - Asthenia
 - Exhaustion
 - Fatigability
 - Fatigue
 - Indolence
 - Lacking energy
 - Lassitude
 - Lethargic
 - Lethargy
 - Listlessness
 - Loss of energy
 - Loss of strength
 - Low energy
 - Nervous exhaustion
 - Overtired
 - Sluggishness
 - Tired all the time
 - Tired out
 - Tiredness
 - Washed out
 - Weakness
 - Weariness
 - Worn out

Preferred Term

Fatigue

Statistical Analysis Plan – Establishes Methods for Summarizing Safety Data

- Safety analysis
 - Analysis usually describes frequencies by arm or dose level, MedDRA System Organ Class, Preferred Term, worst severity (eg, based on CTCAE), timing, outcome of the event, relationship to study drug, and seriousness
 - Death, discontinuations, serious events receive special attention (eg, narratives)
- Ancillary analyses
 - Compliance results can add understanding of safety profile when considering patterns of dose modifications, dose delays, and dose omissions, and reasons for deviations from planned therapy
 - PK data may help describe exposure-toxicity relationships and exaggerated pharmacological effects in individual patients

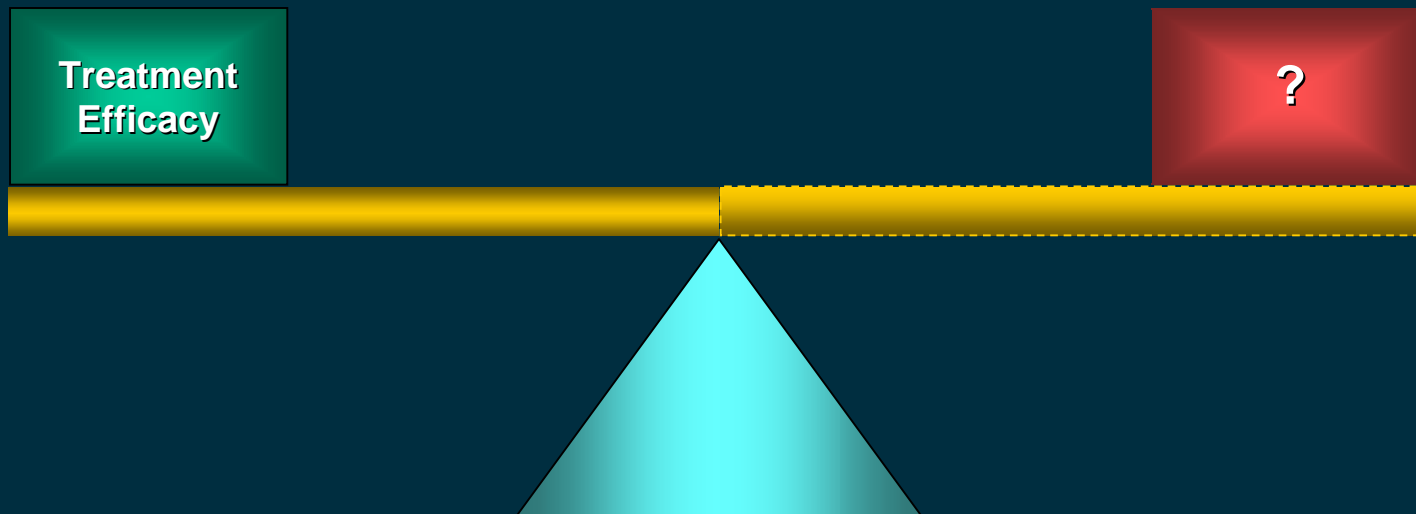
Informed Consent – Provides Important Safety Information to Patients and Families

- Potential study drug risks
 - Preclinical toxicities
 - Clinical toxicities
 - Drug class effects (as appropriate)
- Potential study risks
 - Special procedures
 - Laboratory testing
- Special precautions and restrictions
 - Dietary
 - Medications
 - Activity and exercise
- Time involved
 - Lost time is a toxicity, too

