Patient Perspective: Engaging in the Drug Development Process

Pat Furlong

Parent Project Muscular Dystrophy
JOIN THE FIGHT. END DUCHENNE.

About Duchenne muscular dystrophy

- X-linked, pediatric neuromuscular disease, with onset in early childhood
- Incidence rate: 1:4600 boys (30% spontaneous)
- Diagnosis: 3-5 years of age
- Predictable course
- Progressive loss of function
- 100% lethal

- 60-70% Deletions
- 10% Duplications
- 10-15% point mutations and other small changes

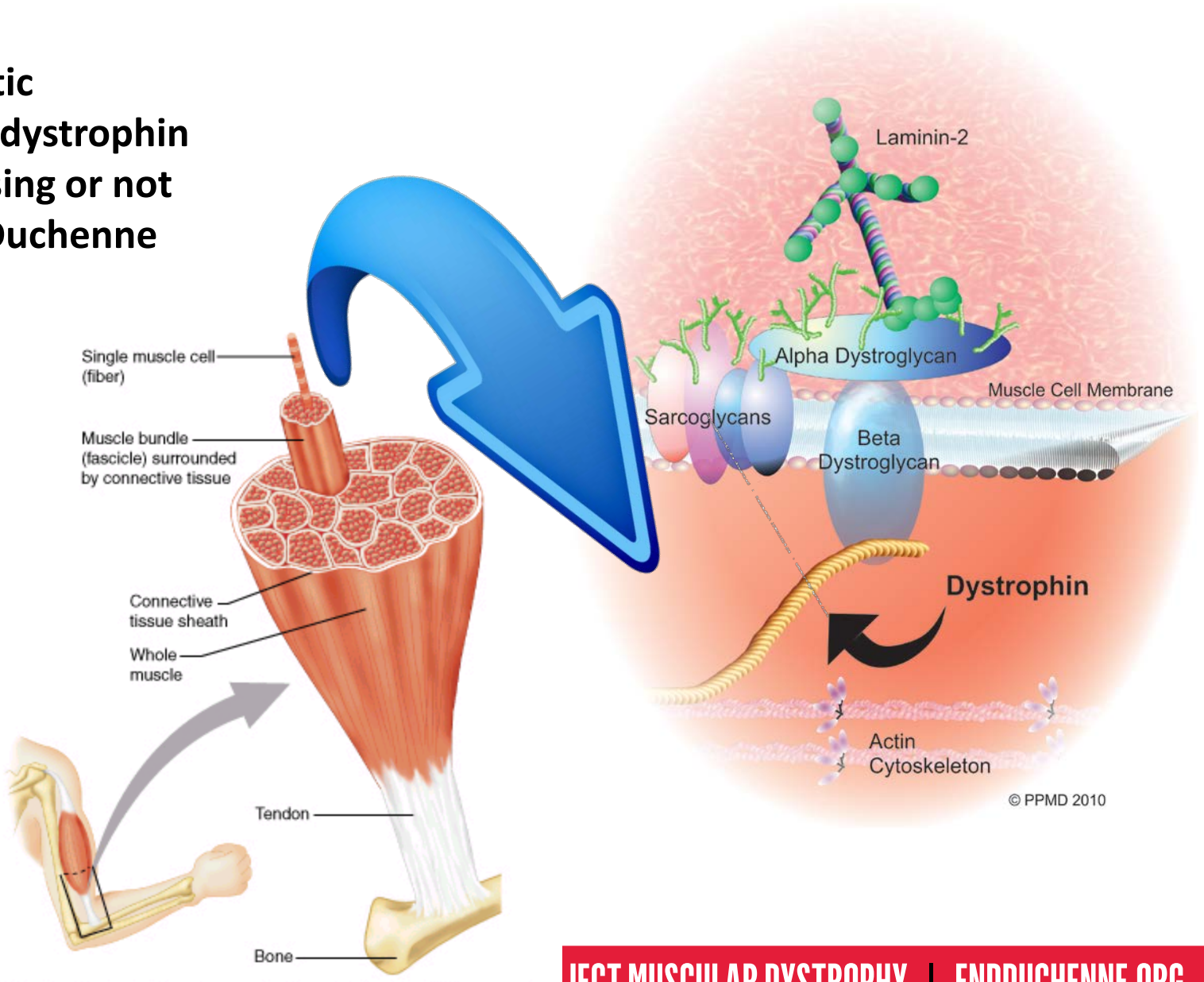
- Largest gene & protein in the human genome
- 2.4 Million base pairs/79 Exons
- **Loss of Dystrophin**

Multi-system Disease:

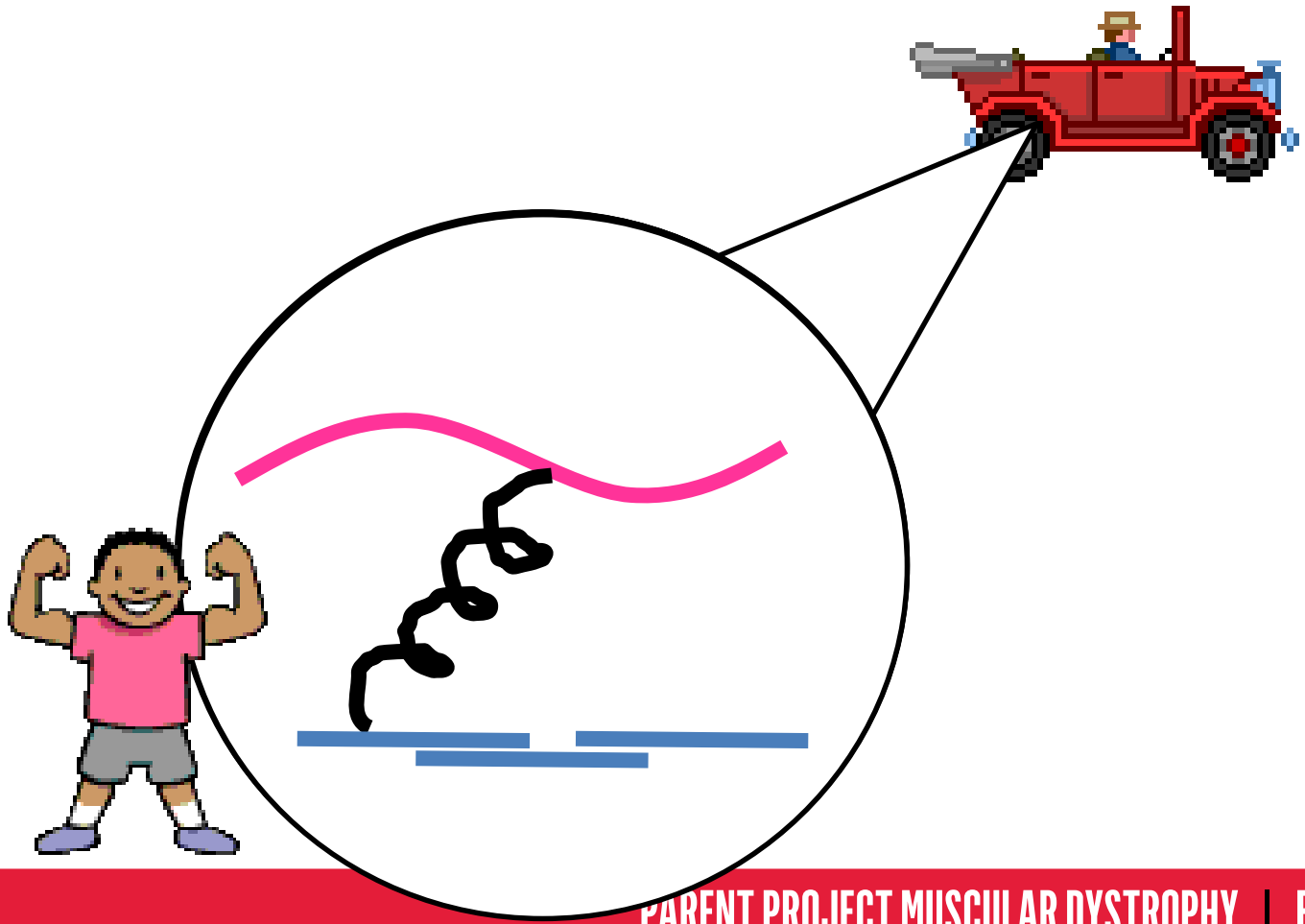
- Skeletal Muscle
- Heart
- Bone
- Smooth Muscle
- Cognitive Function

