

Pediatric Issues in Drug Development

Unique outcome measurement when including
pediatric population

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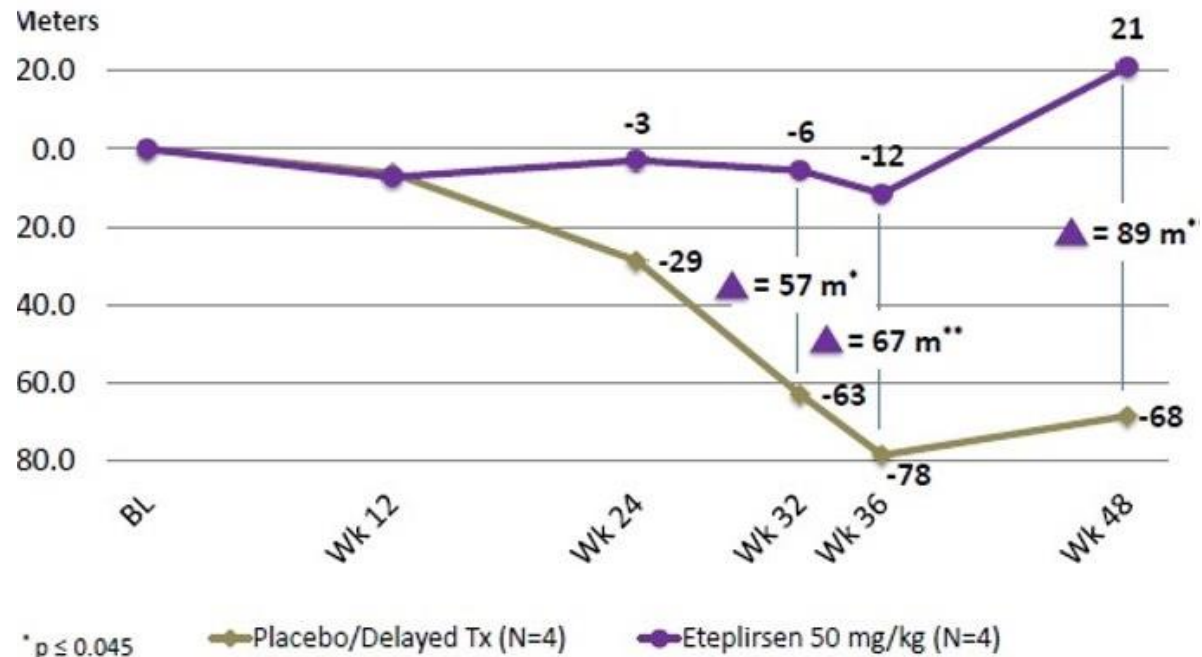
September 21, 2020

Agenda

- History – How we got here
- Issues in outcome measures
- Strategies that can be used to find more novel outcomes
- What has worked and what has not
- Partnerships
- Case study

