Neuromuscular Clinical Trials

Boosting patient engagement and participation

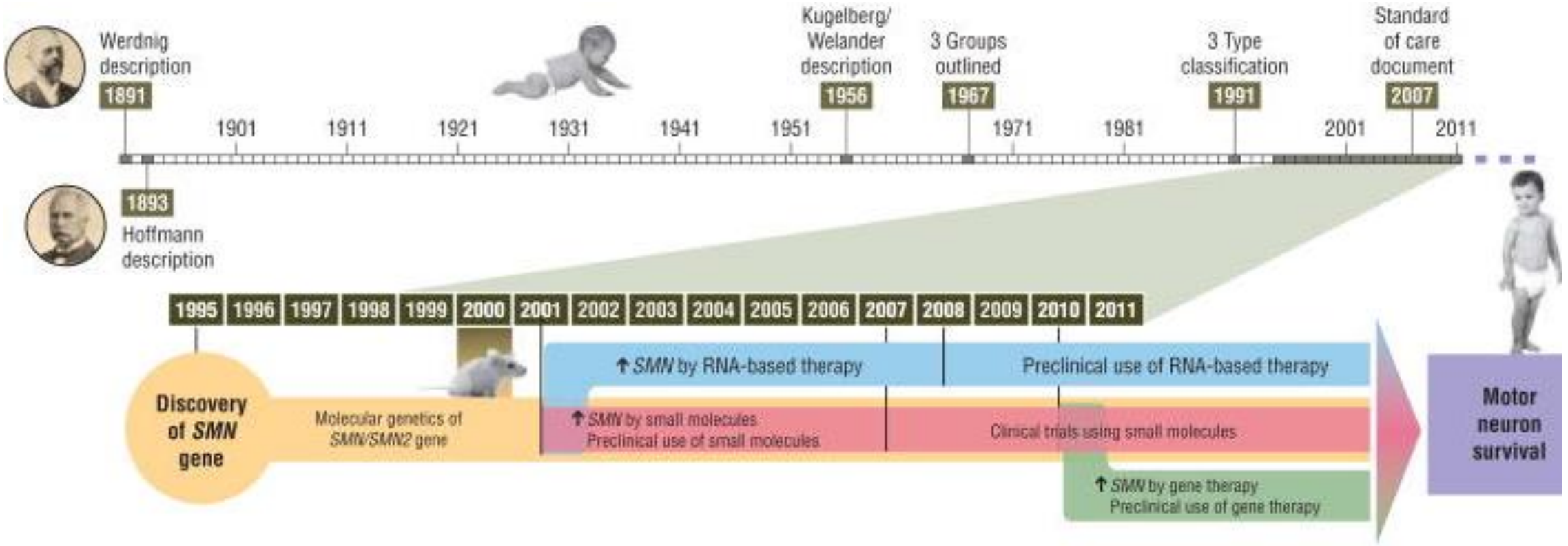
2021

Slide set overview

- **The clinical trial (CT) landscape in neuromuscular disease (NMD)**
  - Current therapeutic landscape
  - Value of CT in therapy development
  - Barriers to CT enrollment
- **Strategies to support enrollment in practice**
  - Within the NMD clinic
  - Outside of an NMD clinic or academic center
- **Increasing patient awareness and engagement**

