Workshop: Development of Evidence Packages for Regulatory and Reimbursement Submissions in Rare Diseases: Real-World Examples

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Participants

- Vasudha Bal: Director, Worldwide Health Outcomes, Value & Access, Novartis Pharmaceuticals Corporation
- Nicola Bonner: Senior Research Manager, Endpoint Development and Outcomes Assessment, Adelphi Values
- Anne Kilburg: Principal Consultant, Wellmera AG
- Alexandra Bowden: Senior Manager, Clinical Outcomes Research and Evaluation, Ultragenyx Pharmaceutical Inc.

2

Workshop Outline

- There are several unique challenges for developing evidence packages in rare diseases. These challenges will be discussed through four presentations:
  - The overall challenges of collecting data to support registration and reimbursement;
  - Challenges associated with developing clinical outcome assessments (COAs) and special considerations associated with clinical trials and regulatory approaches in rare diseases;
  - Evidence needs and requirements for HTA/payer bodies for a positive value assessment and reimbursement;
  - The case study of a healthcare professional administered COA for assessment of physical functioning limitations associated with a rare genetic disease.

3

Overall challenges of collecting data to support registration and reimbursement

Vasudha Bal
Director, Worldwide Health Outcomes, Value & Access,
Novartis Pharmaceuticals Corporation

Challenges creating evidence packages for drug registration in rare diseases

Identifying patients for a trial

- Small number of patients scattered across the globe
- Logistics and expenses

Finding appropriate endpoints

- Standards may not be established

Collecting QoL data

- Very few COA measures available that were developed per FDA Guidance

Retaining patients in trials over long trial periods

- Keeping investigators and patients motivated to stay on in a trial in multi year trials, especially in rare diseases where progression is slow

Issues with powering trials and missing data

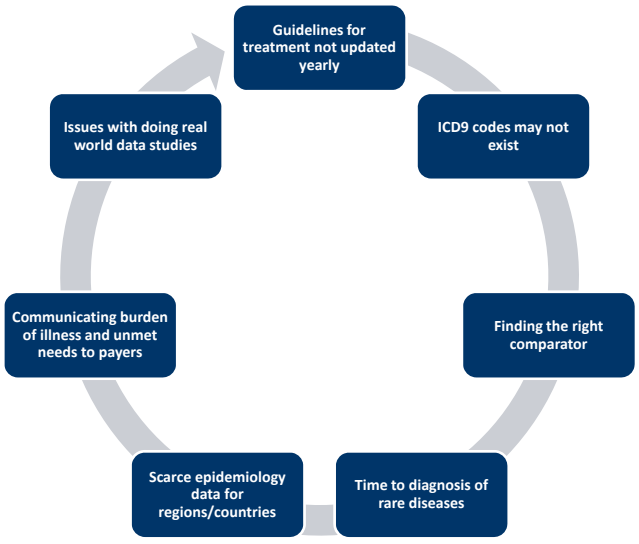
- Small room for errors and missing data

Identifying appropriate comparators and designing head to head trials

- Adapting trial design to meet trial design of other drugs could be challenging
- Sometimes the only other comparator may be approved only in a few countries

5

Challenges for creating reimbursement packages in rare diseases



6

Guidelines for diagnosis, monitoring and treatment

Unlike other therapeutic areas, treatment guidelines for rare diseases are updated once every few years

- Especially an issue if new drugs are approved right after a guideline
- These guidelines are used by payers for formulary/payer policy decisions

Rare diseases do not always have clear guidelines for diagnosis and monitoring patients over time

- Patients could be lost to follow up

If ICD9 codes do not exist...

Presents huge challenge, especially while planning for real world evidence studies

- Example, there was no ICD 9 code for Cushing's Disease, the closest was Cushing's syndrome
- Development of an ICD10 code required development of a case finding algorithm with KOLs and use of claims database analyses
- This algorithm needs to be further validated using medical charts – to confirm its sensitivity and specificity

Issues with RWE studies

Trying to find databases with rare disease populations that match with clinical trial populations? Good luck!

