EVALUATING THE VALUE OF WHOLE EXOME SEQUENCING FOR PARENTS OF CHILDREN WITH RARE GENETIC DISEASES

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OBJECTIVES: Patients with rare genetic diseases often experience a diagnostic odyssey, no diagnosis, or delay in obtaining a diagnosis, due to lengthy diagnostic work-ups. Whole-exome sequencing (WES) can rapidly identify the mutation(s) responsible for rare, single-gene diseases. Before incorporating this new technology into clinical practice, we must understand the value of diagnostic information. We aimed to identify key attributes surrounding the value of a diagnosis to each potential parent during the decision-making process.

METHODS: Using a multi-phase approach to identify attributes, we conducted an IRB-approved annual survey of adults (n=46-81), duration of diagnosis (6 months, 3 years, 5 years, 10 years).

RESULTS: The survey was administered to n=300 parents of children with rare diseases (diagnosed and undiagnosed) to evaluate willingness-to-pay for: WES, a diagnosis, and a faster diagnosis.

Conclusions: The DCE survey was pre-tested in a sample of parents of children with rare diseases (n=5) and attributes were further refined. Results: The DCE included six attributes, each with four levels: type of diagnostic (genomic sequencing, other genetic testing, operative procedures, series of tests and procedures), chance of a diagnosis (5/10, 4/10, 6/10, 9/10); negative impact of diagnostic test results (lifestyle restrictions, victim of discrimination, labeled by others, no impact); positive impact of diagnosis to treatment (symptomatic therapy, out-of-pocket costs $0, $10,000); time to obtain a diagnosis (6 months, 3 years, 5 years, 10 years).

Conclusions: The MSNQ, measuring mood/depression, reported reliability and content validity for MS patients. Although 9 CF-specific COAs were identified in this study, only the CFQ-R measures exhibit content validity and CFRSD appears potentially suitable for assessment of CF-related symptoms and impacts in CF clinical trials. Further data relating to content validity of CFQ-R may be required to support future labeling approvals.

PATIENT-REPORTED OUTCOME MEASURES FOR MULTIPLE SCLEROSIS PHASE IV CLINICAL TRIALS: A SYSTEMATIC REVIEW

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OBJECTIVES: To identify and appraise the reporting on psychometric properties of selected patient-reported outcome measures (PROMs) used in multiple sclerosis (MS) clinical trials, and to identify PROMs potentially suitable for Phase IV use. METHODS: We systematically searched PubMed, Clinicaltrials.gov, and MS conferences from 2009 onwards to identify PROMs used in MS Phase IV trials. For further assessment, we selected PROMs on health concepts: health-related quality of life (HRQoL), depression, fatigue, and cognition. These PROMs were appraised in the context of the U.S Food and Drug Administration guidance for work reporting on psychometric properties and feasibility of use. RESULTS: Nine CF-specific COAs were identified, Cystic Fibrosis Questionnaire-Revised (CFQ-R) [pediatric 6-11/12-13 years, 14+ years and parent-report 6-13 years] and Cystic Fibrosis Respiratory Symptom Diary (CFRSD) were selected for in-depth review. CFQ-R 14+ provided the most comprehensive conceptual coverage and assessing 52% of the conceptual scheme of the 505 COAs. Pediatric and parent-reported versions of CFQ-R assessed fewer concepts. All versions of CFQ-R have acceptable psychometric properties and are linguistically validated. It has also supported patient claims for respiratory symptoms. Limitations include the acceptability of a 2-week recall period and inconsistencies in concepts measured across pediatric and adult versions. CONCLUSIONS: Cystic Fibrosis Respiratory Symptom Diary (CFRSD) provides a comprehensive assessment of 83% of acute respiratory symptoms in people with cystic fibrosis (CF). Further data relating to content validity of CFRSD may be required to support future labeling approvals.