Current therapeutic landscape for NMDs

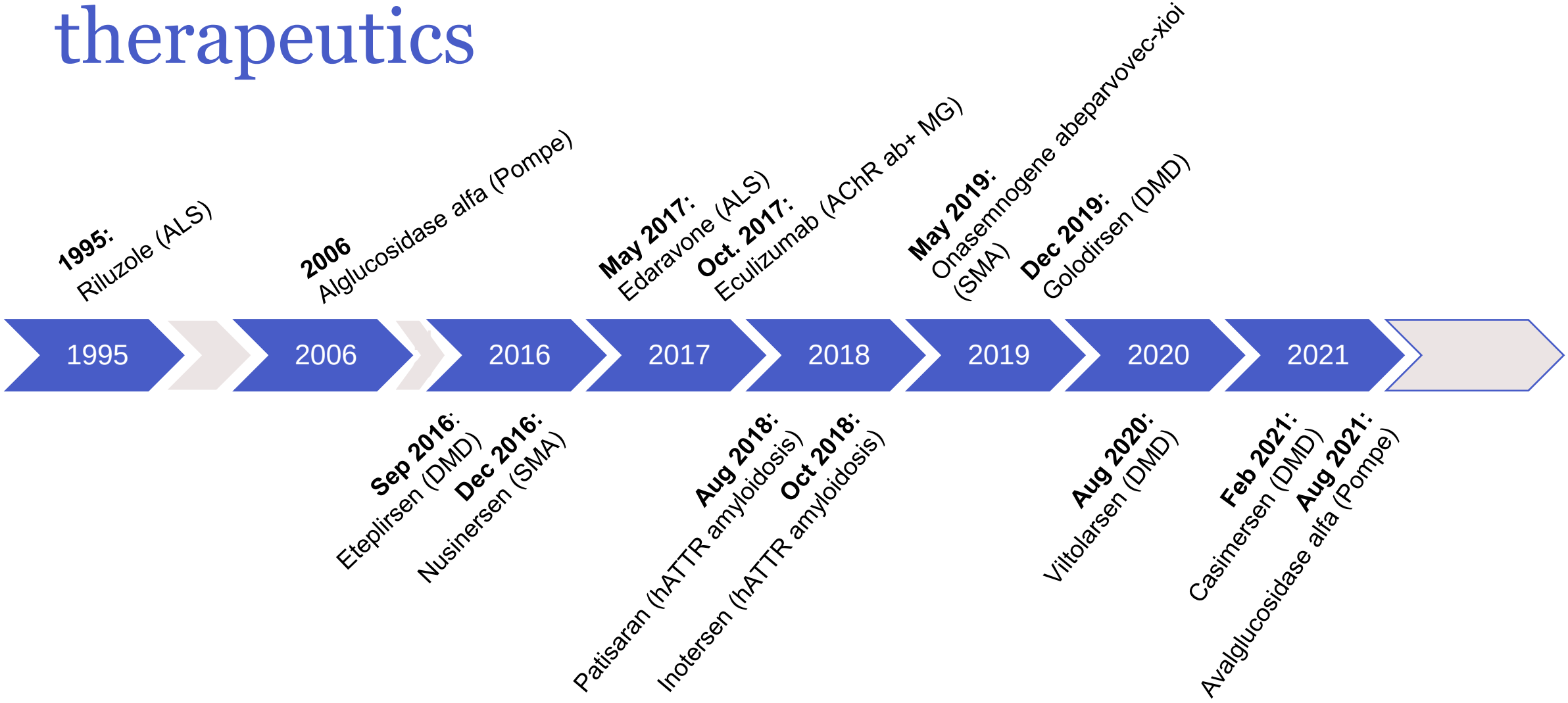
Example: success stories in NMD



- Nusinersen was approved by the US Food and Drug Administration (FDA) for the treatment of SMA in December 2016, followed by onasemnogene abeparvovec-xioi (May 2019) and risdiplam (August 2020).

1. Kolb SJ, 2011. 2. Finkel RS, 2017. 3. Mercuri E, 2018. 4. Day JW, 2021.

Timeline of FDA approvals for NMD therapeutics



1. Benson MD, 2018. 2. Adams D, 2018. 3. Finkel RS, 2017. 4. Mercuri E,, 2018 5. Day JW, 2021. 6. Cartwright MS, 2021. 7. Yao S, 2021 8. Duan D, 2021. 9. Van der Ploeg AT, 2010. 10. Diaz-Manera J, 2021.

FDA-approved treatments for NMDs

MOA	Indication	Agent
Enzyme replacement therapy	Acid maltase deficiency or Pompe's disease	• Alglucosidase alfa • Avalglucosidase alfa
RNA interference agent	Polyneuropathy for hereditary transthyretin (hATTR) amyloidosis	Patisaran
Antisense oligonucleotide (ASO) agents	hATTR amyloidosis	Inotersen
	Spinal muscular atrophy (SMA)	Nusinersen
Exon skipping therapies	Duchenne muscular dystrophy (DMD)	Adeno-associated virus vector-based gene therapy • Eteplirsen (exon 51) • Golodirsen (exon 53) • Viltolarsen (exon 53) • Casimersen (exon 45)
	SMA	Onasemnogene abeparvovec-xioi

1. Benson MD, 2018. 2. Adams D, 2018. 3. Finkel RS, 2017 4. Mercuri E, 2018. 5. Day JW, 2021. 6. Cartwright MS., 2021. 7. Yao S, 2021 8. Duan D., 2021. 9. Van der Ploeg AT, 2010. 10. Diaz-Manera J, 2021

FDA-approved treatments for NMDs (cont)

