Benefit-Risk Assessments in Rare Disorders

THE CASE FOR THERAPEUTIC DEVELOPMENT IN DUCHENNE MUSCULAR DYSTROPHY AS THE PROTOTYPE FOR NEW APPROACHES

Parent Project Muscular Dystrophy
LEADING THE FIGHT TO END DUCHENNE

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Contents

Executive Summary 4

Introduction and Background 5

Figure 1 6

Figure 2 7

Figure 3 8

Comprehensive Conceptual and
Operational Approaches to Benefit-Risk Considerations 9

Figure 4 10

Figure 5 10

Figure 6 11

Considerations in Rare Disorder PFDD 11

Duchenne as a Prototype for Rare
Disorder Benefit-Risk Assessment 12

Survey Data Regarding Duchenne Views on Benefit and Risk 13

The Case for Duchenne Muscular
Dystrophy (Duchenne) as the Prototype for Rare Disease
Benefit-Risk Regulator Decision Making 14

Implications of Duchenne Benefit-Risk Survey Findings
for other Rare Disease Groups 14

Conclusions 14

References 16

Executive Summary

Benefit-risk assessments are essential to the Food and Drug Administration's (FDA) regulatory process for approving therapeutic products, and to informing the patient and physician selection or rejection of approved products. This paper examines the similarities and differences between benefit-risk assessments for common, progressive disorders vs. rare, progressive diseases. In doing so, the paper offers recommendations for a distinct framework for benefit-risk assessments in rare diseases, to recognize the unique aspects associated with such decisions in the rare disease sector.

Benefit-risk assessments are performed by regulators weighing whether a product's benefits outweigh its risks, and by patients and/or caregivers, both independently and with the guidance of physicians and other health care providers. While these assessments can be considered distinct from one another, they also share similar considerations: discussion about benefit-risk tradeoffs, how to measure those tradeoffs, and the strength of evidence required to make a decision. For the development of products requiring FDA approval, existing benefit-risk evaluation processes are well described, particularly in evaluating therapies for more common diseases such as diabetes or heart disease. Overall, the benefit-risk assessments for common disease can be also applied to rare disease, though some aspects of the assessment process require unique considerations.

Current processes and tools for benefit-risk data collection and evaluation for both prevalent and rare disease have been constructed based on assumptions from experiences with common diseases. However, rare diseases require more tailored considerations throughout the assessment process for multiple reasons including limited knowledge of the disease, small patient populations, and — for many — a lack of alternative treatment options. For prevalent disorders in particular, the benefit being considered is often in comparison to other treatment options already available for that disorder. But such a standard is problematic for assessing progressive rare disorders due to few or no treatments available, and the only option to compare benefit to would be disease progression.

Current patient risk (also known as adverse event) assessments in studies involving new compounds for common diseases are often based upon clinical experiences with large populations and a disease history that has been well-characterized. By contrast, many rare diseases do not have sufficient epidemiological studies to characterize the natural history of disease progression, and/or there may be a great deal of variation across patients. Such variation in patient populations, that has not been well-defined, may negatively influence the ability of clinical trial sponsors to characterize benefits and adverse events, particularly since such events could be due to progression of the underlying disease or to treatment interventions. Further, fatal disorders, both common and rare, pose additional challenges in assessing benefit and risk, including the urgency required to address those needs.

Duchenne muscular dystrophy (Duchenne) presents a timely and compelling example of complex and evolving benefit-risk assessment; it is a rare disorder with no approved treatment to stop its ultimately fatal progression in patients, almost all of whom are males and who typically live only until their late 20s. In these circumstances, innovative approaches are required to understand the treatment benefits valued by patients, as well as the patient and/or guardian's willingness to accept potential risks.

Parent Project Muscular Dystrophy (PPMD) recently completed a rigorous survey of 119 Duchenne parents/guardians that provides new information about benefit expectations and risk tolerance relating to Duchenne drug development. Data illustrate the willingness of survey participants to accept some significant risks and side effects in return for slowing or stabilizing the progression of the disease. For example, stopping or slowing muscle weakness were the most highly valued treatment attributes, even in the absence of survival benefits. Additionally, when those attributes were included in the hypothetical treatment, participants were willing to accept an increased risk of death or serious (additional) disability. Such tradeoffs deserve more consideration by regulators charged with making critical product approval or denial decisions for Duchenne and argue for continued revision of the integrated benefit-risk approaches currently used in making such decisions.

These survey data are consistent with the FDA's interest in "patient-focused drug development" (PFDD) and could significantly inform broader benefit-risk regulatory considerations, such as study design and endpoint determinations.