Starting at the Beginning

Due to a genetic mutation, the dystrophin protein is missing or not functional in Duchenne



What does dystrophin *do*?



Dual Diagnosis? Parents, Siblings

DX: Chronic Sorrow

- Consider Disease Burden
- Consider Emotional Impact
- Consider Divorce Rate
- Consider changing relationships
- Consider social networking impact
- Consider the terms used: ‘lethal’, genetic killer of kids….
- Emotional roller coaster (clinicians- hope on the horizon… promising therapies soon…)

A Patient/Parent's Cycle

Upon discovery, parents rush to find information and hope.

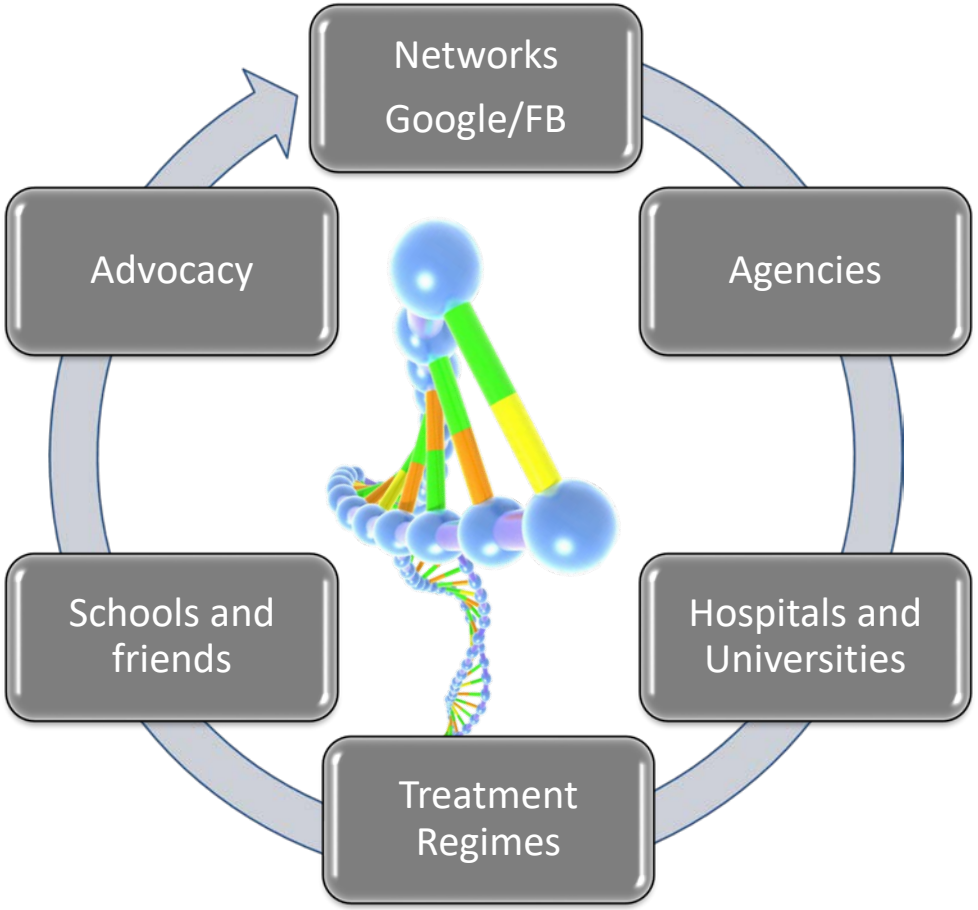
They eventually find the right agencies to partner with.

As a result they find the right resources.

They begin to implement the correct regimes.