MOA	Indication	Agent
Terminal complement inhibitor	AChR ab+ myasthenia gravis	Eculizumab
Glutamate release inhibition	Amyotrophic lateral sclerosis (ALS)	Riluzole
Free radical scavenger	ALS	Edaravone

1. Howard JF, 2017. 2 Chen JJ, 2020. 3. Masrori P, 2020

Off-label standard of care use of drugs in NMD

Sodium channel blockers	Immunosuppressive therapies, various drugs
• Myotonia in myotonic dystrophy type 1 and 2 (mexiletine) • Myotonia, in chloride and sodium channel skeletal muscle channelopathies	• Myasthenia gravis • Idiopathic inflammatory myopathies

Treatment options are still needed for the majority of NMDs

- The prior slides emphasize:
  - Diseases with new treatments
  - Technologies/biotechnology platforms used to design “molecularly targeted therapies for NMD”
- Additional technologies are being evaluated (CRISPR-Cas9 editing, etc.)
- While the NMD landscape is rapidly changing and the potential for new breakthroughs is high, the overwhelming **majority of hereditary NMDs still have no treatment**
- Also, existing FDA-approved drugs can be improved upon:
  - e.g. Current drugs for DMD appear to have modest effects

1. MDA, 2018. 2. Gillmore JD, , 2021

Impact of clinical trial research in neuromuscular disease

Importance of clinical research and trials

- Research informs disease understanding and allows for rigorous testing of drug candidates.

Observational studies, natural history studies, and patient registries	Clinical trials
• Better understand disease • Define patient populations • Identify outcome measures to use for clinical testing	• Evaluate safety and efficacy of emerging drug candidates

Barriers to clinical trial recruitment in NMD

- Hereditary neuromuscular diseases (NMDs) are rare or very rare
- Heterogeneity of NMDs, combined with the low prevalence of disease, can also result in:
  - Lengthy diagnostic journeys for patients (sometimes 1 year or more)
  - Challenges determining the underlying causes of NMDs, and therefore eligibility to participate in CTs
- Narrow inclusion criteria:
  - Decreases the already-small number of patients available to participate
  - Leads to enrollment of study populations that may not represent the broader patient population

1. Crow RA, 2018. 2. Bendixen RM, 2016 3. LoRusso S, 2021

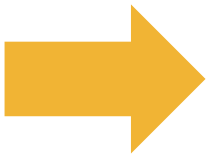
Barriers to clinical trial design in NMD

- Broad phenotypic spectrum of NMDs can hinder clinical trial design (eg, Becker muscular dystrophy)
- Unavailable or incomplete natural history studies can lead to:
  - Difficulty identifying a patient population
  - Lack of data to use as a control when small patient populations make it infeasible to randomize patients to placebo

Recruitment is a major barrier to clinical trial success

- As new therapies move through the pipeline, they encounter challenges at every level[1]
- Trials often terminate early due to a failure to accrue enough participants[1]
- Integrating strategies to streamline clinical trial enrollment into practice may help more clinical trials succeed and ultimately develop approved therapies

Recruitment failures[2]



- Increased cost of drug development due to clinical testing delays
- Ethical implications of exposing research participants to risk without resulting research gains
- Missed opportunities for patients who could have benefited from a CT
- Waste of time, funds, and other resources

1. IQVIA, 2018. 2. Mahon E., 2015. 3. Schutz A, 2017

The NMD research landscape is rich, and clinical trial opportunities abound

- As of 2018, **195 unique molecules** were in development for NMDs by 165 companies in 20 countries, many of which are “next-generation” therapies[1]
- >1000 NMD trials are recruiting worldwide, with 552 in the US (2021)[2]
  - 139 observational (US)
  - 413 interventional (US)
- Assuring awareness of clinical trial opportunities among clinicians and patients is critical to clinical trial success