Duchenne provides a perfect example of the pressing need for a change in framework and processes for rare disease benefit-risk considerations in the development of cures for progressive fatal disorders. This revised approach could also provide a benefit-risk information framework that translates to use in clinical practice. The rationale proposed in this paper and the parent/guardian treatment survey data should compel all stakeholders to maintain a focus on the goal of drug development — to provide patients who have unmet treatment needs with timely new therapeutic options as quickly as possible. Such treatments must be accompanied by sufficient information about the benefits and risks to allow patients and families to make informed choices.

Introduction and Background

What is benefit-risk and why is it a key issue for patients and regulators?

Assessments for the development of new treatments and information for the utilization of approved therapies, are both founded on the basic assumption that combating an illness with powerful interventions will potentially have both positive (benefit) and negative (risk) effects. The extent to which the positives outweigh the negatives provides a measure of relative value for that intervention. Conversely, if a treatment appears to confer more negatives than positives for recipients, it is implied that the risk of the negatives may result in a worse outcome than leaving the disease untreated. Therefore, for product approval decisions, combined benefits (positives) must outweigh total risks (all negatives, especially adverse events), and that approval assessments provide vital information to health care providers.

In drug development, the profile of benefits and risks evolve over the course of clinical studies, so regulators and developers must critically view all such factors over the span of each study that is performed. At times, development of candidate drugs may be halted or discontinued when the composite risks appear out of proportion to the benefits being conferred to the patient. Should a candidate drug advance to the point of having a new drug application (NDA) submitted for review by the FDA, the final "scales of justice" regarding approval or rejection of that NDA rests on the combined assessment of benefits outweighing risks.

Even after approval of a drug, the FDA regularly reassesses the benefit-to-risk profile of marketed products, as manufacturers and health care providers are required to submit any reports of adverse events to the FDA. The regulators also periodically reconsider whether a given drug's benefits continue to outweigh its risks. If new risks are observed, the FDA may choose to add such information to the labeling of the product, which in turn provides important considerations for health care practitioners and their patients/families in the bedside discussions of the benefits and risks of that product.

In clinical practice, it is routine for the health care provider to talk to patients (or in the case of minors, patients and their family members) about all aspects of a treatment — including the risks and the benefits — so that informed choices can be made about treatment options.

Therefore, benefit-risk information is vital in important "bottom line" decisions about:

- Drugs in development, as the basis for regulator decisions on approving or rejecting the applications for new products;
- How benefit and risk factors are weighed in the standard approach for physician-patient/family discussion when considering the use of new therapies for a given disease; and
- Ongoing product updates based on adverse event data that in turn shapes revisions in the benefit-risk information in product labeling.

While fairly straightforward in concept, benefit-risk assessments may be quite difficult to perform. Perspectives among patients, practitioners, and regulators may differ when it comes to benefit and risk valuations of the same therapy and can prove

challenging to reconcile. Regulators are charged to view benefit-risk decisions from the perspective of public health and population-based considerations. As such, regulatory bodies may take an inherently conservative view in terms of what risks might be tolerable or unacceptable across a broad range of patients for a single drug assessment, also known as the *public health/population filter*. However, physicians may see this topic through a different lens, that of seeking to understand the relative benefits and predictability as well as the probability of risks for a range of possible therapies which could be considered for use in one of their patients. This perspective is known as the *disease management filter* or the *practice filter*. Such decisions are based in part on information from product labeling, as well as considering, if available, possible alternatives for treatment which may vary between rare vs. prevalent diseases.

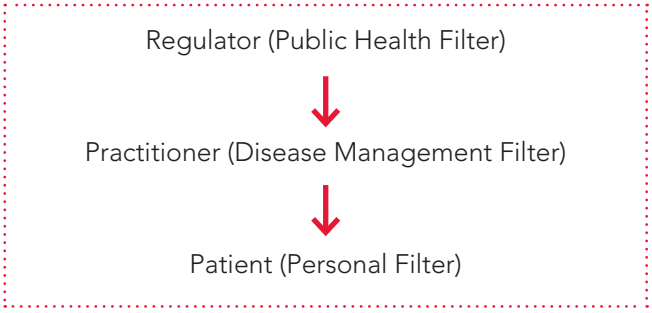
Patients may consult their health care provider or caregivers for assistance to weigh and advise when it comes to selecting one or several best choices during discussions about the likely benefits vs. risks for that individual — otherwise known as the *personal filter*. As patients and their caregivers have become increasingly well informed about treatment selections, their perspective in this process should be a principal decision element.

When regulators take actions to reject or delay approval of a candidate drug, to an extent their filtering removes the possibility for any consideration by practitioners or patients for that delayed option. For diseases that are both progressive and rare, the FDA must take great care in exercising such authority, lest patients be denied an opportunity to consider the spectrum of benefits and risks of a new candidate therapy, especially when no approved therapy exists.

