Rare Disease Endpoint Advancement Pilot Program Workshop: Novel Endpoints for Rare Disease Drug Development

June 7-8, 2023

FDA U.S. FOOD & DRUG ADMINISTRATION | Duke MARGOLIS CENTER for Health Policy

Welcome and Overview

Mark McClellan

Director, Duke-Margolis Center for Health Policy

Statement of Independence

The Robert J. Margolis, MD, Center for Health Policy is part of Duke University, and as such it honors the tradition of academic independence on the part of its faculty and scholars. Neither Duke nor the Margolis Center take partisan positions, but the individual members are free to speak their minds and express their opinions regarding important issues.

For more details on relevant institutional policies, please refer to the Duke Faculty Handbook, including the Code of Conduct and other policies and procedures. In addition, regarding positions on legislation and advocacy, Duke University policies are available at http://publicaffairs.duke.edu/government.

Remote Participation Instructions

Mute & Slides

- **You have been placed on mute**; speakers can mute/unmute throughout

Questions

- Please feel free to type your question into the Q&A box and we will use your questions to inform the open discussion portion of the event

Zoom Issues? Please Zoom message Rasheed Willis or email rwillis@newmediamill.com

Day 1 Meeting Agenda

1:00 pm	Welcome and Overview
1:10 pm	Opening Remarks from FDA
1:25 pm	Session 1: Considerations in Developing Rare Disease Endpoints: Digital Health Technology (DHT)
2:15 pm	Session 2: Considerations in Developing Rare Disease Endpoints: Biomarker Surrogate Endpoints
3:05 pm	Break
3:20 pm	Session 3: Considerations in Developing Rare Disease Endpoints: Clinical Outcome Assessment (COA)
4:10 pm	Session 4: Considerations in Developing Rare Disease Endpoints: Multiple Endpoints, with a Focus on Multicomponent Endpoints
4:55 pm	Closing Remarks and Adjournment

All times listed in ET

Day 2 Meeting Agenda

1:00 pm	Welcome and Overview
1:10 pm	Session 5: RDEA Pilot Program Overview
1:40 pm	Session 6: RDEA Pilot Program – Process Overview
2:10 pm	Session 7: Elements of RDEA Proposals and Meetings
2:40 pm	Session 8: RDEA Pilot Program Q&A
3:05 pm	Break
3:20 pm	Session 9: Experiences and Lessons Learned from Other Meeting Pilot Programs
4:00 pm	Session 10: Public Comments
4:25 pm	Closing Remarks and Adjournment

All times listed in ET

FDA Opening Remarks

Peter Stein, Center for Drug Evaluation and Research (CDER)

Celia Witten, Center for Biologics Evaluation and Research (CBER)

Submitting Written Comments

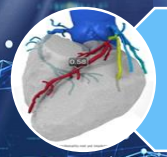
Reminder - stakeholders may submit written comments regarding this event to regulations.gov until July 23, 2023.

Session 1: Considerations in Developing Rare Disease Endpoints: Digital Health Technology (DHT)

1:25 – 2:15 pm ET

Digital Health Technology

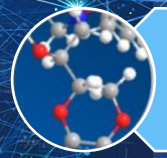
"A system that uses computing platforms, connectivity, software, and sensors for healthcare and related uses"*



Used as a medical product

Incorporated into a medical product (include a pharmacologic product)

Used to develop a medical product



Used to study a medical product

Used as a companion or adjunct to a medical product, including diagnostics and therapeutics.