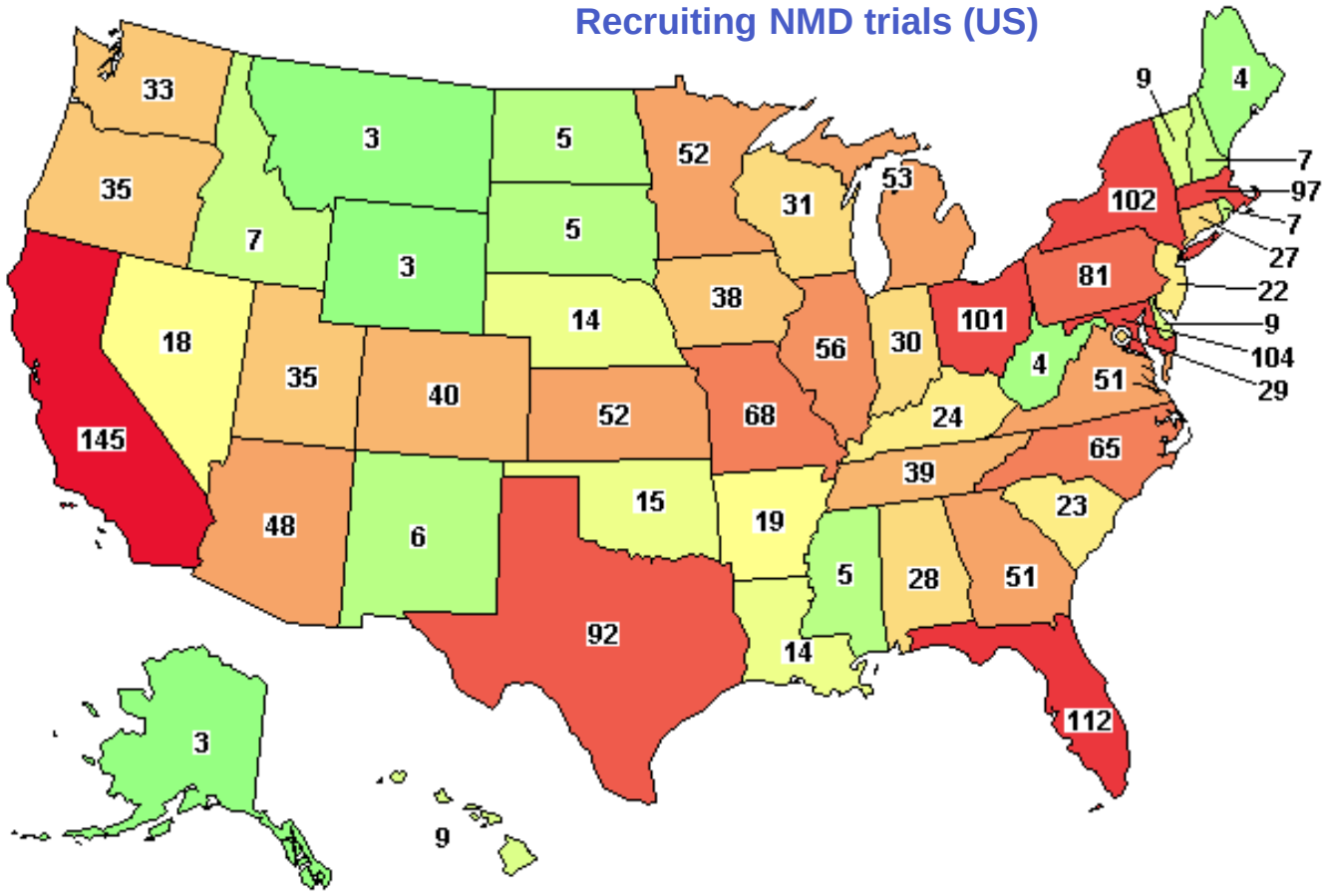


Image from clinicaltrials.gov: https://clinicaltrials.gov/ct2/results/map?recrs=abf&cond=Neuromuscular+Diseases&map=NA%3AUS. Accessed September 13 2021.

1. IQVIA Institute, 2018. 2. Clinicaltrials.gov. Accessed September 13 2021.

Elevating clinical education, engagement, and participation at your clinical site

Role of the clinician

- Clinician attitude and communication with patients can play an important role in CT enrollment[1]
- A study of practicing physicians and nurses across specialties revealed[2]:
  - A high percentage of healthcare providers are familiar with the CT process and are comfortable discussing CTs with their patients
  - Providers refer only a small number of patients to CTs because of:
    - Inability to access CT information
    - Lack of sufficient information and time to evaluate and confidently discuss CT options with patients

1. Mahon, 2015 2. Getz, 2017

CT access varies across clinical settings

- **Large academic medical centers**
  - May already have streamlined care as an MDA Care Center or other tailored NMD clinic
  - Have clinical research coordinators
  - Clinicians are accustomed to speaking to patients about CTs
- **Community practice**
  - Often, clinicians have less experience with CTs
  - Heavy patient-load — less time for CT discussion and recruitment

MDA, 2018.