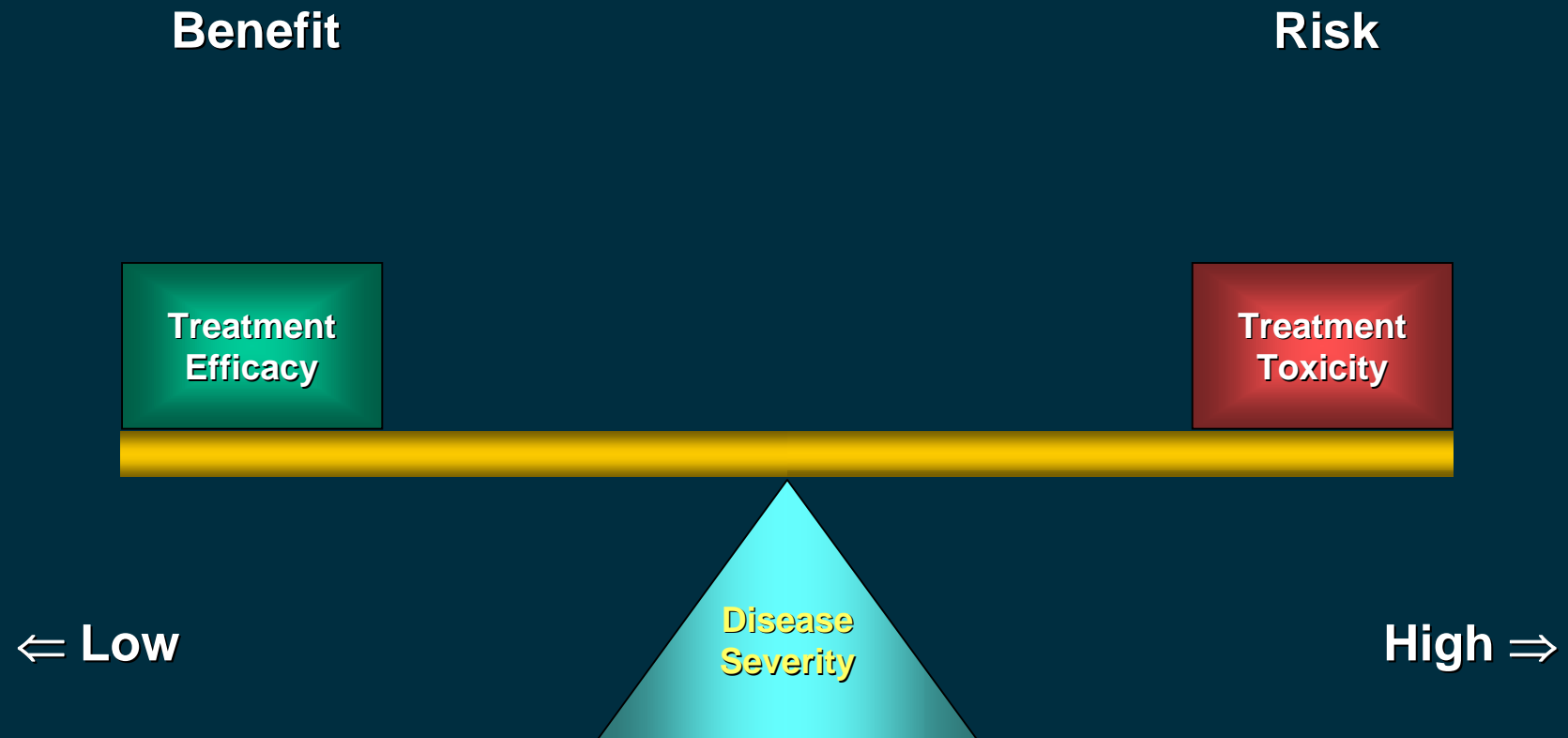
Importance of Safety Profiling: Defining Benefit/Risk Balance