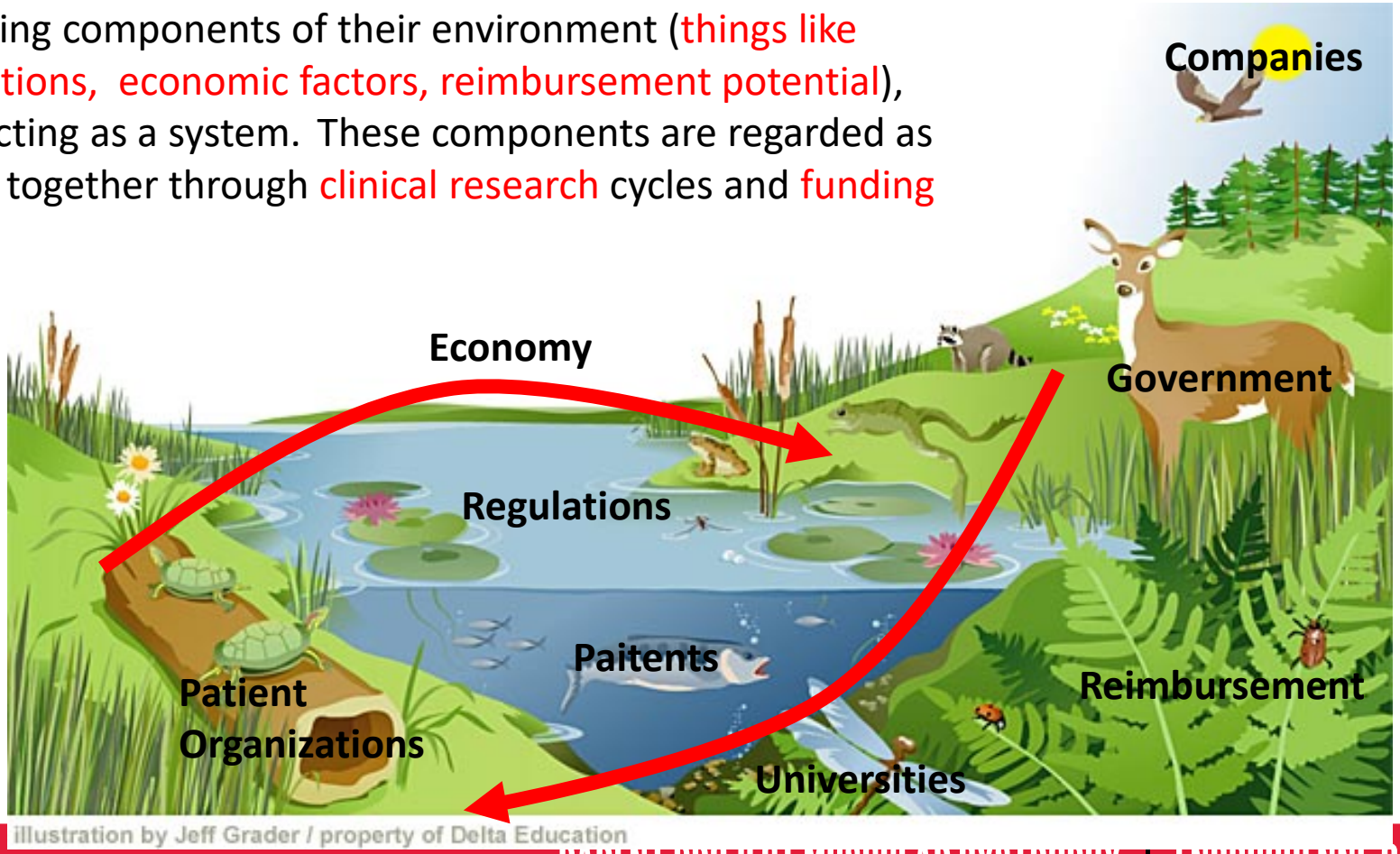
They are now the local experts.

They work to change the cycle.



Why are we here?

A drug development **ecosystem** is a community of stakeholders (universities, companies, patient organizations, patients, government organizations) in conjunction with the nonliving components of their environment (things like regulations, economic factors, reimbursement potential), interacting as a system. These components are regarded as linked together through clinical research cycles and funding flows



Time Line: PPMD Contributions to Duchenne Care and Treatment

Since MD-CARE Act
NIH $ 500 million (over 250m for DMD)
CDC $ 58.9 million (all MD's)
DOD $ 54 million (Duchenne specific)

MD CARE ACT | **DUCHENNECONNECT PATIENT REGISTRY** | **Drug Development INFRASTRUCTURE** | **DRAFT FDA GUIDANCE**

2002 | 2004 | 2006 | 2008 | 2010 | 2012 | 2014 | 2015 | 2016 | 2017 | 2018

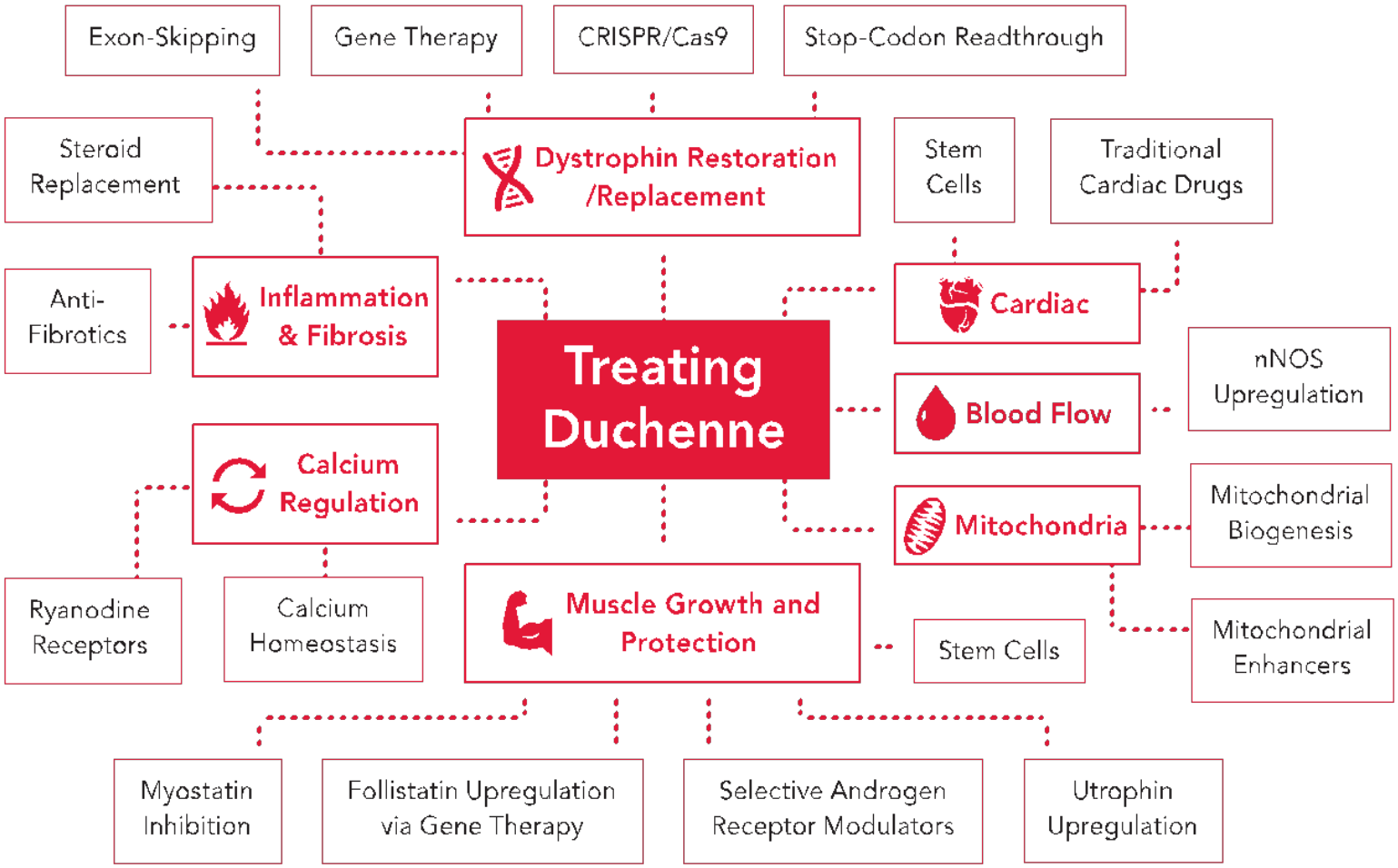
- MDCARE ACT
- Early exon skipping work
- MDCC Action Plan
- Project Catalyst
- DuchenneConnect
- MDCARE ACT Care Considerations
- End Duchenne Program
- Drug Development Round Table
- Follistatin Gene Therapy
- Benefit-Risk Study
- First clinic certified ; FDA Guidance submitted to FDA
- MDCARE ACT
- MD Action Plan Update
- FDA draft Guidance
- Approval of exondys 51
- International preference studies intitated
- Approval of emflaza
- FDA releases Final Guidance on Duchenne
- Gene Therapies Studies initiated