Within the NMD clinic: Integrate a research coordinator into NMD clinic team

- **Research coordinator role:** Identify study candidates, provide patient education about ongoing studies during clinic, coordinate screening/visits recruitment

-24 to -48 hours prior:

- Reviews scheduled patients for week
- Identifies candidates for ongoing studies
- Sends e-mail to clinic team to flag specific patients and next steps

Within the NMD clinic: Integrate a research coordinator into NMD clinic team (cont)

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Research coordination meeting:

- Held weekly
- PIs and research coordinators meet to review study participants and status
- Gives the team an opportunity to discuss any outstanding issues and ensures alignment on next steps

Within the NMD clinic: Integrate a research coordinator into care team (cont)

- The communication to the NMD team:
  - **Flags** specific patients on the clinic schedule
  - **Delineates next steps** for the patient's research participation

Example e-mail communication to NMD team

To: NMD_clinicalstaff
Subject: NMD Clinic: July 7

Team,
See below for NMD clinic list for Tuesday, July 7.

Time	ID	Notes, next steps
13:00	###	LGMD- **GRASP potential, patient enrolled**
13:30	###	**TELEHEALTH-** Myotonic dystrophy Type 1; **Kate to call and schedule END1-research visit; patient wishes to come back**
13:45	###	**NEW**- Emery Dreifuss Dystrophy

Within the NMD clinic: Maintain ongoing lists of potentially eligible patients

- Maintaining lists of patients with interest in CT opportunities allows the care team to quickly identify potential participants when a trial becomes available
  - Can be **disease specific** (eg, DMD, Becker MD, LGMD subtype) or more **general** (patients who have expressed interest in research)
  - Research team members can search by disease to identify potential participants as recruitment approaches
- The **EHR** system can also be a useful resource to help clinicians and coordinators identify potential participants

Each list can be built up to ~1 year prior to study opening

- Study planning can take time and is needed before recruitment can begin
- This study ramp-up time gives teams an opportunity to build up lists on a week-by-week basis at MDA visits

Within the NMD clinic: Ensure clinicians and research staff are aware of studies

- Can be challenging at larger or busier care centers
  - The more ongoing studies at a center, the more challenging
- Holding routine research team meetings is ideal, but time does not always allow for these types of meetings
  - Meetings should include coordinators, PIs, and other physicians involved in study education

Within community practice: tips for improving CT participation

- Connect with a nearby MDA care center provider or academic center
  - Establishing a connection with an institution familiar with ongoing CTs reduces the burden of time-consuming research amidst a heavy patient load
  - Ask them about ongoing study recruitment and post recruitment flyers in the office
- Place cards in the office with info on local study sites and encourage patients to call
  - Patients won't need to commit for a visit if not inclined for personal reasons
- **Direct patients to clinicaltrials.gov**
- Consider referring patients directly to the nearest **MDA clinic**
  - MDA clinics provide multidisciplinary care, educate patients about research opportunities, and allow them to stay informed of future events

Increasing awareness and engagement among patients

Patient participation in NMD clinical trials

- CTs play a key role in development of new treatments for NMDs, but **76%** of the NMD community has never participated in a CT
- A national survey of adults and families living with NMD revealed that:
  - Patients ages 11-17 are most likely to be currently or previously enrolled in a CT
  - Patients diagnosed within the last 10 years are more likely to be enrolled in a CT than those diagnosed more than 10 years ago
  - Among those who have not participated in a CT, 63% would consider doing so
  - CTs top the list of topics related to NMD that patients and caregivers are most interested in learning more about