For common diseases which afflict a significant portion of the population — such as diabetes mellitus or hypertension — considerable information is typically available to regulators, providers, and patients surrounding a range of acceptable therapy options. Thus a number of comparative analyses can be considered and performed for drugs in development. Further, for new candidate drugs for common diseases, well-established reference points exist based on the benefit-risk performance of already approved agents. Thus, regulators have a yardstick to facilitate comparisons of the attributes of approved vs. candidate drugs. In addition, the process and practices for studying the benefit and risks of well-described prevalent diseases is often pursued with the aid of detailed FDA guidances (process advice and established practices from prior development programs), which serve as roadmaps from previous drug approvals to explore and characterize new treatments for the same disease.

Figure 1

Decision Filters



For rare disorders (as defined in the Orphan Drug Act), information regarding natural history of the disease, as well as the likely source and cause for the disease, may not be known or well-understood (or at least not well-described). Additionally, there may be few past studies of such patients to provide sufficient data for conclusions about the potential benefit and risk factors, as well as few or no previously approved treatments to serve as comparators for a candidate drug, and no regulatory guidances (study help guides) to assist drug developers in charting a course of studies for candidate therapies. In such circumstances, the absence of a roadmap, vehicle and helpful process guide often delays and confounds the development of new compounds, as additional precious time is consumed in establishing baseline reference points (such as validated trial endpoints or biomarkers). Such circumstances which consume excessive amounts of time and resources, compared to drug development for common disorders, may in turn discourage companies from investing in the development of innovative treatments for rare disease.

Figure 2

Tools for Regulatory Decision Makers

Tool	Prevalent Disease	Rare Disease
Guidance	Typical	Unavailable (in general)
Precedents	Multiple	Limited
Established endpoints	Multiple, validated	Exploratory or undefined

Even when some roadmap for drug development exists, gathering data to characterize the benefit and risks of a new compound (for prevalent or rare disorders) is complicated, as illustrated by the following factors that must be addressed and potentially hinder development programs. In such situations, there are a number of variables in clinical trial design and assessment, which may influence development decisions, and include:

a. Measurement variables: Multiple efficacy and safety endpoints for studies of the same disease may lead to uncertainty about what measures can validate or support clinically meaningful outcomes. In addition, views differ among rare disease experts regarding the best ways to measure outcomes for patients, where surrogate endpoints or refined measures have not been validated or accepted across all stakeholder groups.

b. Frequency variables: Significant uncertainty surrounding rare (low frequency) but potentially serious adverse events may delay development programs when additional preapproval studies are required to gather more extensive safety data. Adverse events are a concern for any candidate drug under study, but especially when regulators are faced with a limited number of patients available for studies involving rare diseases. This concern relates to whether serious adverse reactions, which are not evident in small clinical trials for approval decisions, might be detected later when larger numbers of patients are exposed to the new treatment commercially.

c. Response variables: Across clinical trial treatment groups and subgroups of a given disease, there may be a broad range of responses for the outcomes being measured. Such variability may occur in common disorders when subtypes of a disease family may exhibit differing response levels in given measurements. For rare diseases, there may be insufficient data about the causes of the disorder, or whether there may be genetic or other subtypes of the disease — which may predict response to new treatments. There may also be concerns that in clinical trials (for rare or common diseases) that a candidate treatment might work (have efficacy) in a distinct subset of patients, but without being able to identify that subset in advance, the positive effects for that group might be masked by negative efficacy outcomes in a broader trial which includes multiple subsets (ie. responders plus nonresponders), which are combined in data analyses.

d. Timing variables: Potential for delayed onset of drug effect, as well as sustainability of effect or of delayed detection of safety findings, are major concerns for developers and regulators. The positive and negative effects of a treatment over time may be quite variable. Hence there is a concern, especially in the regulator community, that benefit response effects may either appear late, or conversely be positive in earlier stages, but decline in benefit over time. Such potential concerns may lead to regulator insistence on prolonged observations in development studies. Extended observations in studies may be useful so that the actual effects of the candidate drug can be better described in product labeling and related communications. Approaches to anticipate post-approval use may yield improved information for patients and prescribers by providing a more comprehensive picture of expected benefits vs. risks over time based on information from such studies. While much concern is focused on declining benefit over time, regulators and patients also have concern regarding how to capture late or delayed drug safety issues, which might occur weeks to months after treatment discontinuation. For rare disorders, it may be difficult to distinguish when disease progression or a diminished effect of the therapy over time may be the causal factor in new event findings over time.