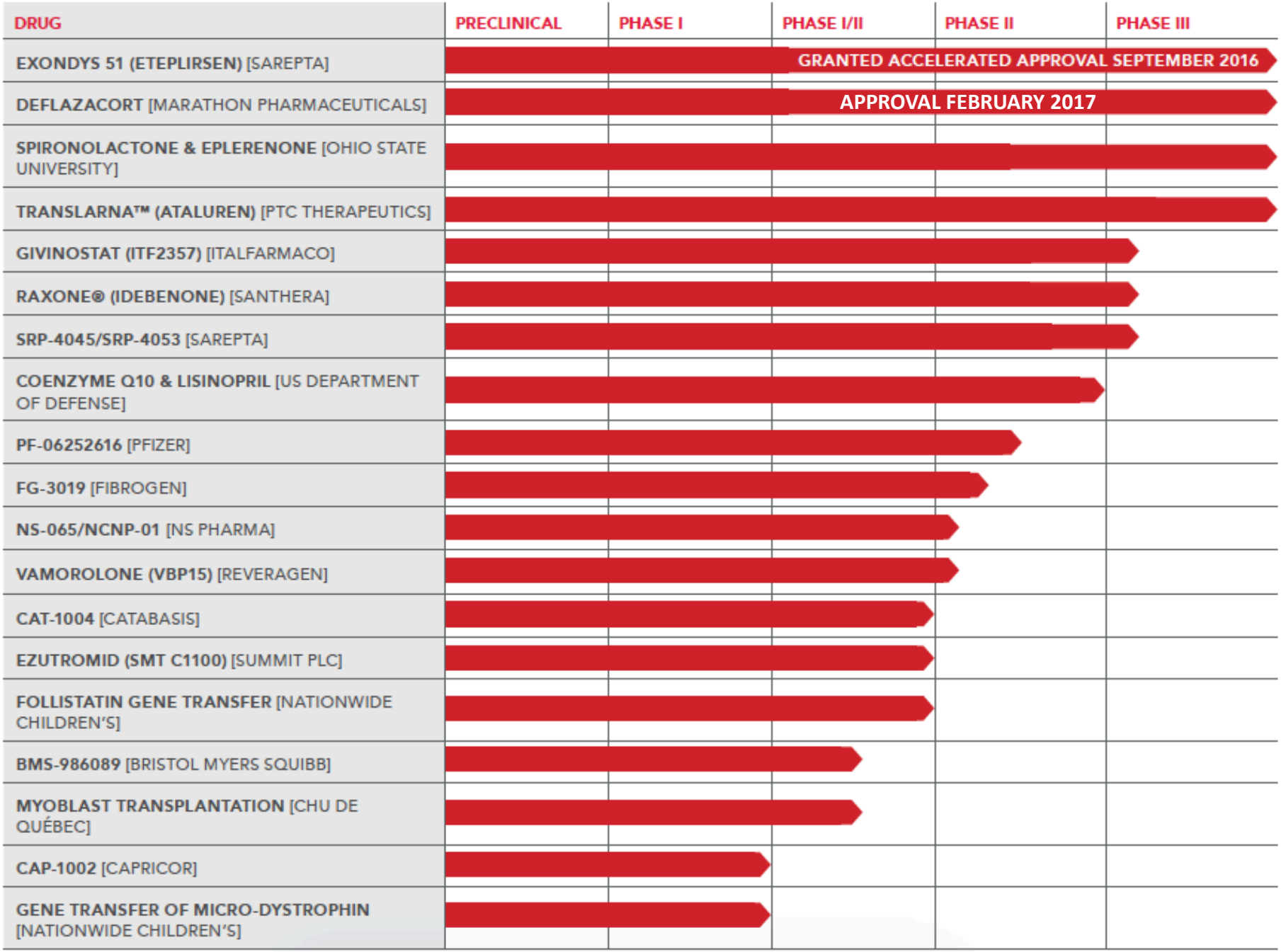
Where Are We Now?

-LAT
- *Tota*
-No n
-Aver
-No g
-No p

- TOTAL NIH funding all MDs ($780M)
- >18 new drugs in DMD trials
- >22 others in preclinical development
- Care guidelines for DMD disseminated globally & update underway
- DMD Lifespan increased by 10+ years
- Natural History Studies, Registries and other drug development tools

Clinical Trials in Duchenne




DRUG
PRECLINICAL
PHASE I
PHASE I/II
PHASE II
PHASE III
EXONDYS 51 (ETEPLIRSEN) [SAREPTA]
GRANTED ACCELERATED APPROVAL SEPTEMBER 2016
DEFLAZACORT [MARATHON PHARMACEUTICALS]
APPROVAL FEBRUARY 2017
SPIRONOLACTONE & EPLERENONE [OHIO STATE UNIVERSITY]
TRANSLARNA™ (ATALUREN) [PTC THERAPEUTICS]
GIVINOSTAT (ITF2357) [ITALFARMACO]
RAXONE® (IDEBENONE) [SANTHERA]
SRP-4045/SRP-4053 [SAREPTA]
COENZYME Q10 & LISINOPRIL [US DEPARTMENT OF DEFENSE]
PF-06252616 [PFIZER]
FG-3019 [FIBROGEN]
NS-065/NCNP-01 [NS PHARMA]
VAMOROLONE (VBP15) [REVERAGEN]
CAT-1004 [CATABASIS]
EZUTROMID (SMT C1100) [SUMMIT PLC]
FOLLISTATIN GENE TRANSFER [NATIONWIDE CHILDREN'S]
BMS-986089 [BRISTOL MYERS SQUIBB]
MYOBLAST TRANSPLANTATION [CHU DE QUÉBEC]
CAP-1002 [CAPRICOR]
GENE TRANSFER OF MICRO-DYSTROPHIN [NATIONWIDE CHILDREN'S]

BROADLY ENGAGING THE DEVELOPMENT PIPELINE

For over two decades, Parent Project Muscular Dystrophy (PPMD) has contributed to each stage of the drug development pipeline, awarding grants, filling in critical gaps, convening stakeholders, and redefining the clinical trial landscape.





