Patient Perspective: Engaging in the Drug Development Process

Pat Furlong
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
• Largest gene & protein in the human genome
• 2.4 Million base pairs/79 Exons
• Loss of Dystrophin

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

Multi-system Disease:
- Skeletal Muscle
- Heart
- Bone
- Smooth Muscle
- Cognitive Function
Due to a genetic mutation, the dystrophin protein is missing or not functional in Duchenne.
What does dystrophin do?
**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.
Since MD-CARE Act
NIH $500 million (over
250m for DMD)
CDC $58.9 million (all
MD's)
DOD $54 million
(Duchenne specific)

Time Line: PPMD Contributions to
Duchenne Care and Treatment

Putting Patients First

Guidance for Industry
Duchenne Muscular Dystrophy
Developing Drugs for
Treatment over the Spectrum
of Disease

MD CARE ACT
DuchenneConnect
Drug Development
DRAFT FDA
Gpaency

2002
2004
2006
2008
2010
2012
2014
2015
2016
2017
2018

Early exon skipping
MDCC Action Plan
Project Catalyst
DuchenneConnect
MDCARE-ACT
Care Considerations
End Duchenne
R&D Round Table
Benefit-Risk Study
Falllutilin Gene Therapy
Clin Trial
Drug Development
MDCARE-ACT
MD Action Plan Update
First clinic certified
FDA Guidance
FDA draft Guidance
Gene Therapy Studies initiated
Approval of gene therapy
International preference studies initiated
Gene Therapies Studies initiated
FDA releases Final Guidance on Duchenne
Where Are We Now?

- LATE 1990's
  - Total NIH funding for MD is $17M
  - No new drugs in development
  - Average lifespan for DMD is late teens
  - No guidelines for care
  - No patient registries

• 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

- Exon-Skipping
- Gene Therapy
- CRISPR/Cas9
- Stop-Codon Readthrough

- Steroid Replacement

- Anti-Fibrotics
- Inflammation & Fibrosis

- Calcium Regulation
- Ryanodine Receptors
- Calcium Homeostasis

- Muscle Growth and Protection

- Dystrophin Restoration/Replacement

- Stem Cells
- Traditional Cardiac Drugs
- Cardiac
- Blood Flow
- Mitochondria
- nNOS Upregulation
- Mitochondrial Biogenesis
- Mitochondrial Enhancers
- Myostatin Inhibition
- Follistatin Upregulation via Gene Therapy
- Selective Androgen Receptor Modulators
- Utrophin Upregulation
<table>
<thead>
<tr>
<th>DRUG</th>
<th>PRECLINICAL</th>
<th>PHASE I</th>
<th>PHASE I/II</th>
<th>PHASE II</th>
<th>PHASE III</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXONDYS 51 (ETEPLIRSEN) [SAREPTA]</td>
<td></td>
<td></td>
<td></td>
<td>GRANTED ACCELERATED APPROVAL SEPTEMBER 2016</td>
<td></td>
</tr>
<tr>
<td>DEFLAZACORT [MARATHON PHARMACEUTICALS]</td>
<td></td>
<td></td>
<td></td>
<td>APPROVAL FEBRUARY 2017</td>
<td></td>
</tr>
<tr>
<td>SPIRONOLACTONE &amp; EPLERENONE [OHIO STATE UNIVERSITY]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRANSLARNA™ (ATALUREN) [PTC THERAPEUTICS]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GIVINOSTAT (ITF2357) [ITALFARMACO]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAXONE® (IDEBENONE) [SANHERA]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRP-4045/SRP-4053 [SAREPTA]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COENZYME Q10 &amp; LISINOPRIL [US DEPARTMENT OF DEFENSE]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PF-06252616 [PFIZER]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FG-3019 [FIBROGEN]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS-065/NCNP-01 [NS PHARMA]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAMOROLONE (VBP15) [REVERAGEN]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAT-1004 [CATABASIS]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EZUTROMID (SMT C1100) [SUMMIT PLC]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLLISTATIN GENE TRANSFER [NATIONWIDE CHILDREN’S]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMS-986089 [BRISTOL MYERS SQUIBB]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MYOBLAST TRANSPLANTATION [CHU DE QUÉBEC]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAP-1002 [CAPRICOR]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GENE TRANSFER OF MICRO-DYSTROPHIN [NATIONWIDE CHILDREN’S]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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.
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 suggest ways to make trial more “user-friendly”

• Patients can help with ideas for marketing trials to patients
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
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
Identify unmet medical needs
Symptom priorities
Understand burden of disease
Identify target treatment profile

Understand: risk tolerance,
tolerance for uncertainty,
benefit preferences (trade-offs)
Understand meaningful benefit
Understand preferences of sub-populations and subgroups

Inform endpoint development
Inform which outcome measures to use in trial
Inform development of PRO’s
Ensure you understand preferences of target population of study (trial decision-making)

Labeling
Value based resource allocation
Payer determinations

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

Over 4500 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

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.

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.”

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.