e. Adherence/Compliance variables: It is important to determine whether missing doses of a therapy could result in flare-ups of the disease under treatment, as well as whether there exists a reversibility of positive drug effects over time off the treatment. Further, the ability to manage missed doses with added dose sizes or other adjustments is an issue for study of both rare and prevalent disorders, and this data is useful for product labeling. For many rare diseases, such information may be difficult to obtain from small study sizes.

f. Perspective variables: Societal and regulator perspectives may differ from patient perspectives on "valuation" of treatment attributes. Regulators may view issues from a population perspective (ie what's best for the greater good), while patients focus on individual considerations (ie what might be an opportunity for me, even if it does not benefit most with a similar disease), which may sometimes be in conflict. As previously noted, and especially for rare disorders, there may be a considerable distance between the views of consumer advocates and patients. While advocates are concerned about drug safety but without a vested concern about benefits or benefit-risk balance, patients who have no available treatment may be inclined to accept more risks for lesser benefit than would patients with common diseases and multiple treatment options. Such disparity in views may be challenging to manage, especially if these matters become the subject of media attention.

g. Assessment variables: Multiple quantitative and qualitative approaches to aggregating benefit and risk information exist (are in current use). Different assessment approaches, which may be performed by both regulators and therapy developers, might provide differing conclusions from the same data set. For any disease under study, a clear agreement among stakeholders is vital to a shared expectation for how study information will be interpreted and valued.

h. Uncertainty variables: Unknown risks are "data terrorists" in the benefit-risk regulatory review processes. In theory, adverse event risks based on observations from studies of similar chemical entities, even absent any concrete data for the agent under study, may suggest that additional studies are required to confirm or reject the possibility of a "class effect". Therefore, these risks may warrant extended safety observations prior to regulators making a decision on approvability of a new compound. Such circumstances are less of a concern for prevalent disorders, with approved treatments available to patients, while new information is accrued about development compounds. For those patients with rare progressive diseases for which no therapy may be available, even slight delays in actions on the basis of hypothetical concerns can result in ethical questions about the balance of decision-time tradeoffs being made at the expense of the patient.

Therefore, it is important to appreciate how and why the preceding variables in benefit-risk assessments may be influenced by whether a disorder is common or rare, as shown in the following depiction.

Figure 3

Factors in development study design and assessments

Factor	Prevalent Disease	Rare Disorders
Defined disease endpoints	Multiple	Exploratory
Concern for detecting infrequent safety events	Assessed in large post approval and preapproval trials	Often infeasable preapproval
Variable response subgroups	Use of surrogate markers	Uncharacterized (surrogates)
Sustainability of response	Natural history comparator	Confounded by small study size
Detecting late adverse events	Observational trial use	Distinguishing from disease progression
Impact of non-compliance	Difficult to characterize	As with prevalent
Perspectives on valuation	Importance of comparators	Compare to untreated underlying disease
Quantitative vs. qualitative benefit-risk approaches	Importance of similar approach by regulator and sponsor	Similar approach vital (pre-hoc aggreement)

Given the preceding concerns, it is important to identify factors which may lead to a more informative benefit-risk approach for rare disorders.

Comprehensive Conceptual and Operational Approaches to Benefit-Risk Considerations

Of critical concern is defining up front what measures will be accepted as gold standards for risk and benefit outcomes, and how such measures would inform decision making.

Most authorities would agree that the critical elements for any benefit-risk assessment should incorporate all appropriate benefits and risks, both in the context of pre-approval and post-approval evaluation.

Benefit(s) must measure and capture the known range of possible favorable effects. From regulator perspectives, the concept of "clinically meaningful outcomes" must be well-documented and ideally, independently validated. In many instances, such determinations may not be feasible for rare disorder trials. Risk(s) should encompass potential adverse effects with special attention to the frequency, predictability, seriousness, and temporal relationship of events to development therapies. Ancillary concerns such as convenience of use, are sometimes incorporated into benefit-risk assessments, especially when inconvenience of use or similar factors that lead to noncompliance may impact response to treatment, but tend to be less compelling considerations for rare progressive disorders with no treatments approved.

Benefit-risk data may evolve over a compound's life, depending on what phase of the drug development cycle is being reviewed, with two major subsets, including:

PRE-APPROVAL: Controlled clinical trials to capture information about benefit and risk in well-designed studies involving a subset of the population with the target disease. For rare disorders, one of the critical challenges in drug development is the perceived requirement for placebo controlled trials as a basis for regulator decision making, as well as what stages of a rare progressive disorder are appropriate for early trial enrollment and assessment. In such situations, data from development studies represent evolving observations, however do influence later characterizations of benefit-risk. Further, there are ethical and logistical concerns about the limited number of patients available for rare disease pre-approval studies which should be explored with more vigor.