Solutions

Merge 2 very large claims databases

- Even with use of large databases – some analyses such as comparison of populations on two different drugs often not possible due to sample size problems
- Need to change scope of study and make the most of the available data

Collect data through chart review

- This can be very effective in identifying a large sample of patients, especially if using large specialist centers However – there are disadvantages to this – in that this does not provide information on community practice
- If one tries to obtain information on community practice – a chart study would NOT be feasible – as some centers may only have 1-2 patients (and therefore – would be very inexperienced in treating patients with these rare diseases – resulting in unreliable data)
- Limitations – We do not get patient insights into early stages of the patient journey including diagnosis patterns

Finding the right comparator

Off label use may be common because of considerable unmet need

- When we have a new agent to launch – it is difficult to identify what our comparator should be for economic models – if the only treatment options (as SOC) could be off-label agents
- Newer agents may only be approved in select markets so trial design and logistics could be a challenge
- Difficult to obtain reliable efficacy and safety inputs from these off-label agents for the models – in the absence of RCTs
- Lack of published data makes indirect comparison for payers challenging

Time to diagnosis could be long

Rare diseases may be misdiagnosed or have considerable time delay in diagnosis when physicians of various specialties may not be familiar with these conditions

- High rates of misdiagnosis (e.g., for Cushing's disease) may cause some challenges in the development and use of case-finding algorithms for this disease (e.g. high false positive rates).
- Some rare diseases –may have a wide variety of "non-specific" symptoms (e.g., obesity, diabetes etc.) – which then can cause some limitations in database evaluations designed for case identification (e.g., 32 comorbidities of Cushing's disease).

Scarce epidemiology data for regions/countries

Reliable country specific information on incidence and prevalence of rare diseases is not easy to find

- However reliable country-specific prevalence rates are needed for budget impact models
- Both regulators and payers – are interested in information on incidence and prevalence for indications that they are reviewing

Challenges with burden of illness studies

- Payers may not recognize the unmet need and burden of illness (BOI) for various rare diseases – where they have limited knowledge/experience with these rare diseases
  - This makes RWE very critical for describing BOI
- Payers may require a study to show real-world effectiveness of a new agent – before they will include in their formulary
  - A study collecting real-world effectiveness of a newly approved agent in a rare disease – may take quite a while to complete – given time needed to collect and follow a large enough sample of patients

13

Vasudha Bal
Novartis Pharmaceutical Company

Challenges associated with developing COAs and special considerations associated with clinical trials and regulatory approaches in rare diseases

Nicola Bonner
Senior Research Manager
Endpoint Development and Outcomes Assessment
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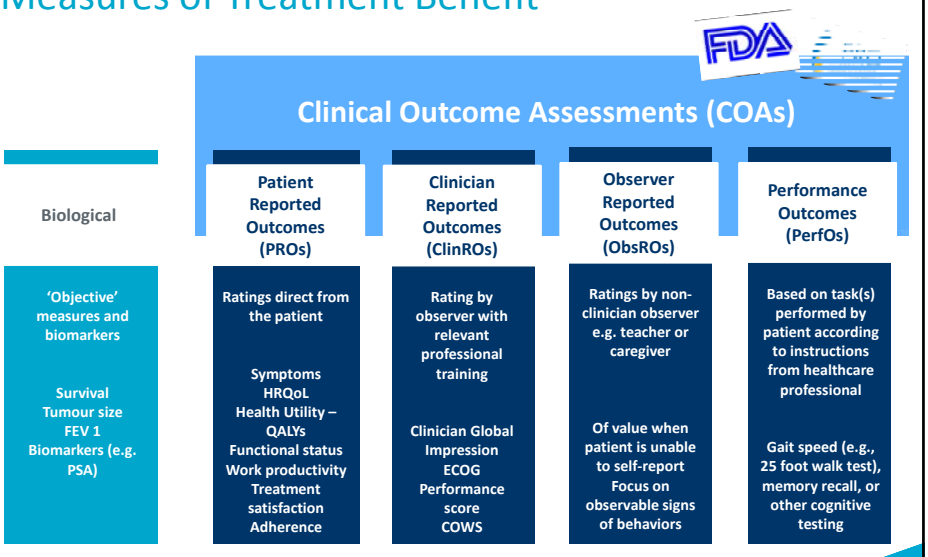
Clinical Outcome Assessments: Measures of Treatment Benefit



16

Overview of COA requirements

- Across all disease areas COAs need to be developed according to regulatory standards
  - FDA PRO Guidance
  - EMA Reflection Paper

- Also increasingly important that they meeting the needs of HTAs and payers
- Even with rare diseases sponsors need to ensure COA endpoints in their trials are 'fit for purpose' and appropriate for the 'context of use'
  - Important not just for regulators but also to ensure true treatment benefit can be demonstrated
  - An important consideration is often who is most appropriate to complete the assessment, i.e. the reporter

Source: U.S. Food and Drug Administration Centre for Drug Evaluation and Research Office of New Drugs

17

Challenges associated with COA development in rare diseases

What challenges have you faced in conducting qualitative or quantitative research to develop or validate clinical outcome assessments?