6-Minute Walk Test Change From Baseline To Week 48

Intent-To-Treat Population: Eteplirsen 50mg/kg vs. Placebo/Delayed-Treatment



Note: Statistical analysis based on Intent-To-Treat Population using ANCOVA test

October
2012

FDA Interactions

April 2013: Dr. Woodcock & CDER to discuss experiences of patients on eteplirsen

CDER requests video & other evidence to support patient experiences

First PRO report given to FDA June 2013



Development of Quantitative Tool



Embarked on development of tool after FDA requested more quantitative data



Grew out of personal experience with disease and experience in trials



Developed personal PRO tool to evaluate effectiveness



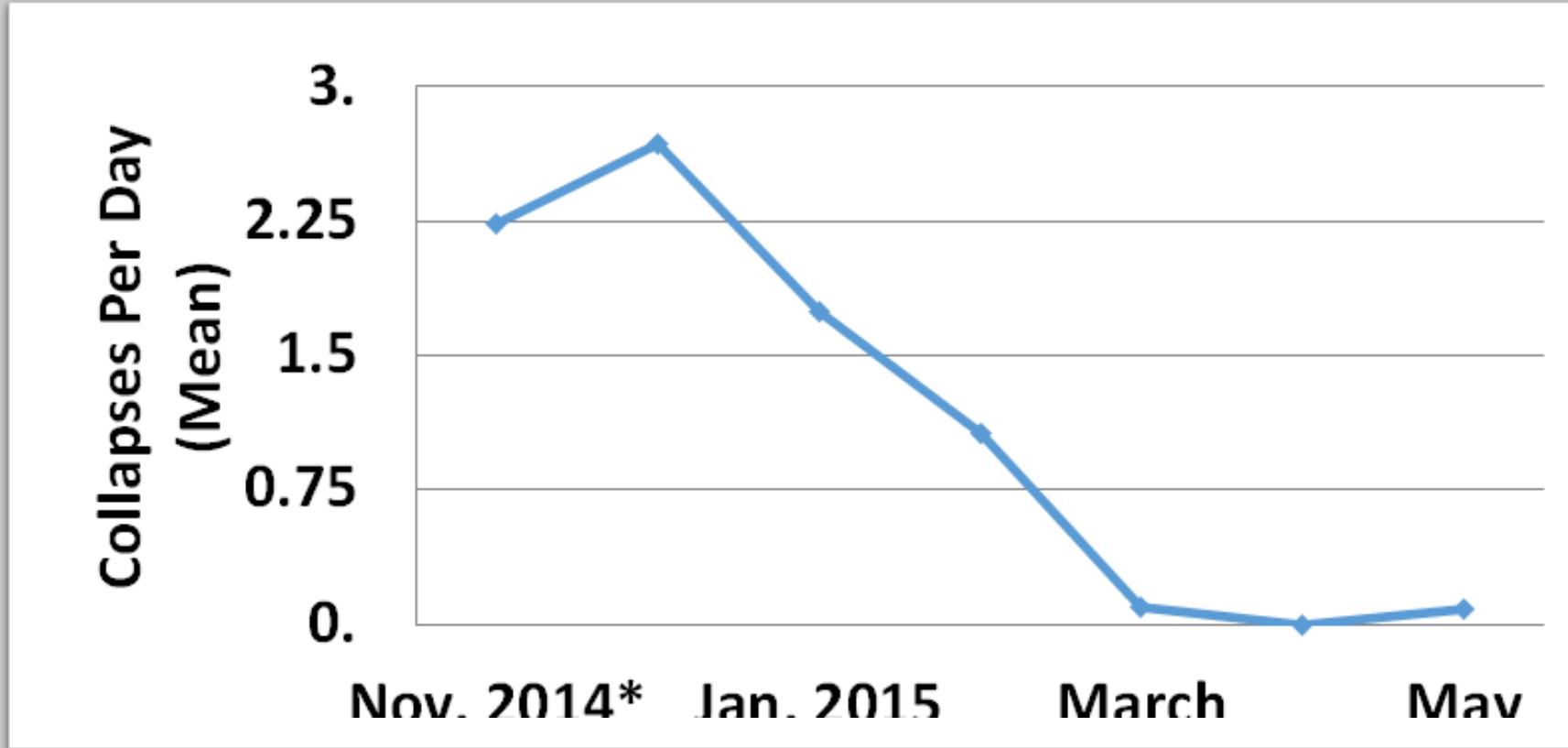
Semi-structured interviews



Rating scales



Additional videos



DIARY OF PATIENT SPONTANEOUS FALLS

Began study 204 in November 2014



What Caregivers Saw



What Caregivers Saw

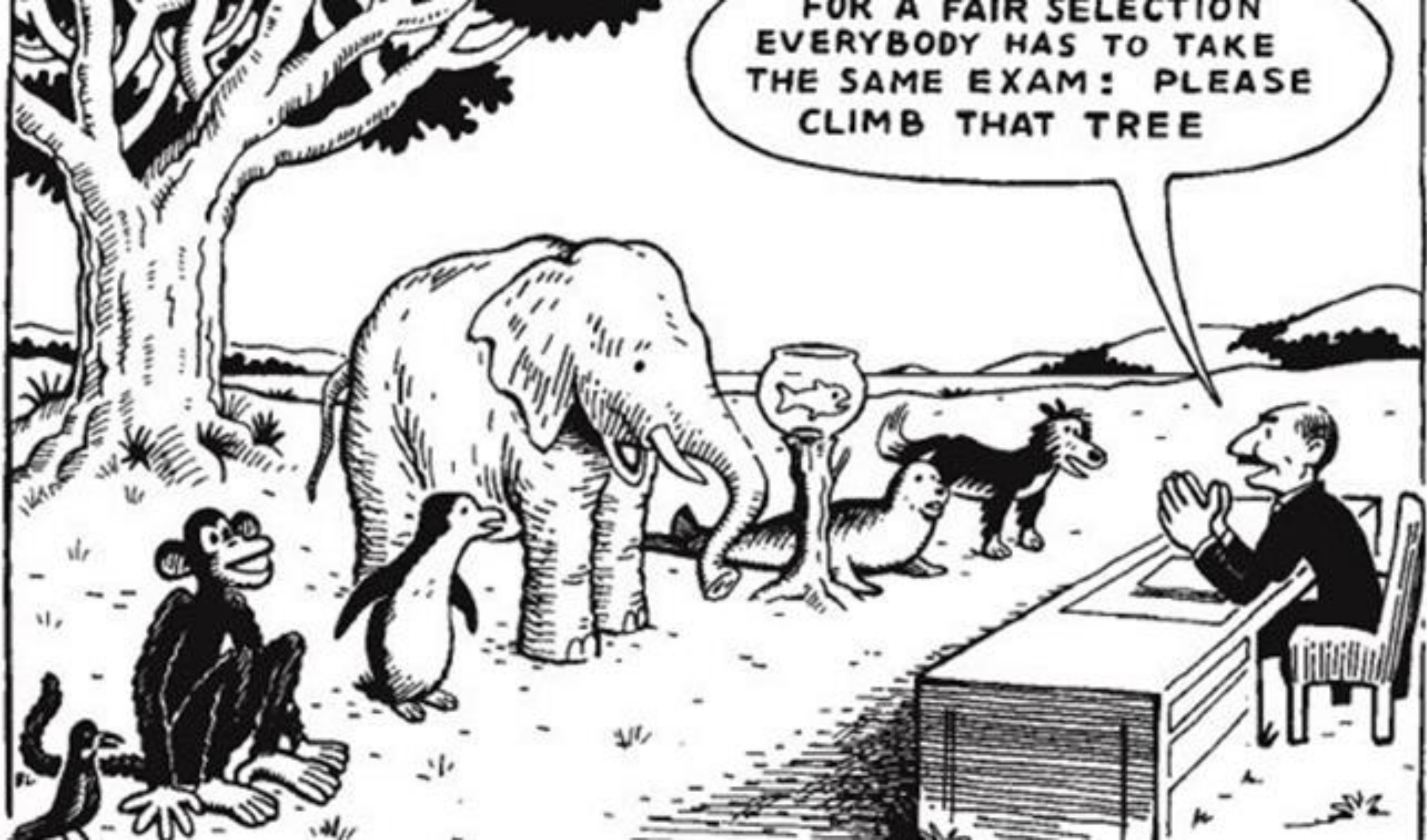


What Caregivers Saw



What Caregivers Saw

FOR A FAIR SELECTION
EVERYBODY HAS TO TAKE
THE SAME EXAM: PLEASE
CLIMB THAT TREE



How

- To capture and analyze patient and caregiver perception of change with sufficient rigor to allow it to become part of the totality of the data, allowing it to:
 - Determine efficacy
 - Inform future study design
 - Ensure access to effective therapies

Issues in existing outcome measures

- Heterogeneous population