POST-APPROVAL: Considerable attention is given to observational trials to gather primarily "safety" data, which may not look at concurrent benefit reassessments. For prevalent diseases, it is understandable that large scale clinical trials likely provided sufficient data to describe the efficacy profile of a candidate treatment pre-approval, and therefore accrual of additional safety data to detect infrequent but concerning adverse reactions is a reasonable focus for post-approval studies. In contrast, for rare diseases, it would be highly desirable to compel ongoing post-approval studies for both benefit and risk factors, in that initial approval studies should ideally be abbreviated in circumstances where no available therapy is approved for the rare disorder under study.

Another key consideration is what is "enough" information to permit decision-making. This discussion is best viewed by contrasting the information needed by doctors vs. regulators.

The preceding section has already addressed some regulator considerations. As to provider deliberations, for rare disorder patients, the majority are cared for in specialty centers, and therefore the expertise resident in those care settings may be a factor in enabling earlier commercial access to development agents — perhaps under more innovative accelerated or conditional approval processes.

It is also important to understand how FDA views benefit-risk in the context of new drug development. According to FDA documents, obtained from their website, benefit-risk is viewed as a subset-domain of regulatory sciences, along with other evolving concepts such as personalized medicine, translational medicine, adaptive design trials, and similar new development concepts/tools.

Subsequent to Food and Drug Administration Safety and Innovation Act (FDASIA) legislation passed in July 2012, the FDA has implemented initial aspects of a required benefit-risk program, and previously published a conceptual benefit-risk framework. This framework includes the following questions and logic sequence for the FDA's approach to the qualitative aspects of benefit-risk determinations, as described on FDA's website:

a. What is the problem? (analysis of condition under study)

b. What other potential interventions exist? (unmet medical need)

c. What is the benefit of the proposed new intervention? (benefits)

d. What are we concerned about? (risk)

e. What can be done to mitigate/monitor the risk concerns? (risk management)

Figure 4 compares and contrasts the potential utility of the FDA framework for evaluating prevalent vs. rare disease characteristics. As might be expected based on the previous discussion of the unique factors that go into decision making for rare disease, the attributes of the current FDA benefit-risk framework are much better supported for prevalent disease.

Figure 4

Adaptation of the FDA Conceptual Framework for Rare Disease Benefit-Risk

Element	Prevalent Diseases	Rare Diseases
Condition under study	Well defined	Exploratory
Unmet need	Most have some available treatment (often many)	No approved therapy
Benefits	Defined frame of reference	Exploratory reference points
Risks	Frequency/severity	As with prevalent
Risk mitigation	Drug specific interventions	As with prevalent

For each preceding factor during a review of a candidate drug, FDA looks at the evidence vs. the uncertainties for each factor, and then reaches conclusions about the balance of benefit vs. risk for the candidate treatment. If benefits outweigh risks, presuming that serious risks can be mitigated by proactive measures, approval is granted.

Contrasting FDA's view with the European Medicines Agency's (EMA) approach to benefit-risk, Europe takes a much more quantitative approach to these determinations, including a template-driven review process for new drug assessments. One of the approaches being employed by EMA for benefit-risk is that of "ProACT URL" which is further described in Figure 5. The factors utilized in that approach provide more opportunity to highlight some of the unique features for rare diseases benefit-risk assessments than does the FDA approach, especially noting that risk tolerance is a distinct consideration in that process.

Figure 5

Adaptation of PROACT-URL Framework for Rare Diseases

Factors	Rare Disease Considerations
Problem/framework	Context of disease/population
Objectives	Unique criteria for favorable/ unfavorable effects
Alternatives	Comparators vs. placebos
Consequences	Performance of alternatives vs. each criteria
Trade-offs	Framing balance of favorable vs. unfavorable effects in context of disease
Uncertainty	Uncertainty associated with effects
Risk tolerance	Relative importance of decision maker's risk attitude
Linked Decisions	Consistency of decision with precedents

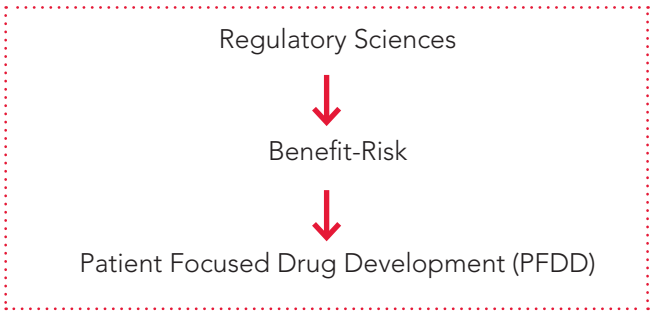
Patient focused drug development (PFDD) is a vital subset of benefit-risk determinations and is currently an evolving project pursuit within FDA which includes engaging patient communities in the initial PFDD public hearings. While those efforts should be applauded, it is vital to better understand the unique

nature of rare disease PFDD/benefit-risk through the development of new data and creative approaches — both of which capture the perceptions and expectations of patients who suffer from the diseases under study, in order to facilitate development improvements as soon as possible.