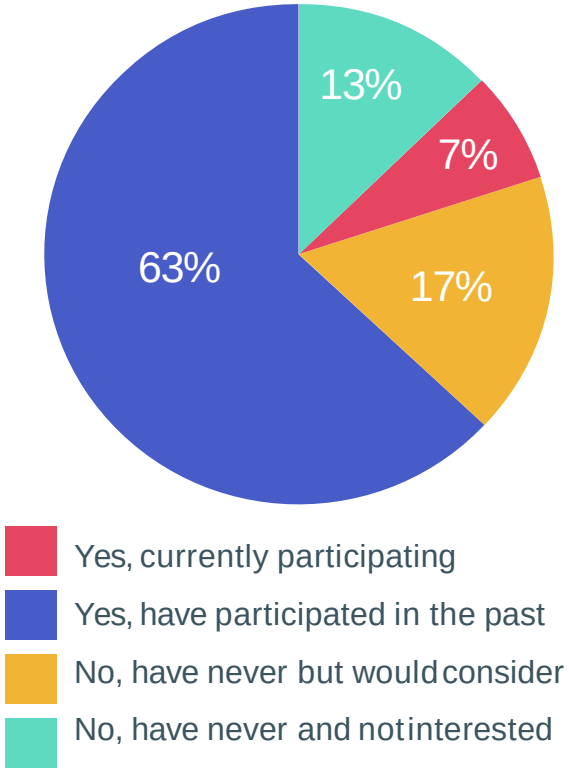
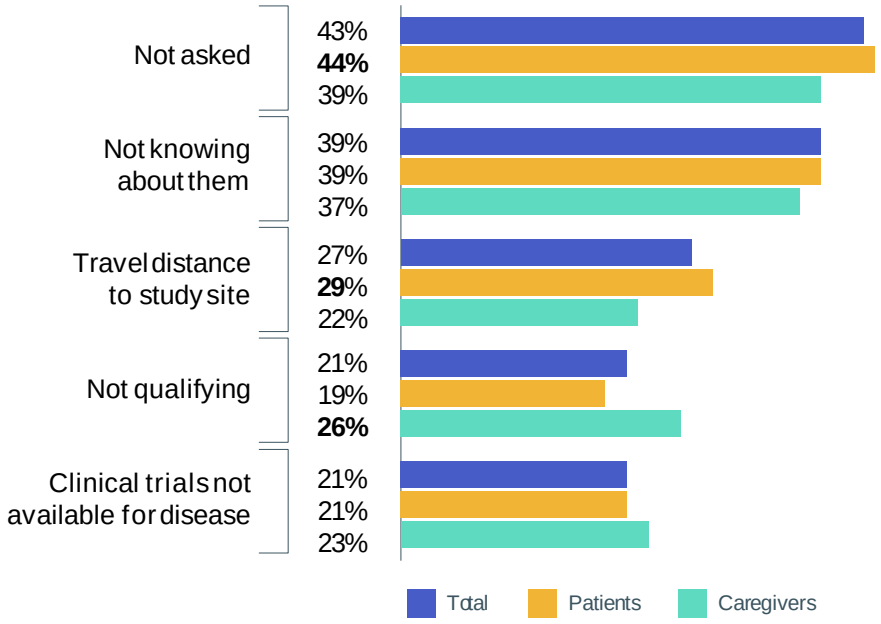


Figure adapted from MDA 2018.
MDA, 2018. ONEvoice survey.

Patients may be interested in participating in clinical trials, but face uncertainty

- **Though >60% of patients report interest in CTs, participation remains low[1,2]**
- The greatest reported barriers to CT enrollment are:
  - Not being asked or not knowing about CTs
  - Concerns about logistics — cost, transportation, language
- **Additional barriers cited by patients include:**
  - Fear of being placed in the placebo group
  - Fear that participation in one study will disqualify them from more promising future trials
  - Worry about access to drugs at the conclusion of the CT
  - Assumption that they are too old

Reasons for not participating in CT



Bolding indicates statistical significance.

Figure adapted from MDA 2018.

1. MDA, 2018. ONEvoice survey. 2. Peay, 2018.

Engage and educate patients: Plan disease-specific family days

- Plan disease-specific family days where individuals can obtain relevant information about their diagnosis and related events
  - Can be timed to coincide with ongoing studies that need an activated local group of patients to prime interest in study recruitment
  - Enjoyable opportunity to work with patients and families outside of the clinic
  - Provides patient education, patient community discussion, advocacy, research updates
- These events can also help keep patients engaged with the MDA clinic