DISCOVERY & PRECLINICAL

- Exploratory research awards
- Validation & replication study services
- Updated Duchenne Care Consideration Guidelines & Family Guide
- Duchenne Newborn Screening Program
- The Duchenne Registry
- ChildMuscleWeakness.org – an early diagnosis program
- AAP motor delay tool
- ICD-10 code refinement

TRIAL READINESS/ PHASE 1

- Certified Duchenne Care Center program & Clinical Trial Awareness program
- Duchenne Specialty Care Workshops
- PPMD / C-Path Duchenne Regulatory Science Consortium
- Duchenne Drug Development Roundtable – engaging sponsors in pre-competitive space
- Partnering with federal agencies (MDCC, FDA, CDC, NIH, DoD, CMS, SSA)
- The Duchenne Registry trial readiness services
- Duchenne FDA Guidance for industry

PHASE 2/3 & RECRUITMENT

- Trial education and recruitment
- Duchenne community engagement
- Leading creation of forward thinking expert publications, i.e.: Putting Patients First: Patients are Waiting, & numerous patient & caregiver preference study publications
- Advisory Committee & IND meeting support
- Leading passage of 5 federal bills, securing Duchenne-specific federal funding, & supporting rare disease legislation

REGULATORY APPROVAL

- Clinical trial support
- Drug development research awards
- FDA & regulatory engagement
- The Duchenne Registry trial recruitment services
- Multichannel community outreach & education series
- Clinical trial participant education
- Expert consultation informing trial enrollment & design

POST-MARKET & ACCESS

- Pioneering access, coverage, & reimbursement strategy
- Decode Duchenne, free genetic testing
- Patient engagement initiatives
- Post-marketing strategy development
- Payer engagement

FDA Engagement – A collaborative Community

- **Meetings with Division of Neurology**
- **Duchenne Policy Forum (December 2013)**
- **PPMD submits Draft Guidance (June, 2014)**
- **NIH/FDA/PPMD meeting –dystrophin quantification methodologies (February, 2015)**
- **FDA releases Draft Guidance (June, 2015)**
- **FDA releases Final Guidance (February, 2018)**

Setting the stage for the draft guidance

WHY INVOLVE PATIENTS IN PROTOCOL DESIGN?

- **Ultimately to develop a better protocol design which will save time**
- **Patients can serve as a sounding board about:**
  - Outcome measures and endpoints
  - Exclusionary criteria
  - Perception of Risks versus Benefits
- **Patients can can suggest ways to make trial more “user-friendly”**
- **Patients can help with ideas for marketing trials to patients**

Courtesy of sjogren's foundation

WHAT WE HAVE LEARNED ABOUT PATIENT ENGAGEMENT…

- **Should have long term commitment**
- **Involve patients early on in design process**
- **Diversity among members**
- **Safe environment to share openly**
- **Sponsors staff should ask questions to learn – not just validate**

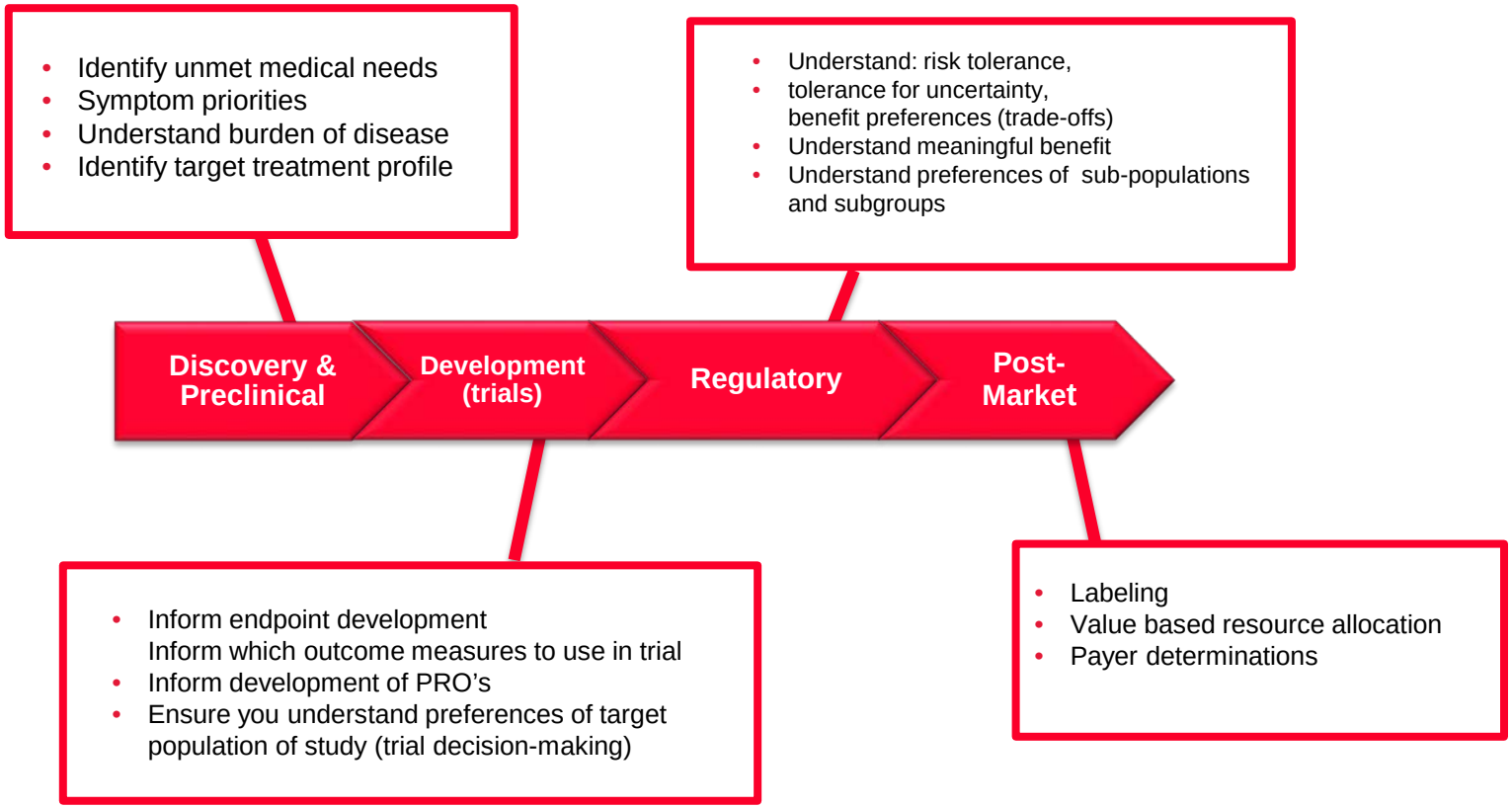
Courtesy of sjogren's foundation

HOW CAN PATIENT ADVOCACY ORGANIZATIONS HELP?