*Definition from FDA-NIH BEST Glossary. Available at https://www.ncbi.nlm.nih.gov/books/NBK338448/

There is a large spectrum of DHTs available for potential use

DHTs may take the form of hardware and/or software

Consumer general wellness product (e.g., sleep monitor, basic pedometer)

Electronic patient-reported outcome (ePRO) instrument

Continuous blood glucose monitor

Digital therapy virtual reality device

Electrocardiograph (ECG) software for over-the-counter use

Portable electroencephalogram (EEG)

DHTs should be fit-for-purpose when used in a clinical investigation

Fit-for-purpose: a conclusion that the level of validation associated with a DHT is sufficient to support its proposed use in the clinical investigation

- Clinical event or characteristic of interest
- Ability of DHT to measure clinical event or characteristic of interest
- Population of interest, including age, technical aptitude, and education level, as appropriate
- DHT design and operation (for example, physical properties, power needs, alerts)

Applies to bring your own DHT or general-purpose computing platform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Development of movement monitoring device and SV95C

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Muscular Dystrophy UK
Fighting muscle-wasting conditions
MDUK Oxford Neuromuscular Centre

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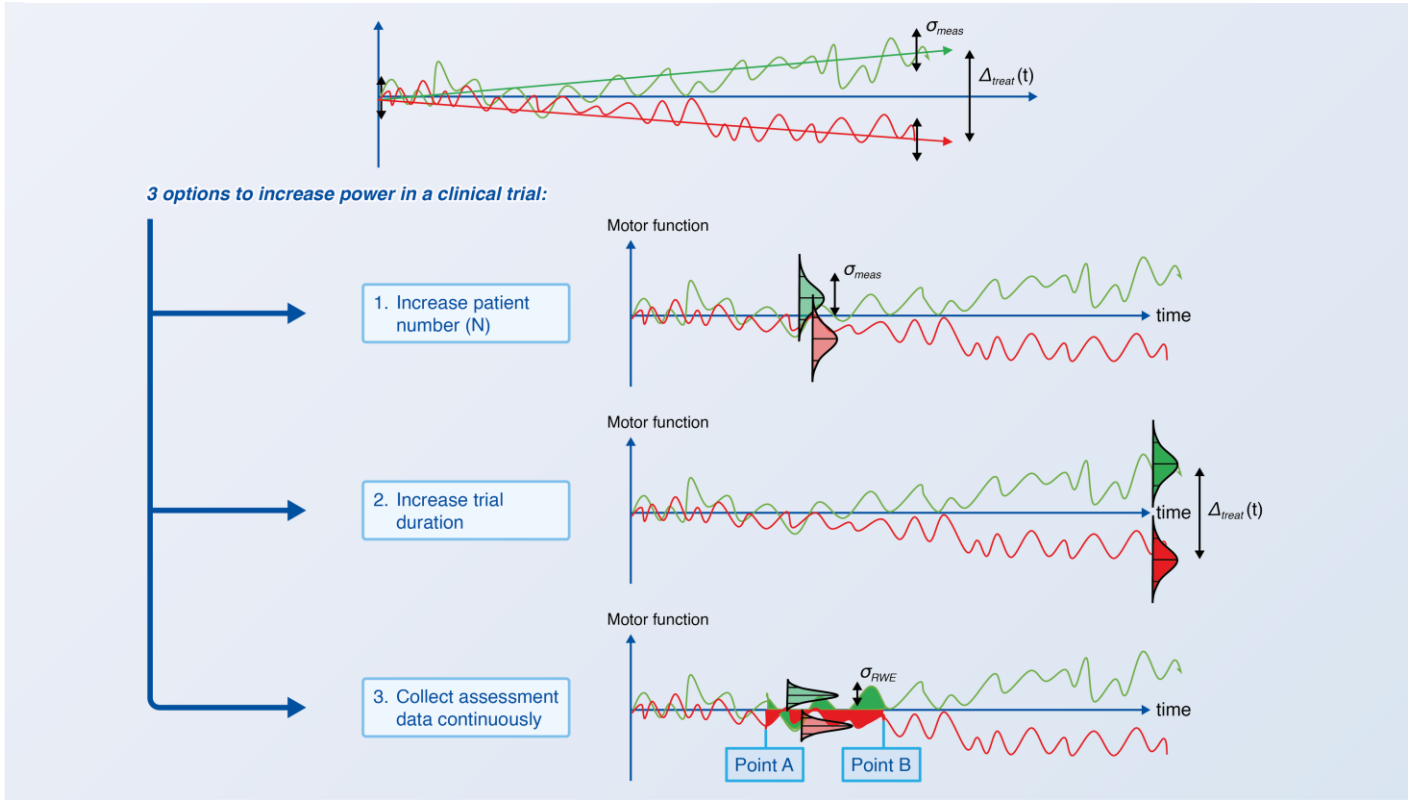
Characteristic	Central nervous system therapies	Non-central nervous system therapies
Probability of success in phase 3, %	46	66
Probability of success overall, %	8	15
Phase 2 and 3 development time, years	8.1	6.1
New drug application to approval time, years	1.9	1.2
Average number of patients in trials	10,000–60,000	300–500
Average cost of development	$1–5 billion	$600 million–$1 billion