A NOVEL MEASURE TO ASSESS SELF-REPORTED PHYSICAL FUNCTIONING IN PATIENTS WITH SPORADIC INCLUSION BODY MYOSITIS (sIBM)

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OBJECTIVES: sIBM is a progressive idiopathic inflammatory myopathy characterized by atrophy and weakness of proximal and distal muscle groups with the knee extensors and wrist/finger flexors frequently involved as well as dysphagic processes. Progressive weakness results in a loss of independence and the need for assistive devices and supportive care. While no pharmacological treatments for sIBM are currently available, there is much interest in novel therapies. To gain a better understanding of the benefit of new therapies and track clinical progression, a patient-reported measure (PROM) of physical function, the sIBM Physical Functioning Assessment (sIFA), was developed. sIFA was rigorously developed in accordance with FDA PRO Guidance. This included literature review, medical expert and direct patient input. A single-visit, observational study involving sequential concept elicitation and cognitive debriefing interviews was conducted. Standard qualitative analytical methods were used to analyze patient responses, and test the reliability, content validity, and construct validity of the sIFA items.

RESULTS: Twenty concept elicitation and 19 cognitive debriefing interviews were conducted as well as consultation with six sIBM expert physicians. sIBM patients (n=78) varied in age (mean 67±15, range 46–81), duration of diagnosis (1–10 years), and functional impairment. The resultant FORMS consists of 11 items scored on a 0 (no difficulty) to 10 (unable to do) numerical rating scale. sIFA items are aligned with the functional impacts of sIBM described in the literature expert review and identified as relevant and important to sIBM patients. The draft conceptual framework includes items related to upper extremity, lower extremity, general function and swallowing. Cognitive testing of paper and ePRO versions support the sIFA as a robust tool in a broad range of populations.

UNDERSTANDING THE SUITABILITY OF CYSTIC FIBROSIS (CF)-SPECIFIC CLINICAL OUTCOMES ASSESSMENTS FOR CLINICAL TRIALS AND TO SUPPORT MEDICAL PRODUCT LABELING

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OBJECTIVES: To identify and review the suitability of cystic fibrosis (CF)-specific clinical outcome assessments (COAs) for clinical trial assessment of novel CF therapies and to support product labeling. METHODS: CF-specific COAs were identified and critically appraised. This included terms and via clinical trials. COA utilization in CF clinical trials and previous success in supporting product labeling was also explored. In line with best-practice, conceptual coverage of identified COAs was assessed by mapping items to a patient-centered conceptual model of CF symptoms and impacts. COAs with the most comprehensive conceptual coverage were further evaluated for content validity, psychometric properties and feasibility of use. RESULTS: Nine CF-specific COAs were identified, Cystic Fibrosis Questionnaire-Revised (CFQ-R) [pediatric 6-11/12-13 years, 14+ years and parent-report 6-13 years] and Cystic Fibrosis Respiratory Symptom Diary (CFRSD) were selected for in-depth review. CFQ-R 14+ provided the most comprehensive conceptual coverage by assessing 52% of the conceptual scheme of the 505 COAs. Pediatric and parent-reported versions of CFQ-R assessed fewer concepts. All versions of CFQ-R have acceptable psychometric properties and are linguistically validated. It has also supported patient claims for respiratory symptoms. Limitations include the acceptability of a 2-week recall period and inconsistencies in concepts measured across pediatric and adult versions. CONCLUSIONS: Cystic Fibrosis Respiratory Symptom Diary (CFRSD) provides a comprehensive assessment of 83% of acute respiratory symptoms in people with cystic fibrosis (CF). Further data relating to content validity of CFRSD may be required to support future labeling approvals.
regular sleeplessness symptoms and insomnia/SD. More women were affected, 67% of patients aged 65-74 (2.5 M) and 73% of patients age 75 (1.3 M) were female (p<0.05). Approximately 1.1 M patients age 65+ self-reported using a product containing DPH/DOX. Women were more likely to use DPH/DOX than men (21% [526 K] vs. 12% [150 K]) age 65-74 (p<0.05). 19% (348 K) vs. 11% age 75+ (76 K) (p<0.05). However, men using these products were reported to have a larger proportion of users, though men reported using these products more frequently. Further study on the use and safety of the OTC agents in older populations is recommended.

PND52 BURDEN OF ILLNESS FOR PATIENTS WITH FAMILIAL AMYLOIDOTIC POLYNEUROPATHY (FAP) BASINS EARLY AND INCREASES WITH DISEASE PROGRESSION
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OBJECTIVES: To examine quality-of-life (QOL) data from the pooled-protocol population (n=200) of two 18-week randomized clinical trials of ESL (045 and 046), both with an 8-week taper/conversion period and a 10-week efficacy period. The primary efficacy endpoint for these trials was study exit due to: worsening seizure type, increased seizure frequency (SF), or investigator judgment. Predictors of monotherapy treatment continuation after 10 weeks were examined using stepwise logistic regression. Covariates included ESL dose, demographics, disease duration, baseline SF, baseline AEDs, number of AEDs, change in SF, and changes in the QOLIE-31 subscale scores (Cognitive Functioning, Emotional Well-being, Fatigue, Medication Effects, Overall QOL, Seizure Worry [SW], and Social Functioning) during the taper/conversion period. A separate model included change in SF to test whether predictors were independent of efficacy during taper/conversion.