Benefit

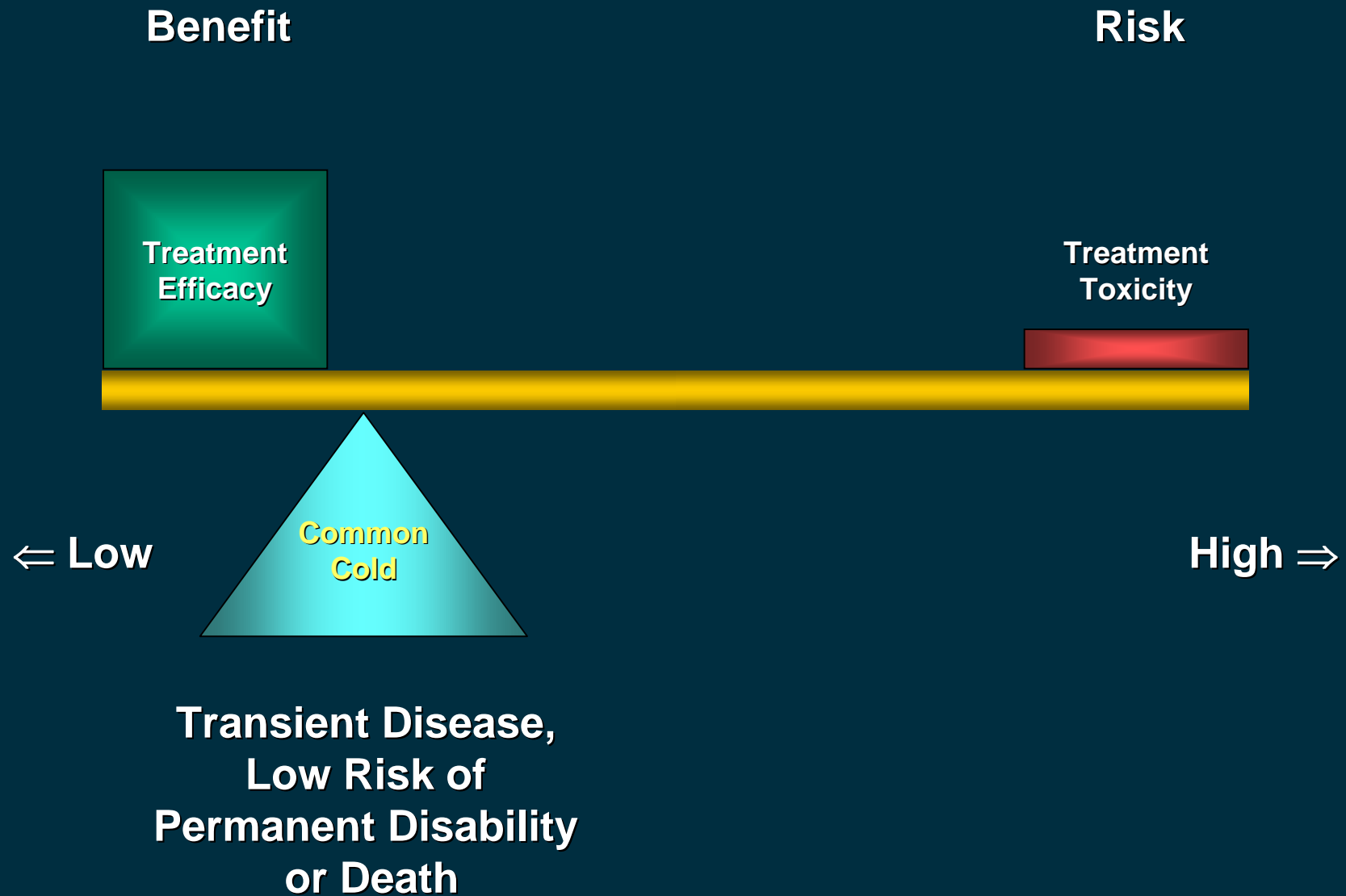
Risk



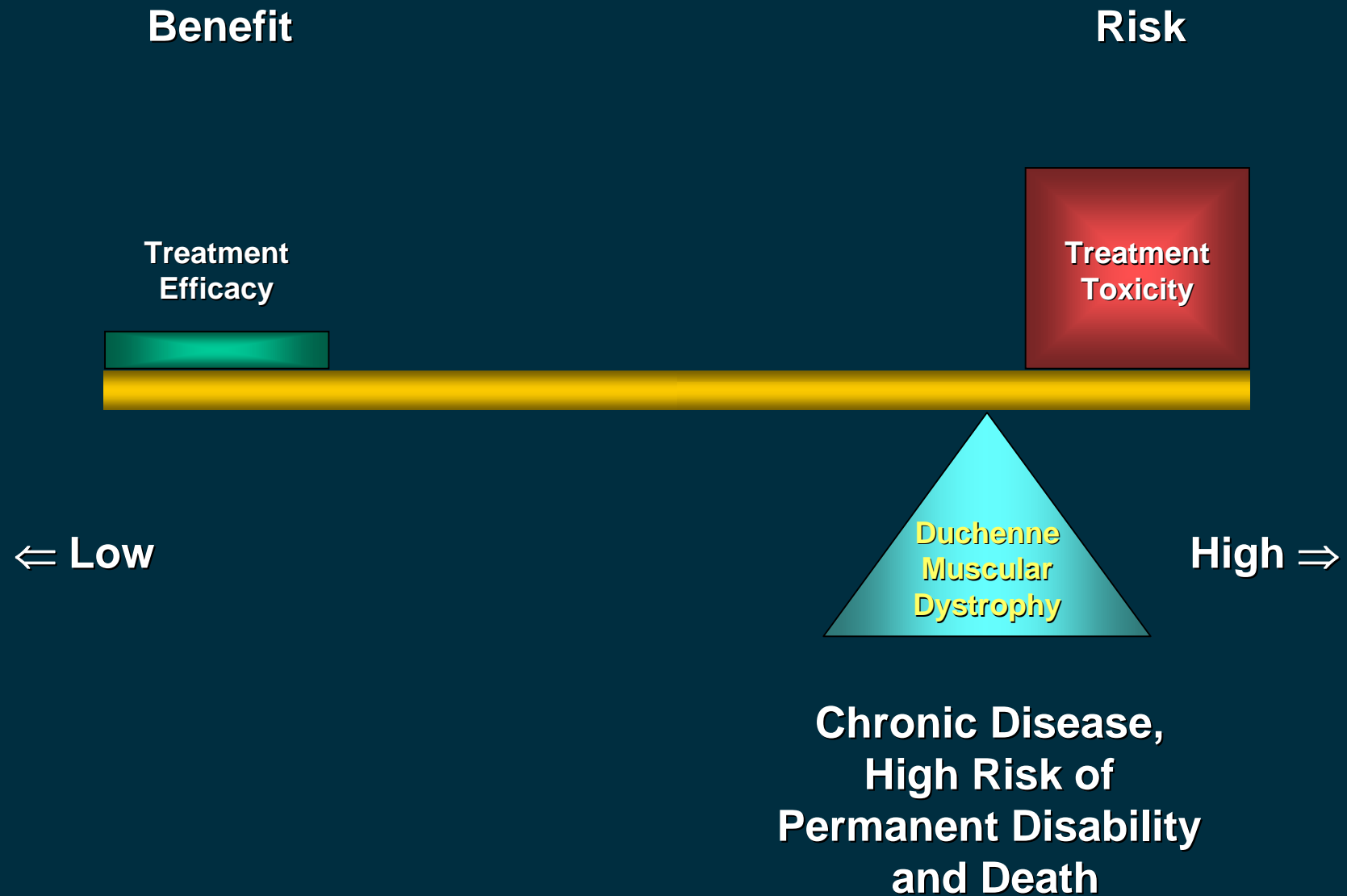
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Importance of Safety Profiling: Defining Benefit/Risk Balance



Importance of Safety Profiling: Defining Benefit/Risk Balance



Benefit:Risk Analyses in Congenital Muscular Diseases

- Therapeutic intent affects magnitude of benefits
 - Curative > partial disease-reversing > disease-stabilizing
- Nature of adverse events affects magnitude of risk
 - Frequent > infrequent
 - Severe > mild
 - Dose-limiting (eg, nausea) > inconvenient (eg, skin striae)
 - Irreversible > reversible
 - Late > early
- Length of treatment affects magnitude of risk
 - Long-term > short-term
- Prognosis affects benefit:risk pivot point
 - Worse prognosis increases risk tolerance

Complexities and Implication for Risk/Benefit Analyses in Congenital Muscular Diseases

- Onset in childhood creates contradictions
 - Patients/parents are often less risk adverse than investigators, IRBs, and regulatory agencies
- Disease-mediated damage becomes fixed over time
 - Benefit/risk changes as patient ages
 - Youngest patients may have best benefit:risk
- Disease or current therapies confound toxicity assessments
 - These factors must be weighed in benefit:risk analyses
- Patient populations are small
 - Ability to detect low-frequency, long-term risks is limited
 - Large safety database at time of FDA registration is untenable
 - Post-marketing registries take on substantial importance

Conclusions

- Safety is obviously a requisite clinical trial endpoint
- Careful consideration of safety background data, patient safeguards, appropriate monitoring, and available analytical tools is critical to study conduct and development planning
- Resources have been developed to refine endpoint characterization and reporting, eg,
 - CTCAE (<http://ctep.cancer.gov/forms/CTCAEv3.pdf>)
 - MedDRA (<http://www.meddramsso.com>)
- Special benefit:risk considerations in muscle disease will likely require developmental innovation and regulatory adaptation

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