- Important context is often missing
- Behavior can influence in-clinic capture (toddler refuse on command)
- May not be capturing what is meaningful to the patient/caregiver
 - Timed function testing
- Travel and medical anxiety can confound data
- Need to capture change in patient specific ways
- Rarely are the outcomes "patient informed"
 - Patient reported outcomes, surveys, in-clinic questionnaires, clin-RO

Mission: Capture Data that reflects what is meaningful to patients and their families

- Listen to the patient community
 - Using empathy, creativity, critical thinking
- Are the experiences and priorities reflected in current outcomes
 - Do they need to be modified
 - Should new ones be developed
- Is the concept of interest truly meaningful
 - 6MWT in DMD
- Is important context being captured or missed
 - Fatigue scales in mitochondrial disorder
- Does it account of patient heterogeneity
 - HQ in Prader Willi

Developing meaningful outcome measures

Qualitative Interviews

- Patients, caregivers and KOL's should inform the Qualitative Interview guide
- Done at screening, end of randomization and during OLE
- Specific questions that all for objective quantification of symptom trajectory
- Rates of caregiver reported, patient-specific change are compared between treated and placebo arms

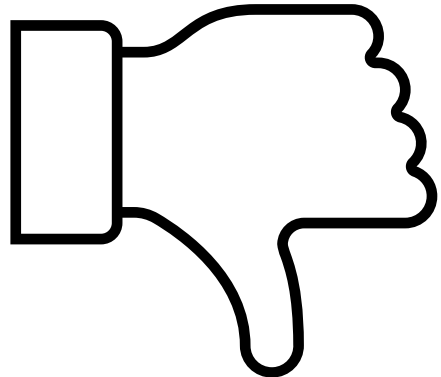
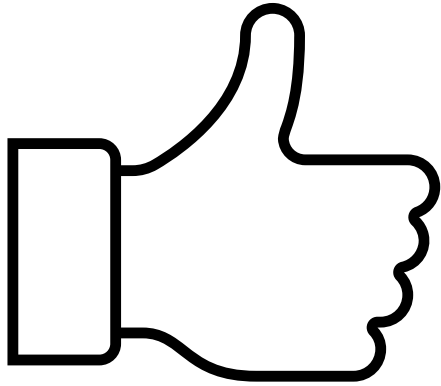
Mixed Methods