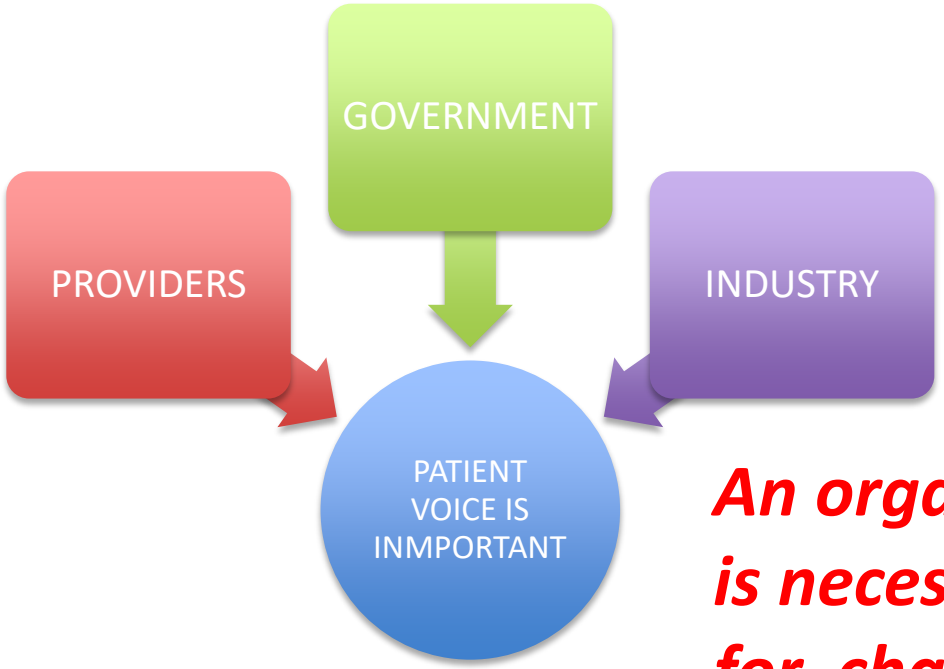
- **Help educate clinical trial sponsors about the disease**
- **Introduce sponsors to patients for engagement opportunities**
- **Introduce sponsors to key opinion leaders in disease field that are well respected among patients**
- **Connect sponsors with clinical trial sites interested in the disease and who have the patient population**
- **Help recruit patients when trial is ready**

Courtesy of sjogren's foundation

Patient Preference Information (PPI) through the drug development continuum

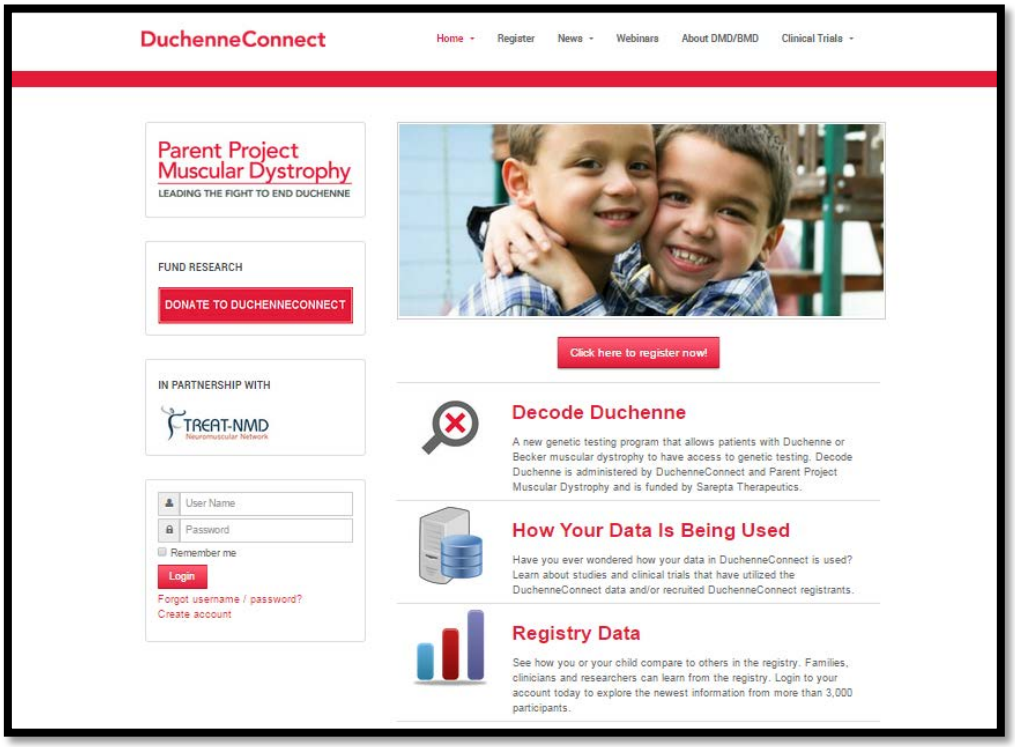


What Have We Learned: Importance of the Patient Voice



An organized patient voice is necessary and important for change.

The Duchenne Registry

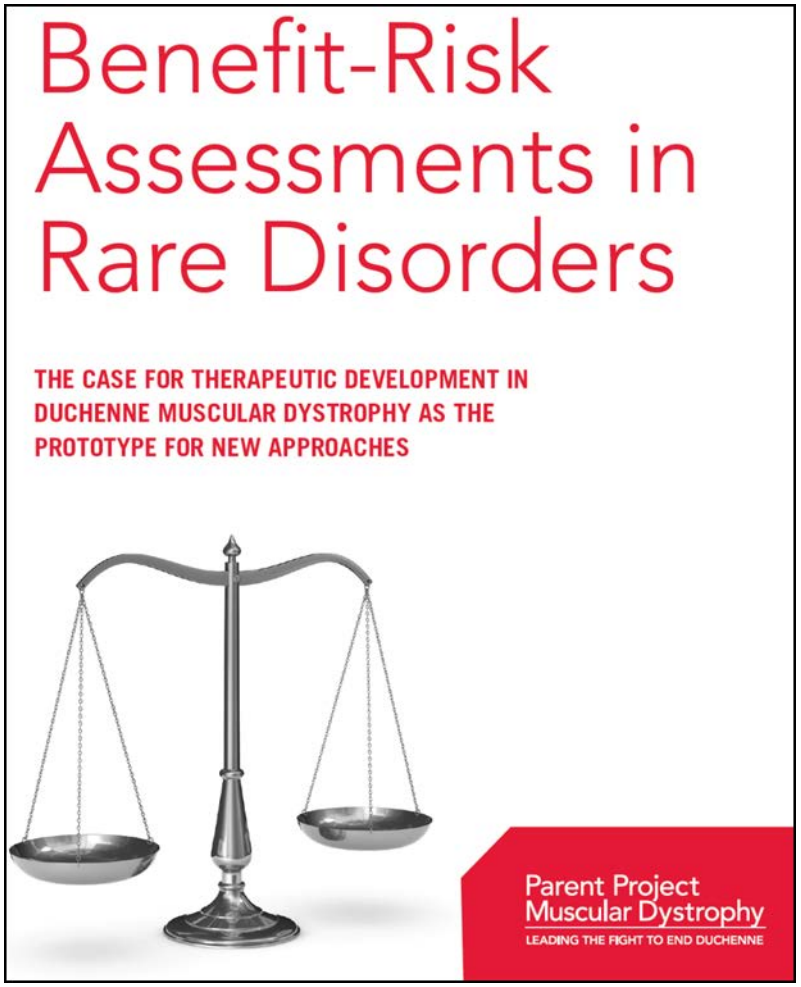


Data Collected

- Patient demographics
- Diagnosis
- Ambulation and assistive devices
- Family history
- **Genetic test report**
- Cardiac data (MRI & echo)
- Pulmonary data (spirometry)
- Corticosteroids and other medication use
- Learning and behaviour diagnoses
- Insurance information
- Clinical trial participation

Over4500 patients registered

Advancing benefit-risk methods



PPMD has been **advocating for methods** to assess the benefits-risks of treatments for rare disease.