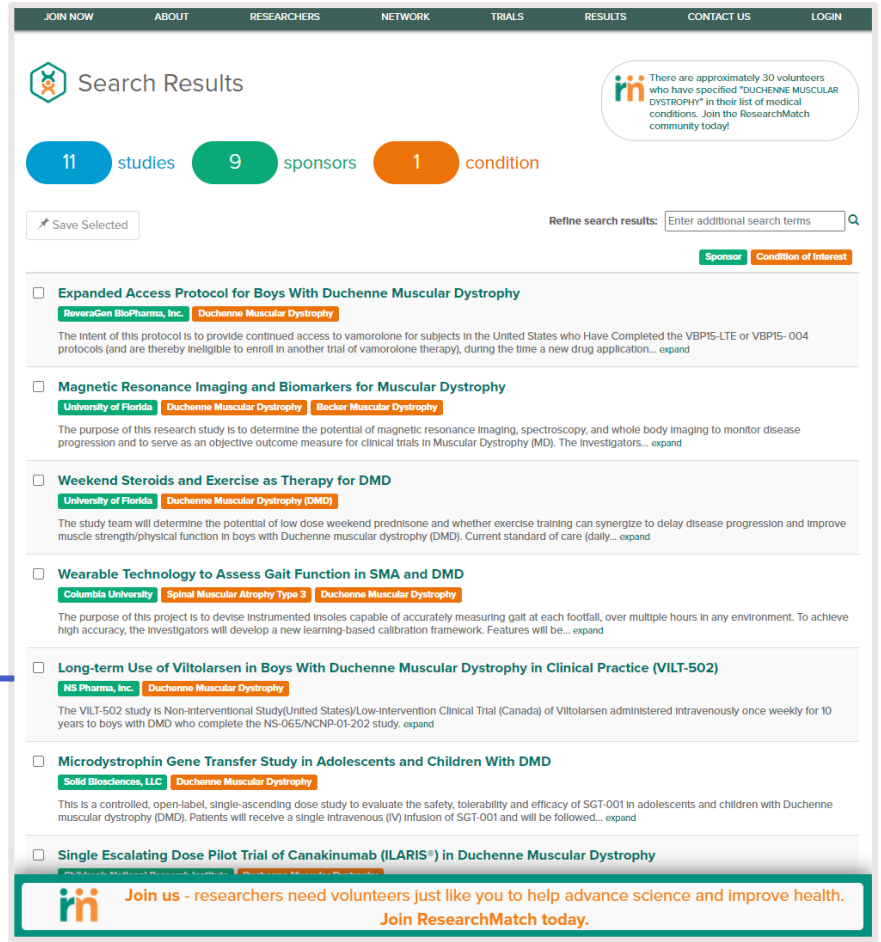
Flyer from LGMD Patient Day 2020, University of Kansas Medical Center

Image courtesy of Dr. C Farmakidis

Engage and educate patients: Develop resources for the office or clinic

- Develop and post flyers or place an iPad pre-loaded with clinical trial finder links in the office
  - **TrialsToday.org**
  - Clinicaltrials.gov
  - MDA.org/research/clinical-trials

Example search on *TrialsToday*:
- Duchenne muscular dystrophy
- 5 years old
- Male
- No distance limit



1https://www.trialstoday.org/.

Engage and educate patients: Develop resources for the office or clinic (cont)

- Develop and post flyers or place an iPad pre-loaded with clinical trial finder links in the office
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  - **Clinicaltrials.gov**
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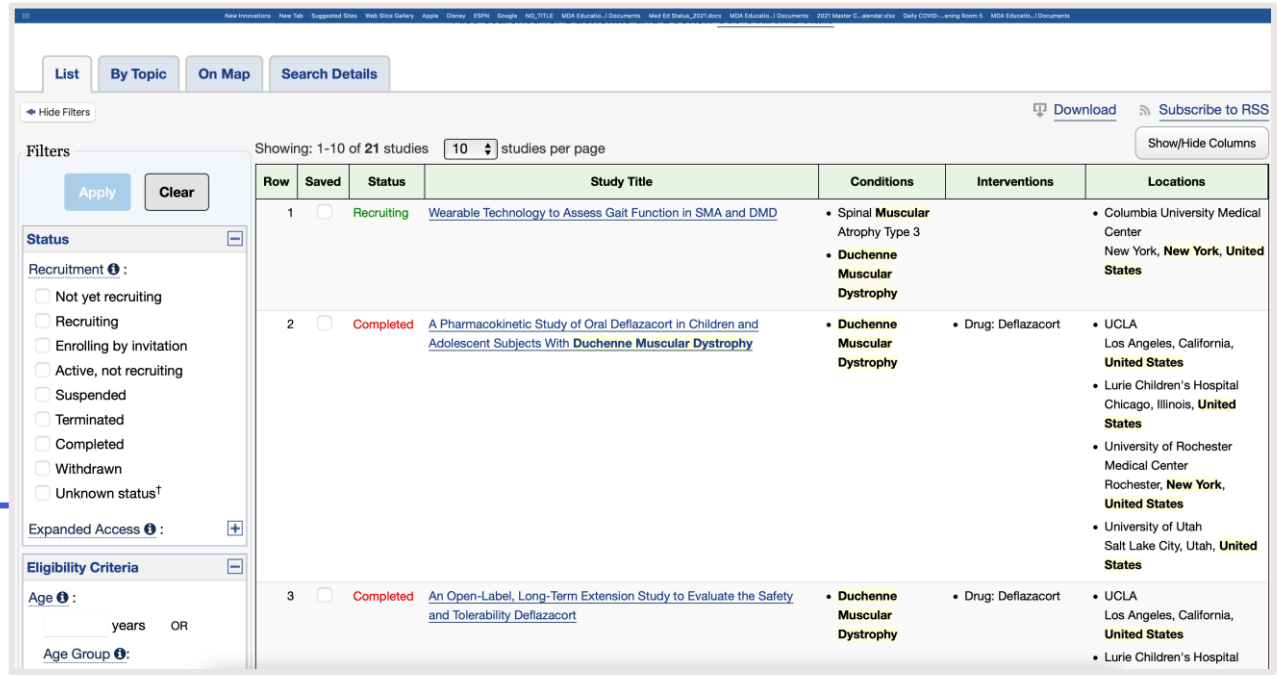