Combining Qualitative Interview with Remote Video Capture

- Goal is to capture onset, stabilization and evolution of disease hallmarks during an intervention
 - Video capture of each disease hallmark combined with QI conducted for context and caregiver impression of change
 - Video data can be captured before start up, baseline and prescribed timepoints during study
 - Captures caregiver impression of patient trajectory within each domain, critical when interpreting study results
 - Demonstrates feasibility of long term, remote follow up

Novel Outcome Design and Validation

- Sponsor selects from a menu of tasks based on trial inclusion criteria
- Caregivers watch training videos that standardizes capture procedures
- Caregivers capture their children performing those tasks in their home environment using a mobile app
- A QC check verifies that the videos have been captured properly and sends back any that do not meet the success criteria for reshoot
- Trained KOL's (DMD PT) serving as central raters, score for change in the video (MD compensations) with a validated scorecard
- The change over time is calculated over time



What has worked, what has not:

Partnering with patients, caregivers and the disease communities

Allowing patients to have improvement in symptom & patient-specific ways

Partnering with FDA via critical path for guidance

Allowing patients and caregivers to be repositories of data

Using a clinical outcome measure that doesn't give visibility to smaller, nuanced changes

Off the shelf, made for a different disorder outcome measure

Assessments that are not important to patients/families

Questionnaires, surveys and PROs that have recycled and riddled with queries that are either not relevant nor applicable to the participant (gallon of milk example)

Past studies in DMD with no definitive answers

- ·Tadalafil – vasodilator
 - ·Sildenafil - vasodilator
 - ·Epicatechin – mitochondrial
 - ·L-citrulline and metformin – NO donor
 - ·Suvodirsen – exon skipping
 - ·MNK-1441 – anti-inflammatory
 - ·Domagrozumab – myostatin inhibition
 - ·RG6206 – myostatin inhibition
 - ·Drisapersen – exon skipping
 - ·Exutromid – utrophin upregulation
 - ·Ataluren – stop codon
 - ·Halofuginone – anti-fibrotic
- ·Flavocoxid – anti-inflammatory
 - ·BMN-044 – exon skipping
 - ·EGCg – anti-oxidant
 - ·BMN-053
 - ·IGF-1
 - ·Penxotifylline – anti-inflammatory
 - ·Rimeporide – calcium/sodium
 - ·ACE-031 – myostatin inhibitor
 - ·Gentamycin – stop codon
 - ·Creatine and glutamate – unknown
 - ·CRD-007 – unknown
 - ·Oxatomide – anti-histamine

Remote Assessments

"Allowing the clinical trial experience to fit into the lives of patients & families"

- Better Trial Experience
 - Decrease patient burden
 - Offers a more equal opportunity for study participation
- Better Data
 - Home based capture can better reflect function in daily life – particularly pediatric and cognitively- affected population
 - Clinic data capture included confounds that are often not recognized or accounted for:
 - Travel fatigue
 - Clinic fatigue
 - Medical anxiety, trauma or depression
 - Vacation mode

Caregiver Perception of Change Example

- New Ability
- Can generate hypotheses about potential future standardized tasks

- Caregiver Choice
- Can more fully characterize the individual patients' trajectories

Underlying Quality & Sops

- Remote studies need to be run in accordance with well-defined SOPs and Study Specific Procedures
- SOPs:
 - GxP Documentation
 - Training
 - EConsent/Consent
 - TMF
 - AS Reporting
 - Protocol Deviation
 - Record Retention
 - Audit (Internal/External)
- GxP Documentation System
- GxP Training
- Software Development & Cycle
- IT Change Control
- Configuration and Version Control
- Quality Agreement
- Disaster Recovery
- Record Retention
- Secure and Data Policy
- Vendor Selection
- Electronic Signatures



Case Study

Standardized
Assessment

Case Study

Standardized
Assessment



Case Study

Standardized Assessment



Patient Specific Outcomes



Patient Specific Outcomes



Patient Specific Outcomes



Patient Specific Outcomes

A blue ribbon graphic with a 3D effect, featuring a dark blue shadow on the left and bottom edges. The text "Thank you!" is written in white on the top surface of the ribbon.

Thank you!

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