We have also:

- Validated this work
- Studied caregiver worries
- Published a white paper on benefit risk

Benefit Risk Study

- Pilot study of 11 clinicians and 115 parents
  - Most parents describe undertaking B/R assessment
  - Parents
    - Most expected direct benefit
    - Few considered trial failure
    - Most had decided to participate before consenting
    - Clinicians
    - Felt responsible to balance consent with hope
    - Felt that they had more influence on parental decisions than parents felt that they did

Peay HL, et al. Watching time tick by…": Decision making for Duchenne muscular dystrophy trials. Contemp Clin Trials. 2016 Jan;46:1-6.

Benefit Risk Study

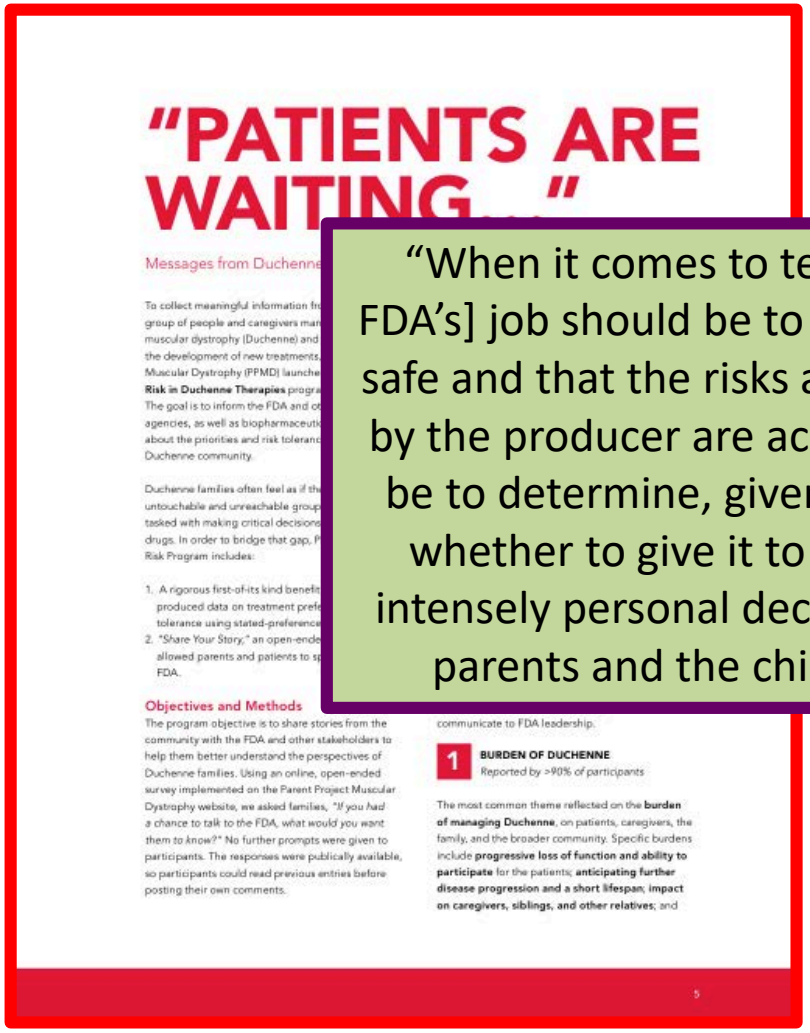
- Participants prioritized protection of muscle function over any other attribute, including longer lifespan
- Participants' most significant worries were related to the child's illness progression and care.
- Parents have great concerns about DMD's effect on their child's strength, and are willing to accept risk and uncertainty for a treatment that would slow or stop muscle weakness.

Peay HL, et al. Watching time tick by…": Decision making for Duchenne muscular dystrophy trials. Contemp Clin Trials. 2016 Jan;46:1-6.

Parent Perceptions of Clinical Trials

- Therapeutic misconception
  - Study of 38 parents involved in the PTC Phase 2
  - *ALL* parents reported expecting some direct benefit of the drug
    - all reported being well informed via multiple sources of information (PI, advocacy, research, etc.)
    - “I did my research so thoroughly that I was convinced it was a cure.”

Peay H., et al. Expectations and experiences of investigators and parents involved in a clinical trial for Duchenne/Becker muscular dystrophy. Clinic Trials. 2014 Feb; 11(1):77-85.



"PATIENTS ARE WAITING..."

Messages from Duchenne

To collect meaningful information fr
group of people and caregivers mar
muscular dystrophy (Duchenne) and
the development of new treatments.
Muscular Dystrophy (PPMD) launche
Risk in Duchenne Therapies progra
The goal is to inform the FDA and o
agencies, as well as biopharmaceuti
about the priorities and risk toleranc
Duchenne community.

Duchenne families often feel as if th
untouchable and unreachable group
tasked with making critical decisions
drugs. In order to bridge that gap, P
Risk Program includes:

1. A rigorous first-of-its kind benefit
produced data on treatment pref
tolerance using stated-preference
2. "Share Your Story," an open-ende
allowed parents and patients to s
FDA.

Objectives and Methods

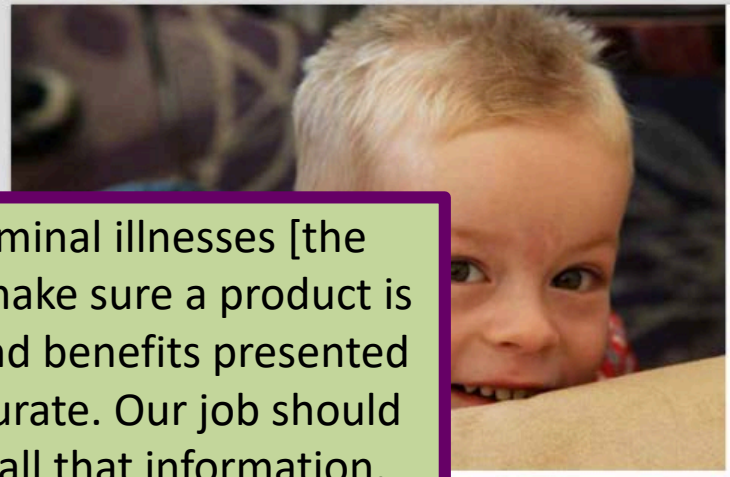
The program objective is to share stories from the community with the FDA and other stakeholders to help them better understand the perspectives of Duchenne families. Using an online, open-ended survey implemented on the Parent Project Muscular Dystrophy website, we asked families, *"If you had a chance to talk to the FDA, what would you want them to know?"* No further prompts were given to participants. The responses were publically available, so participants could read previous entries before posting their own comments.

communicate to FDA leadership.