Sufficient background information about the diseases to understand the condition	Identification of participants for conducting research
Longer timelines than for non-rare conditions	Sufficient sample sizes to achieve robust results e.g. achieving saturation
Need to conduct research across multiple countries, or target specific countries or regions where incidence of the disease is more common	High levels of heterogeneity in the population
Identifying patients that are not currently on treatment or involved in clinical trials to take part in quantitative studies	Achieving required sample sizes sufficient to conduct and power analyses

18

How can difficulties in COA research in rare diseases be overcome?

- Engagement with specialist clinical sites and/or expert clinicians
- Engage patient advocacy groups
- Involve 'patient experts'

- Use creative qualitative research methods
  - Combined CE and CD interviews
  - Conduct interviews via telephone or video conference service
  - Use digital research options
- Use of natural history studies to understand the disease population ('context of use') and evaluate feasibility and appropriateness of COA instruments/endpoints

19

Special considerations/regulatory approaches for rare diseases

The examples provided below are based on experience of different projects worked on at Adelphi Values. Specific considerations for each sponsor or indication should be discussed with regulatory agencies.

Sample sizes

- Smaller sample sizes to support evidence requirements may be more acceptable than in non-rare or orphan indications.
- More acceptable to use patients for multiple phases of instrument development.

Population of interest

- Input from caregivers or clinicians rather than directly from patients in all cases.

Use of existing COAs

- Regulatory agencies may be open to use of existing COAs not necessarily developed for target indication with appropriate validation.

Quantitative studies

- Less emphasis on need for independent quantitative validation studies.
- Pooling of trial data may be acceptable.

Interactions with regulatory authorities

- The FDA in particular are open to regular interaction with sponsors
- Use of post-marketing studies to provide additional evidence

Conclusion: considerations for COA development in rare diseases

- Engage with regulators as much as possible throughout the development/submission process.
- Using or adapting existing instruments often an appealing approach BUT don't rule out instrument development.
- Use patients as key members of the development and validation process as they are very knowledgeable in their disease area.
- Think about how methods can be adapted/used creatively to maximise the samples you have access to.

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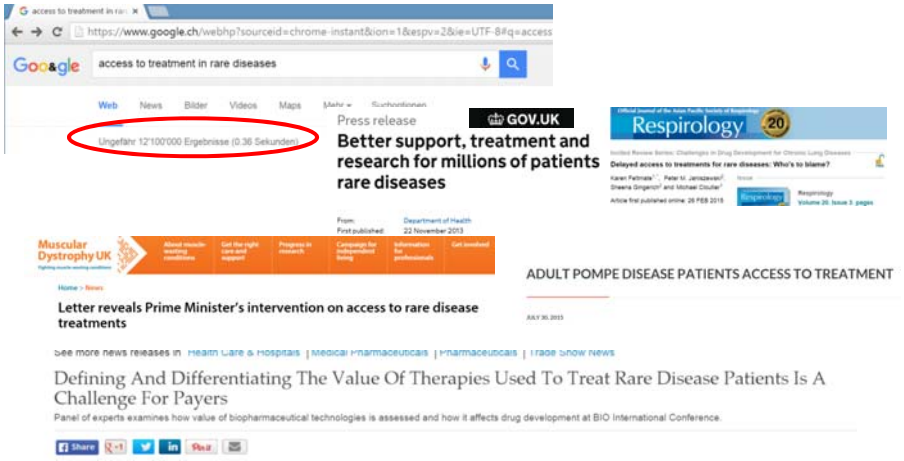
Evidence Needs and Requirements for HTA/Payer Bodies for a Positive Value Assessment and Reimbursement