RESULTS: Change in SF during the 8-week taper period and the 10-week period was the only predictor of remaining on ESL monotherapy. Mean change was 9.6 (SD: 20.98) for 181 subjects remaining on monotherapy, indicating a reduction in worry. Mean change for 19 subjects who exited was -4.8 (SD: 20.79). Each point increase in SF was associated with a 3% increase in the odds of remaining on monotherapy (odds ratio [OR]: 1.03; 95% CI: 1.01, 1.06). Results were similar with inclusion of SF change in this model (OR: 1.03; 95% CI: 1.01, 1.06). CONCLUSIONS: In this pooled, per-protocol population analysis, change in a subject's level of seizure worry was moderately predictive of remaining on ESL monotherapy. This may be a surrogate for severity of epilepsy and the value of such predictors needs additional research and assessment.

PND54 A NOVEL CONCEPTUAL MODEL OF CYSTIC FIBROSIS BASED ON QUALITATIVE PATIENT RESEARCH
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OBJECTIVES: Despite the wealth of qualitative studies exploring the experiences of patients with cystic fibrosis (CF), currently no conceptual model of CF exists. Conceptual models are a valuable way to communicate relevant patient-centered concepts and guide future clinical trials and relationships between patients and health professionals. This study aimed to use patient-derived qualitative insights to develop a conceptual model of CF. A targeted literature review was performed to identify qualitative studies describing the lived experience of people aged ≥ 6 years with CF. CF social media forums were also reviewed to supplement the published data by providing patient-derived quotes where none were already in the literature. Data were coded using Atlas.Ti software, and analysed to develop the conceptual model. Where possible, any differences in concepts according to age were identified. RESULTS: 31 qualitative articles and 26 social media entries were reviewed, containing data from 2000 patients aged 6-67. Data from these sources were synthesized to develop a conceptual model of CF, comprising: 23 symptom concepts categorized into 3 domains (respiratory, gastrointestinal/urinary, flu-like symptoms), 28 impact concepts categorized into 9 domains (social, financial, difficulties, psychological, future concerns, daily activities, emotional, physical functioning, and work or school), sleep, and 5 treatment satisfaction concepts categorized into 2 domains (satisfaction with treatment administration, treatment adherence). Differences in impact concepts were apparent, based on the patient’s age (e.g. bullying was only reported by children and financial issues only by adults. CONCLUSIONS: To our knowledge, this is the first patient-centered conceptual model for CF, reflecting the symptom and impact burdens of CF on patients’ lives as identified through qualitative patient-derived data. As such, this model provides an important critical framework to assess the conceptual relevance and patient-centeredness of outcome assessments ahead of selection for future clinical trials and clinical practice.

PND54 AWARENESS AND KNOWLEDGE OF FOLIC ACID INTAKE FOR THE PREVENTION OF NEURAL TUBE DEFECTS AMONG WOMEN OF CHILDBEARING AGE
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OBJECTIVES: To assess the factors that affect taking folic acid supplements among women of childbearing age. METHODS: A baseline survey was conducted among women of childbearing age at West Virginia University (n=179) from January to March 2014. Multinomial logistic regression model was used to examine the factors that affect taking folic acid supplements. RESULTS: Around 42% of participants reported taking folic acid supplements. Factors that were associated with taking folic acid supplements use included awareness that folic acid prevent neural tube defects and perceived benefits that folic acid can prevent neural tube defects, and receiving advice from the doctor about using birth control. CONCLUSIONS: Although the women in this survey were aware and have knowledge that folic acid prevent birth defects; a large number of them reported not taking folic acid supplements. The reported potential association of of folic acid with current anti-epileptic drugs (AEDs). METHODS: Analysis of efficacy and QOL data from the pooled-protocol population (n=200) of two 18-week randomized clinical trials of ESL (045 and 046), both with an 8-week taper/conversion period and a 10-week efficacy period. The primary efficacy endpoint for these trials was study exit due to: worsening seizure type, increased seizure frequency (SF), or investigator judgment. Predictors of monotherapy treatment continuation after 10 weeks were examined using stepwise logistic regression. Covariates included ESL dose, demographics, disease duration, baseline SF, baseline AEDs, number of AEDs, change in SF, and changes in the QOLIE-31 subscale scores (Cognitive Functioning, Emotional Well-being, Fatigue, Medication Effects, Overall QOL, Seizure Worry [SW], and Social Functioning) during the taper/conversion period. A separate model included change in SF to test whether predictors were independent of efficacy during taper/conversion.