Example search on *Clinicaltrials.gov*:
- All studies
- Duchenne muscular dystrophy
- United States
- Within 50 miles of New York State

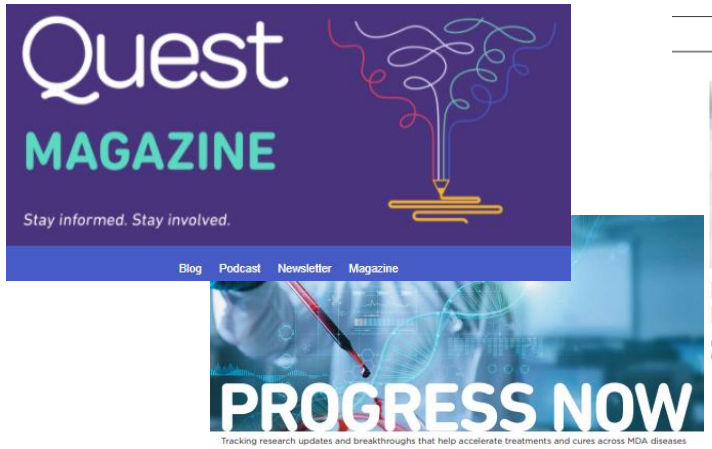
https://clinicaltrials.gov

Engage and educate patients: Develop resources for the office or clinic (cont)

- Utilize resources published by disease-specific organizations to share info with patients
- Display in clinic, make copies for patients to take home, request copies for reading room
- Refer patients to subscribe to MDA Quest magazine (MDA.org/quest)

Quest magazine

Progress Now research section announces CT openings



Quest blog

Clinical Trial Alerts posted as they open; option to receive as email alerts

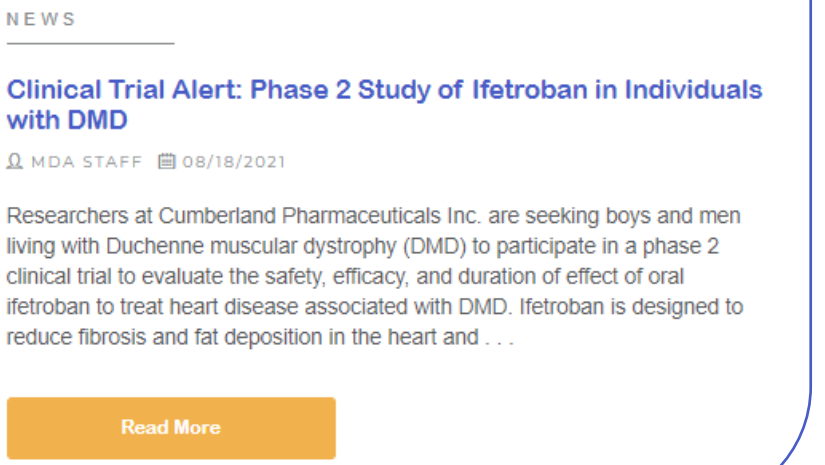


Image on left from MDA.org/quest. Quest Issue 3, 2021. Image on right from MDA.org.

Engage and educate patients: Express enthusiasm!

- Expressing enthusiasm for research can be contagious
- Patients can notice physician enthusiasm and may help increase their personal interest in learning more about study participation

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2. Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. *N Engl J Med*. 2017;377(18):1723-1732. doi:10.1056/NEJMoa1702752
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4. Day JW, Finkel RS, Chiriboga CA, et al. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy in patients with two copies of SMN2 (STR1VE): an open-label, single-arm, multicentre, phase 3 trial. *Lancet Neurol.* 2021;20(4):284-293. doi:10.1016/S1474-4422(21)00001-6
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