Anne Kilburg, Wellmera AG

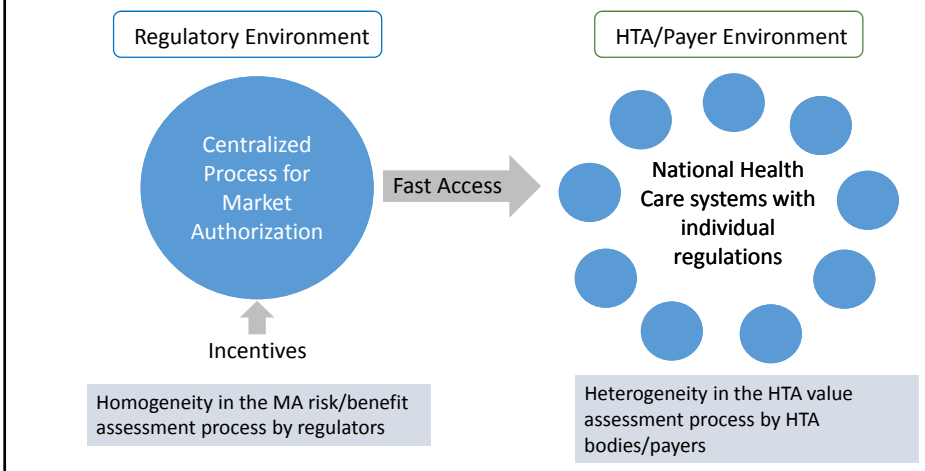
November 10, 2015

ISPOR 18th Annual European Congress, Milan, Italy

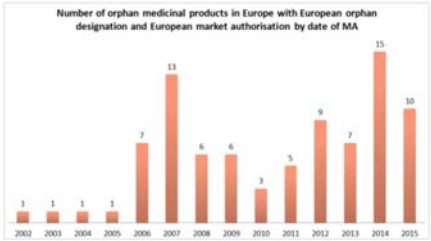
Increasing Interest in the Topic «Access to Treatment in Rare Diseases»

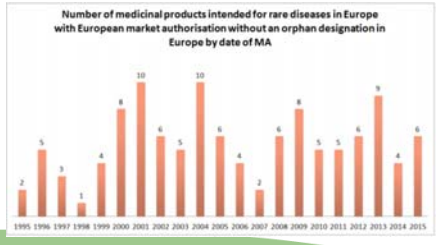


Regulatory vs HTA value assessment in rare diseases – Current Situation



Access to Treatments in Rare Diseases





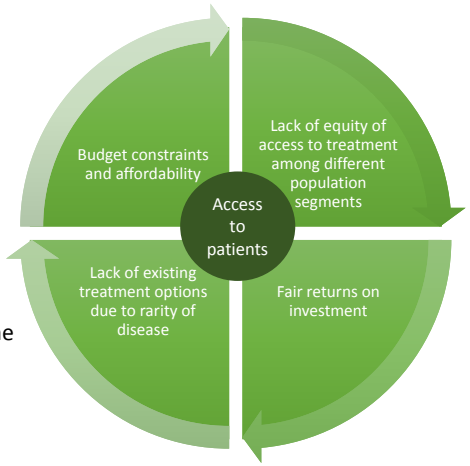
Source: www.orphanet.org

- The majority of rare disease/orphan drugs (OD) are antineoplastic and immunomudulating agents followed by ODs treatments used in metabolic diseases or the alimentary tract
- Despite MA, access to patients is not a given:
  - Only 34% of new drugs launched between 2005 and 2010 in one of six major markets were finally accessible to patients in all other five markets [1]
  - Access to ODs/rare disease treatments varies among geographies: Whereas 90% of ODs are available in France, NL, Denmark, only 33% are available in Spain, Greece and Romania [2]
- Since 1983, 7% more orphan drugs have been approved in the United States than in Europe [3]
- There are fewer denials of orphan drug coverage by U.S. payers than by European payers. [3]
- While U.S. payers often require prior authorization as a condition of reimbursement, European health authorities employ more stringent conditions (e.g. restrictions, coverage with evidence development). [3]

(1) Feltmate K et al, 2015
(2) Tordrup et al, 2014
(3) Tufts CSDD Report 2014

Challenges for HTA/Payers and Manufacturers

- Lack of cost-effectiveness
- High unmet need
- Paucity of information on the natural history of the disease



- Small, heterogeneous populations
- Limited evidence on treatment effect
- High development cost

Measures to incentivise developement and accelerate access to orphan drugs

Orphan Drug Legislation	Orphan Drug Marketing Authorization	Incentives	Reimbursement
Legislation, National Rare Disease Plans, Cross-border Regulation, Orphan Drug Designation	Accelerated Procedures, e.g. Fast-track approval, priority review	Financial and non-financial incentives, e.g. tax credits for research cost, marketing exclusivity; free scientific advcie and protocol assistance	Fast track HTA, relaxed criteria, post marketing surveillance, co-funding, managed entry schemes, e.g. Individual reimbursement, ATU, compassionate use