In this process, it will be important to gather data regarding patient and/or caregiver views of benefit expectations and risk for specific disorders. The goal here would be to enhance understanding of the range of benefits valued by patients, and to improve characterization of risk tolerance from the patient's viewpoint when it comes to diseases with few or no alternative therapies. Ideally, regulators should provide assistance and incentives, wherever possible, to overcome limitations in the implementation of gathering such data. Such approaches could provide a much-improved frame of reference for regulators to use in their benefit-risk decision making. Further, it would be valuable to the development process to have new data and insights from PFDD-related work more rapidly flow into benefit-risk decision processes.

Figure 6

Regulator Conceptual Orientation to Benefit-Risk (Hierarchy)



Considerations in Rare Disorder PFDD

Factors in benefit-risk determinations that are unique to rare diseases may include a variety of elements in clinical trials. Pivotal registration trials in rare disease are often limited in the factors that can be used for more comprehensive benefit-risk determination because of unique trial design issues. Such limitations include:

- Generally, no FDA approved treatment is available for the rare disease under study, and thus there is no reasonable comparator, which tends to compel the use of placebo controls. For pediatric patients with progressively fatal rare diseases, who have no other alternatives for care, the notion of enrolling in randomized trials with the likelihood of receiving placebo creates challenging ethical and practical dilemmas for patients, parents, and study sponsors (i.e. restricting access to hope).

- Small populations eligible for controlled studies and fewer centers qualified to care for rare diseases and thus study candidate agents (limited access to investigators), create logistical barriers to the enrollment of eligible patients and thus, a limited pool of patient data for analysis (restricted access to patients).

- Absence of comprehensive baseline epidemiologic studies and natural history of disease complicate the development of reliable clinical outcome measures, highlighting the importance of robust data sets, including patient registries (access to basic points of reference).

Perhaps the most important consideration in rare disease trials should be the progression of untreated disease as an inherent risk in the assessment of benefit-risk when no treatment options are available. In prevalent diseases, no such constraint exists for either trial or care practices, as approved treatment options exist, and thus the "calculus" of rare diseases benefit-risk, as in the absence of options, is inherently different. Therefore, rare disease is deserving of distinct regulatory benefit-risk approaches from those for mainstream disorders.

Another complicating factor in making regulatory decisions based on benefit-risk is that the viewpoints of different stakeholders for these assessments may be as varied as the number of different stakeholders. Outcome measures and expectations may be drastically divergent as illustrated by a review of current scientific and lay literature about rare and common disorders. For patients, it may be "presumed" by some authors that patients may reasonably expect perfect benefit with no risk, for non-life-threatening disorders as new agents become available.

Conversely for patients with progressive fatal diseases, risk tolerance may be implied as being nearly limitless. As an illustration of rare disease stakeholder characterizations, the following descriptors may be useful as exploratory discussions across such groups proceed:

- Caregivers – Indirect metrics of care complexity may be used as one way to calibrate benefits and impact of treatments, as well as the cost and care complexity impact.

- Investigators – May be open-minded about risk tolerance expectations in early phases of study, and may aspire to be objective observers lest trial results be biased by their views.

- Health care providers – Desire for sufficient data before using new drugs, and thus have higher expectations for benefit-risk information at the time of new product access than investigators.

- Regulators – "Safety first" is FDA's cornerstone program that focuses on ensuring that new products not confer any undue public health risks. This program does not articulate any distinction between mainstream diseases and rare diseases with unmet needs.

- Payers – Concern surrounding aggregate incremental costs of multiple niche disease drugs, which may have current and future implications for reimbursement of rare disease therapies (in the absence of long term outcomes data) and thus may require more information at the time of initial reimbursement decisions.

- Policymakers – Considerations may include perception, relativity, theory and accountability, factors in terms of convincing such parties of a need for more rare disease incentives of this nature. It is understood that elected and appointed officials are prevailed upon by countless constituencies, often with conflicting goals, and this means that for benefit-risk, any rationale for new policies could require significant advocacy and must be convincing to the regulators who may also be consulted by the policymakers for relevant concerns.

- Patient advocacy – Organizations may be focused principally on access and benefit rather than safety and it will be important for all groups to agree on how basic regulatory standards should be preserved, and how a balanced perspective of benefit and risk can be crafted to embrace unique aspects for rare disorders.