RESULTS: Change in SF during the 8-week taper period and the 10-week period was the only predictor of remaining on ESL monotherapy. Mean change was 9.6 (SD: 20.98) for 181 subjects remaining on monotherapy, indicating a reduction in worry. Mean change for 19 subjects who exited was -4.8 (SD: 20.79). Each point increase in SF was associated with a 3% increase in the odds of remaining on monotherapy (odds ratio [OR]: 1.03; 95% CI: 1.01, 1.06). Results were similar with inclusion of SF change in this model (OR: 1.03; 95% CI: 1.01, 1.06). CONCLUSIONS: In this pooled, per-protocol population analysis, change in a subject’s level of seizure worry was moderately predictive of remaining on ESL monotherapy. This may be a surrogate for severity of epilepsy and the value of such predictors needs additional research and assessment.

PND57 QUALITY-OF-LIFE PREDICTORS OF TREATMENT CONTINUATION ON ESICLABARZEPINE ACETATE MONOTHERAPY AMONG SUBJECTS WITH REFRACTORY PARTIAL-ONSET SEIZURES
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OBJECTIVES: To examine quality-of-life (QOL) predictors of treatment continuation on esiclabarzepine acetate (ESL) monotherapy (1200 or 1600 mg/day) among subjects with refractory partial-onset seizures associated with current anti-epileptic drugs (AEDs). METHODS: Analysis of efficacy and QOL data from the pooled-protocol population (n=200) of two 18-week randomized clinical trials of ESL (045 and 046), both with an 8-week taper/conversion period and a 10-week efficacy period. The primary efficacy endpoint for these trials was study exit due to: worsening seizure type, increased seizure frequency (SF), or investigator judgment. Predictors of monotherapy treatment continuation after 10 weeks were examined using stepwise logistic regression. Covariates included ESL dose, demographics, disease duration, baseline SF, baseline AEDs, number of AEDs, change in SF, and changes in the QOLIE-31 subscale scores (Cognitive Functioning, Emotional Well-being, Fatigue, Medication Effects, Overall QOL, Seizure Worry [SW], and Social Functioning) during the taper/conversion period. A separate model included change in SF to test whether predictors were independent of efficacy during taper/conversion.

RESULTS: Change in SF during the 8-week taper period and the 10-week period was the only predictor of remaining on ESL monotherapy. Mean change was 9.6 (SD: 20.98) for 181 subjects remaining on monotherapy, indicating a reduction in worry. Mean change for 19 subjects who exited was -4.8 (SD: 20.79). Each point increase in SF was associated with a 3% increase in the odds of remaining on monotherapy (odds ratio [OR]: 1.03; 95% CI: 1.01, 1.06). Results were similar with inclusion of SF change in this model (OR: 1.03; 95% CI: 1.01, 1.06). CONCLUSIONS: In this pooled, per-protocol population analysis, change in a subject’s level of seizure worry was moderately predictive of remaining on ESL monotherapy. This may be a surrogate for severity of epilepsy and the value of such predictors needs additional research and assessment.

PND59 QUALITY OF LIFE IN NEUROMYELITIS OPTICA: A SYSTEMATIC REVIEW
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OBJECTIVES: Neuromyelitis optica (NMO) is an inflammatory CNS disease, that presents with severe optic neuritis and transverse myelitis. It is often accompanied by severe motor and sensory disability. In the past few years, NMO has gained lot of inter- est and shares a controversial relationship with multiple sclerosis (MS). It is not yet known whether NMO differs in its effect on quality of life (QoL) when compared with MS. We aimed to evaluate the QoL in patients with NMO by conducting a systematic