Sources: Todrup et al, 2014; Gammie et al., 2015

HTA/payer approaches to overcome challenges to the value assessment of a drug for funding and reimbursement

Standard HTA Evidence Criteria

- Demonstrating therapeutic benefit against an active and relevant comparator (e.g. H2H)
- Hard endpoints preferred, or surrogacy must be strongly validated
- HRQoL data: mainly use of utilities or well validated generic and disease-specific instruments in the target population
- Clearly defined eligible population
- Cost-effectiveness demonstrated
- Budget impact evaluated
- Level of innovation

HTA Criteria applied to rare diseases

- Policies for rare diseases in place
- Lower thresholds on efficacy and safety
- Lower significance levels of clinical benefit (higher levels of uncertainty) accepted
- By default benefit considered proven
- Consideration of unmet need
- Higher ICER thresholds accepted
- Economic data not considered in orphan drug assessments
- Alternative access routes (i.e. Specific funds, ATU etc.)
- Conditional reimbursement
- Involvement of patient groups
- Consideration of degree of innovation

29

Examples of HTA/Payer Value Assessments: The same evidence package can lead to very different Value assessment outcomes

Product	Clinical Data	Assessment Outcome					
		NICE	HAS	AIFA	SMC	G-BA	TLV
Teysuno (tegafur/ gimeracil/ oteracil) Advanced gastric CA	- Multicenter open-label Phase III RCT (n=527) - Active comparator arm - Teysuno + Cisplatin non-inferior to 5-FU + Cisplatin for the 1º endpoint – OS: 0.6 mo improvement, HR 0.94 [0.82, 1.07]						

30

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33

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Kalydeco (Ivacaftor) Cystic Fibrosis	- Two multicenter Phase III RCTs (n=213) - Placebo-controlled - Statistical significant benefit for 1° endpoint – FEV1 through 24 weeks - 55% less likely to have pulmonary exacerbations or worsening of symptoms requiring antibiotic treatment or hospitalizations						

34

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35

Conclusions

- Despite criteria for HTA assessments of treatments in rare diseases have been relaxed over time to facilitate and accelerate access to patients, there is still a huge heterogeneity in P&R outcomes between HC systems
- To address those challenges, drug developers should plan early in the development process:
  - Conduct horizon scanning on new precendent cases in the disease areas of interest and changes in HTA & coverage policies
  - Seek scientific advice with HTA and regulators early in the development process
  - Consider collecting evidence on value attributes outside the classical clinical and economic evidence
  - Consider different methods of evidence generation (i.e. adaptive trial designs etc.)
  - Use different qualitative and quantitative methods to assess the market access risk and inform investment decisions

36

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ultragenyx pharmaceutical

Development and Administration of a Disease Specific Scale for GNE Myopathy

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Topics

- Development and Administration of a Disease Specific Scale for GNE Myopathy
  - What is GNE Myopathy?
  - GNE Myopathy Patient Evaluation Study
  - Development of the GNE Myopathy-Functional Activities Scale (GNEM-FAS)
  - Examples of scoring the GNEM-FAS

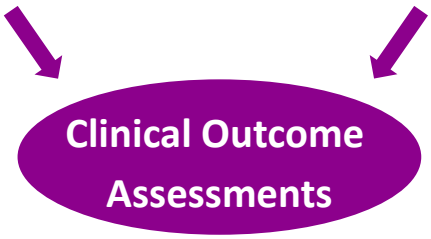
What is GNE Myopathy?

- An autosomal recessive myopathy presenting with distal leg weakness in early adulthood
- Progressive loss in muscle strength results in a characteristic pattern of profound weakness
- Upper and lower extremity muscle weakness eventually leads to limitations in physical function

GNE Myopathy Patient Evaluation Study

Functional outcomes
- Muscle strength (HHD*)
  - 6MWT*
- Walking speed test
  - Sit to stand
- Weighted arm lift

Patient reported outcomes
- Patient interviews/observations
  - Muscular Dystrophy Functional Rating Scales (MDFRS)
- Individualised Neuromuscular Quality of Life (INQoL)