When attempting to harmonize the myriad of viewpoints on benefit-risk, it is clear that since patients are the only parties in the drug development process who directly experience the risks, and who should be making informed decisions about their willingness to tolerate those risks for a chance at benefit, their perspective should be of foremost consideration. All other stakeholders should therefore view their roles as facilitators of benefit-risk information to enable informed choices by those patients.

In addition, the benefit-risk approach for regulatory review of drug development projects does not explicitly incorporate patient perspective concerns at present. In this regard, rare disease communities would be well-served to provide data to regulators that could facilitate and expedite new approaches to these assessments.

Duchenne as a Prototype for Rare Disorder Benefit-Risk Assessment

When considering the preceding discussion about benefit-risk for drug development involving rare disorders, several themes are notable and include the importance of timely new treatments for unmet needs. This is especially true for a rare disease that is progressive, life threatening, and has no approved therapy that arrests the disease's assault on patients' life and limb. It is also important to assure sufficient information for patients and caregivers to allow informed decisions.

Given those considerations, Duchenne provides a compelling illustration of such elements – it does indeed take away young boys' limbs, and over time, their lives. Duchenne has no FDA approved interventions to combat the disease's assault, and the inherent risk of an untreatable disorder progressing relentlessly over time is devastating to patients, as well as their families. Further, the nature of this

disease permits patients to preserve cognition and thus they can be active participants in determining what benefit expectations and risk tolerance are important to their existence. As many patients with rare diseases are minors, parental involvement in these deliberations is vital.

Of additional importance are the ethical dilemmas imposed by placebo-controlled trials which create an imperative to consider new approaches and expedite trials, as well as early access, for patients who otherwise must face physical decline without hope for reversal.

Regulators have noted that the prior absence of reliable and well-documented benefit-risk prioritization from patients and/or caregivers perspectives regarding many rare disorders have impaired their insight as to weighing unique positives and negatives of candidate therapies. As will be detailed in subsequent discussion, new data from Duchenne patient surveys provides the basis for revisiting how better to calibrate benefit-risk decision making.

In a "Safety First" environment, it should be noted that such a perspective may equate to the "precautionary principle," which argues that any new technology development must disprove real and theoretical risks prior to being adopted for general use. However, this principle disadvantages rare disorders patients. In essence, those taking a precautionary principle view may be considering new drug candidates as guilty of being unsafe until proven innocent. Though such an approach may be defensible in some circumstances for prevalent disorders with other treatment options, it should be seen as unacceptable for rare diseases with no treatment alternatives.

One counter-proposal has been offered by Lofstedt *et al.* in a thoughtful discussion of "Tolerability of risk approach and the management of pharmaceutical risks." Parents and patients with rare, untreatable disorders, such as Duchenne, may have remarkably different views on an acceptable range of benefits and the level of willingness to tolerate risks compared to those with mainstream, nonfatal disorders. In this light, it is logical to propose that as more data for disease-specific benefit-risk factors becomes available, regulators should embrace those new insights as the basis for patient-focused benefit-risk decision making, and integrate these new considerations into their reviews. Therefore, further information should be provided to the reviewers directly by the patients or their caregivers, which may improve understanding of new perceptions of benefit expectations, as well as risk tolerance, and thus lead to modification of the framework for rare disease assessments.

Survey Data Regarding Duchenne Views on Benefit and Risk

Parent Project Muscular Dystrophy (PPMD) recently completed a rigorous survey of 119 Duchenne parents/guardians that provides new information about benefit expectations and risk tolerance relating to Duchenne drug development. Data illustrates the willingness of survey participants to accept some significant risks and side effects in return for slowing or stabilizing the progression of the disease. For example, stopping or slowing muscle weakness were the most highly valued treatment attributes, even in the absence of survival benefits. Additionally, when those attributes were included in the hypothetical treatment, participants were willing to accept an increased risk of death or serious (additional) disability. A small difference in preferences of parents/guardians of ambulatory and non-ambulatory children was identified (P=0.044), but this is likely due to difference in within-group consistency rather than across-group preferences.

Benefit-risk tradeoffs, as described above, deserve more consideration by regulators in decision making for Duchenne and argue for continued revision of the integrated benefit-risk approaches currently used in the decision processes for rare disease product approval. These survey data are consistent with the FDA's interest in PFDD and could significantly inform broader benefit-risk regulatory considerations, such as study design and endpoint determinations. PPMD and collaborators plan to submit the data for publication in the fourth quarter of 2013.