1 BURDEN OF DUCHENNE

Reported by >90% of participants

The most common theme reflected on the **burden of managing Duchenne**, on patients, caregivers, the family, and the broader community. Specific burdens include **progressive loss of function and ability to participate** for the patients; **anticipating further disease progression and a short lifespan; impact on caregivers, siblings, and other relatives**; and



lity of life and life span. Some
come the risks that may come
nts, feeling that doing something
n just waiting for their child to
and die."

ach tick of the clock very loudly in
worried that science will take too
elop a treatment that will slow/
e progression. Our bigger worry
ce will develop it and the FDA will
g to approve it."

to clinical trials and new treatment options.

"All of us as parents know what the outcome is if we don't try something. I beg you to fast track drugs and treatments through the Duchenne pipeline. Time is something our boys do not have."

"Because DMD shortens the life span of those afflicted, I would encourage the FDA to consider being more aggressive with the approval of certain drugs where the benefits

3 INCREASED FLEXIBILITY

Reported by 62% of participants

To meet the urgent need for new treatment options, more than half of the participants urged the FDA, sponsors, and other stakeholders to come together and **facilitate a faster, more flexible drug development and approval process**. This major theme includes requests to **harmonize efforts between U.S. and other regulatory bodies** to allow

"When it comes to terminal illnesses [the FDA's] job should be to make sure a product is safe and that the risks and benefits presented by the producer are accurate. Our job should be to determine, given all that information, whether to give it to our children. It is an intensely personal decision that involves the parents and the child with Duchenne."

CLINICAL BENEFIT vs MEANINGFUL BENEFIT

6 MWT

4 STAIR CLIMB

Life Span

- Slow/Halt Progression
- Walk/Stand
- Self-Feed
- Touch Head
- Turn Over in Bed
- Wrist and Finger Function
- Breathing

Clinical Trials: Burden of Participation (in real time!)

- **The difference between being a patient and being a subject**.
  - When you are a patient, you are treated with urgency. You don't have to wait months on end for people to tell you what's happening with your condition. People don't sit on paperwork that delays your care for weeks at a time.
  - When you're a subject, you have no right to expect urgency. the research wheels slowly churn was very difficult, and the timelines are constantly moving out further and further.
  - Care: One example - an echocardiogram isn't supposed to hurt, right? when you're a subject, the tech tells you, "I've got to get the pictures for the study." Tough luck for your kid, in other words.
  - I did not understand that companies would not feel any obligation towards the kids who sacrificed so much for clinical trial participation. I thought that once our kids had given their pound of flesh, so to speak, that there would be a sense of obligation in return

Informed Consent

- **Nobody can prepare you for the roller coaster your family will ride when you sign up for a trial… simply signing an informed consent doesn't prepare you for the physical and emotional impact of a trial.**

Emotional and Physical Burden

- I **did not know how hard it would be on my son**. I was so desperate to get him on some drug, any drug, that I did not consider the fact that we were medicalizing his life at a time where he would ordinarily only be going to the hospital once or twice per year. He was a much sadder kid during that year on placebo - so sick of the airport, so sick of the hospital, so tired of being away from home. I don't think that I respected his opinion and desires enough in weighing our decisions.
- Less important than his feelings is that I did not expect how many logistics would be added to our lives - it was like having another part-time job. I had to make travel arrangements each week, arrange childcare each week, submit expense receipts each week for taxis, etc., I underestimated the toll that the simple logistics would take, and the fun family times that they replaced. I also underestimated the toll on my other children, who missed both their brother and me in the frequent travel, and whose needs always got usurped by the trial.

TIME and Sacrifice

- **we have spent a total of 28 nights in hospital and 52 days as inpatients**
- **give blood, urine, sweat, tears and access to every part of his body and life…**
- **complied with every test and measure with military precision**
- **stopped him drinking and eating the things he loves to adhere to strict protocols, foods that actually give him pleasure and make him enjoy his life like chocolate and lemonade**

Cost of Participation

- **Required to be patient when 3 month trials have turned into over five months,**
- **changed our whole families diets,**
- **sacrificed holidays, cut back on luxuries to afford to take part in trials because although the company covered travel costs, they don't cover childcare costs for siblings,**
- **loss of earnings through taking unpaid leave**
- **cost of the number of presents I have had to get him for taking part is probably in the thousands.**

Financial Burden

- **I did not know expensive it would be**. The costs vary per trial, I had to go part time with work, pay for child care once per week for my other children, etc. At one point, the hospital was so behind in reimbursement that I was out an additional $6,000 in covered expenses. I was not prepared in advance for the financial toll on my family.

Uncertainty

- **countless nights I laid on a rock hard camp bed watching him sleep, watching him take every breath, watching the minutes of the clock tick by, seeing them turn into hours and then days praying he will be ok and that he won't encounter an adverse event.**
- **Who knows what could happen to the first children exposed to this drug?**

Placebo

- Use of Placebo:
  - I thought that if we really were able to identify who was on drug and who wasn't, that they would just use an untreated control group alongside the treated group, not put them through the pain and damage of a year's worth of fake injections and needless surgery.

Rolling with the Punches

On Friday, Sam had surgery to place an internal port for his weekly clinical trial infusions. It did not go as planned. The surgeon saw the port they had placed was too small and had to remove it**.** Unfortunately, and unbeknownst to us, the hospital did not stock larger ports. The surgeon spoke with our doctor's team (who had spoken with her, as she was out on vacation), and his new recommendation was an external catheter.... We ok'ed this believing our doctor thought it was the best option. The problem with this was we were not informed of the restrictions an external catheter would place on Sam. Our doctor told her team to make sure the surgeon told us, but someone dropped the ball. These restrictions have to do with swimming and showering. Swimming is restricted with it, and showering is difficult at best. There are also major care differences. The internal port requires us to do no extra care at home. The external catheter requires daily flushing with heparin and cap and dressing changes. It's also far more prone to infection. Because Sam is immune-suppressed, this could be quite the issue. Another major issue was no care instructions or supplies given to us upon discharge. We were told what to watch for regarding post surgery infection, but that's it. And since we had not been informed of the care differences, we did not know we should have been given supplies and further instruction.

More Punches…and still

So we arrived home after discharge thinking all was well. I decided to Google information on his external catheter. That's when I discovered the restrictions and extra care. We phone the surgery department to try to figure out what was going on. Now after speaking with our doctor, and agreeing with us that swimming, Sam's only form of exercise, is of utmost importance, we are needing to schedule him for another surgery to remove the external catheter and place an internal port of the correct size. Putting Sam under for surgery is never an easy decision. He has more risks than the average child. But he's healthy, and we all believe the benefits are worth it. We don't know yet when the surgery will be. We're trying for the soonest possible so he can get back in the pool

Parent Project Muscular Dystrophy

JOIN THE FIGHT. END DUCHENNE.

ENDDUCHENNE.ORG