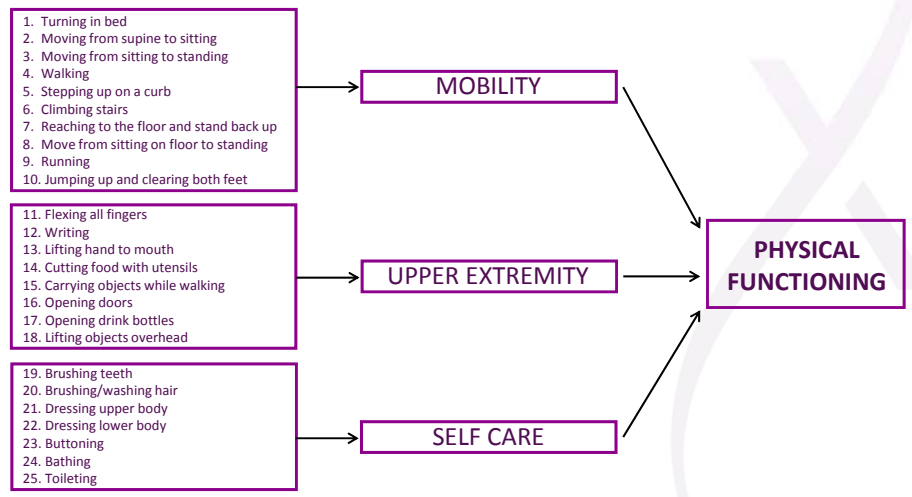


*HHD=hand held dynamometry; 6MWT=6 minute walk test

Patient Evaluation Study: Results

- Lower and upper extremity muscle strength
  - Hand Held Dynamometry (HHD) able to quantify muscle weakness
  - Composite score was defined to reflect co-ordinated engagement of muscle groups required for gross motor function
- Lower and upper extremity function
  - Inefficient and compensatory gait based on 6MWT
  - Impaired gait speed and ability to change speed
  - Difficulty rising from standing position
  - Limitations in upper limb function
- Clinical Observation/Patient Interviews
  - Directly observe difficulty performing movements involving upper and lower extremities
  - Identify impact of GNE Myopathy on QoL and Physical Functioning

GNEM-Functional Activities Scale



GNEM-FAS: Scoring

- Rating scale: 0 – 4
  - 0 = DEPENDENT: unable or requires MAX assistance of person
  - 1 = DEPENDENT: requires MIN – MOD assistance of person
  - 2 = INDEPENDENT: WITH devices and/or external support
  - 3 = INDEPENDENT: slowly/some difficulty, NO external support or devices
  - 4= INDEPENDENT: NO limitations, NO compensations, NO devices
- Total score: 100
  - MOBILITY SUBSCORE = 40
  - UPPER EXTREMITY SUBSCORE = 32
  - SELF CARE SUBSCORE = 28
- Recall period: current and typical performance

GNEM-FAS: Psychometric Analysis

- Domain scores correlate well with relevant functional outcomes assessments
- Construct validity analyses demonstrated the relevance and the unique contribution of each item
- Repeated measurements within pre-defined stable patient populations demonstrate the test-retest reliability
- Able to discriminate between known groups of patients

GNEM-FAS: Mobility Example

- Items: moving from supine to sitting, sitting to standing
  - "To drag myself out of bed I have to pull on the covers to roll myself onto my side and then push on the bed to sit up. I pull on my legs and then place my feet on the floor before standing up."
- Item score:
  - 0 = DEPENDENT: unable or requires MAX assistance of person
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GNEM-FAS: Upper Extremity Example

- Items: lifting hand to mouth
  - "It's very hard for me to drink from a cup by myself. I need to have my elbow positioned on the table to support my arm in an upright position and a caregiver place the full cup (with a lid on) in my hand before I am able to drink from it."
- Item score:
  - 0 = DEPENDENT: unable or requires MAX assistance of person
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GNEM-FAS: Self Care Example

- Items: brushing teeth
  - "I am able take care of my personal hygiene but when standing to brush my teeth I need to lean against the wall or on my cane to maintain my balance while continuing to brush."
- Item score:
  - 0 = DEPENDENT: unable or requires MAX assistance of person
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Summary

- Results of the GNE Myopathy patient evaluation study led to the development of the GNEM-FAS
- Psychometric properties suggest that the GNEM-FAS is a valid and reliable outcome to assess physical functioning
- GNEM-FAS currently being evaluated in clinical trials
- Future potential to use GNEM-FAS in a clinical setting

Acknowledgements

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Nicola Bonner

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Questions?

51