The Case for Duchenne Muscular Dystrophy (Duchenne) as the Prototype for Rare Disease Benefit-Risk Regulator Decision Making

The findings from the preceding survey provide an informative range of input from caregivers on benefit expectation and risk tolerance. Such observations deserve focused attention in discussions with regulators and company sponsors in order to encourage consistency in collection of such information in all trials going forward, including periodic advisement about such factors for regulators to share with the stakeholder community. It is also vital to incorporate those patient expectations as reference points on a disease specific basis for use by regulators through development of review guidances and toolboxes. The preceding comparison of prevalent vs. rare disorder benefit-risk assessments in this paper highlights and acknowledges the distinctive differences for rare diseases that should lead to new and separate approaches to benefit-risk assessments for rare diseases.

Implications of Duchenne Benefit-Risk Survey Findings for other Rare Disease Groups

The new survey data regarding Duchenne benefit-risk prioritization represents an important advancement in disease specific data. Within the context of this survey process, muscle weakness accounted for the largest proportion of the variation in treatment priorities. The evidence suggests that the presence of side effects and risks could be compensated for by a treatment that stops progression of muscle weakness; however, parents were not willing to accept unlimited risk for a treatment that stops progression of muscle weakness.

Such insights will certainly deserve further study, and the nature of this approach should be considered for replication in other rare diseases with similar characteristics. It is also conceivable that the survey data may inform the consideration of approved drugs for reimbursement and to lay the comparative groundwork for future Duchenne and other development programs. Data from those affected, and waiting less than patiently for treatments, provides valuable reference points for regulators and practitioners making decisions about relative benefit and risk.

Conclusions

Based on the preceding information presented in this paper, PPMD submits that rare diseases are unique in considerations of, and requirements for, benefit-risk decision-making. Therefore, it is proposed that new approaches for regulatory benefit-risk assessments be considered for rare diseases, using the Duchenne data as the pilot for further expanding this effort. We have termed this approach as "BRAVE-rare diseases", or **B**enefit **R**isk **A**ssessment, **V**aluation (and) **E**pidemiology (for) rare diseases.

This approach is indicated for patients who live under ongoing risk from a rare progressive, fatal disease for which no current therapy is approved by FDA. These patients deserve unique and urgent consideration of their views on benefit expectations and risk tolerance in decision making processes.

Such approaches should encompass elements including more integration of patient and/or caregiver and health care provider views on benefit expectations, as well as risk tolerance, in routine regulatory processes for review and approval of rare disease development plans and applications. These efforts must be pursued in more expedited fashion and tailored for disease specific considerations. In deliberations where the views of regulators, developers, and patients may be in conflict, the patient's perspective should receive priority consideration. Rare disease is deserving of distinct regulatory benefit-risk approaches from those for mainstream disorders. Therefore, prevalent disorders with other treatment options are clearly different from rare diseases and a precautionary principle approach should be seen as unacceptable for rare diseases with no treatment alternatives. Furthermore, additional information should be provided to the reviewers directly by the patients or their caregivers, which may improve understanding of new perceptions of benefit expectations, as well as risk tolerance, and thus lead to modification of the framework for rare disease assessments.

This paper offers a call for rare disease stakeholders to refocus on the goal of drug development and provide patients having unmet needs new therapy options that are offered along with sufficient information about the benefits and risks to allow informed choices. Providing regulators with a more relevant frame of reference for benefit and risk, from the patient perspective, for use in product approval decisions, should assure appropriate consideration of the unique aspects of rare diseases. This approach would also be consistent with regulator missions to **protect** and **promote** the public health. Further, utilizing patient benefit and risk views can expedite development, as well as the nature of approval information for prescribers based on labeling to incorporate patient perceptions. Integrating patient and/or caregiver perspective on treatment priorities and risk tolerance should allow the FDA to refine their decision "yardsticks" and facilitate development, approval, and labeling of new drugs using such data. Such improvements would lead to patients, families, and providers being able to make informed decisions about treating rare disorders, even if those decisions include managing significant risk and uncertainty. These decisions should be approached with the understanding that all medicines have some inherent risks, and that patients may have differing views on tolerability of risks, as well as expectations for particular benefits. Providing the most appropriate information, coupled with expedited access, allows those whose health hangs in the balance to make considerate choices.

Undue restrictions on information access, or on access to potential new cures, for patients with unmet needs should be avoided at all costs in societies that value the health of all their members, and their right to make informed personal choices. Progressive fatal rare diseases such as Duchenne deserve renewed and urgent attention for more creative approaches in drug development and assessments, which better incorporates patient needs and perspectives in those processes. This paper describes one such objective approach means to further those interests through patient surveys of benefit expectations and risk tolerance.

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Parent Project Muscular Dystrophy

LEADING THE FIGHT TO END DUCHENNE

Our Mission

Parent Project Muscular Dystrophy's mission is to end Duchenne. We accelerate research, raise our voices in Washington, demand optimal care for all young men, and educate the global community.

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