Source: Tufts Center for Drug Discovery and Development, 2012 [45].



Background

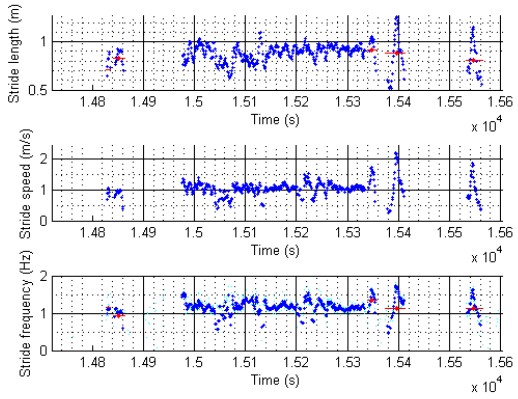
Clinical Gold Standard → New Biomarker Qualification

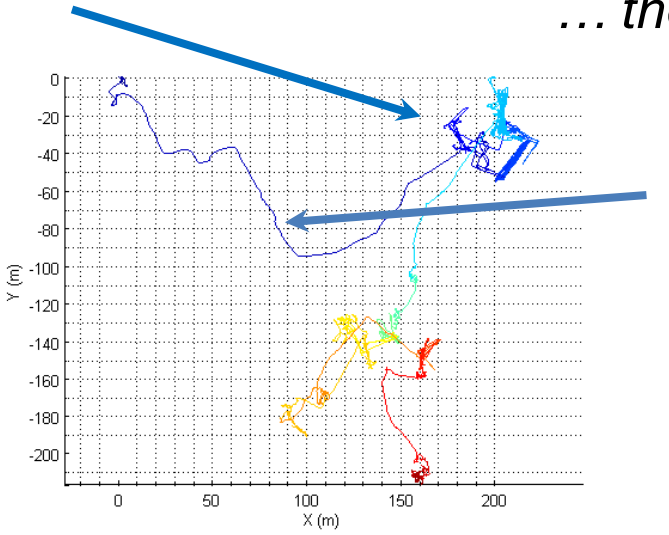
Major challenges of current state (2)

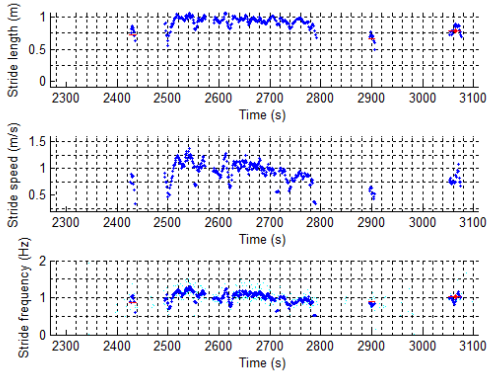
Short duration tests are deeply influenced by patients reflexes, longer tests by motivation

Patient performs the 6MWT...

… then flies away after







Background

Clinical Gold Standard → New Biomarker Qualification

Major challenges of current state (3)

Patients with rare disease may travel a lot to access the research center

npj | digital medicine

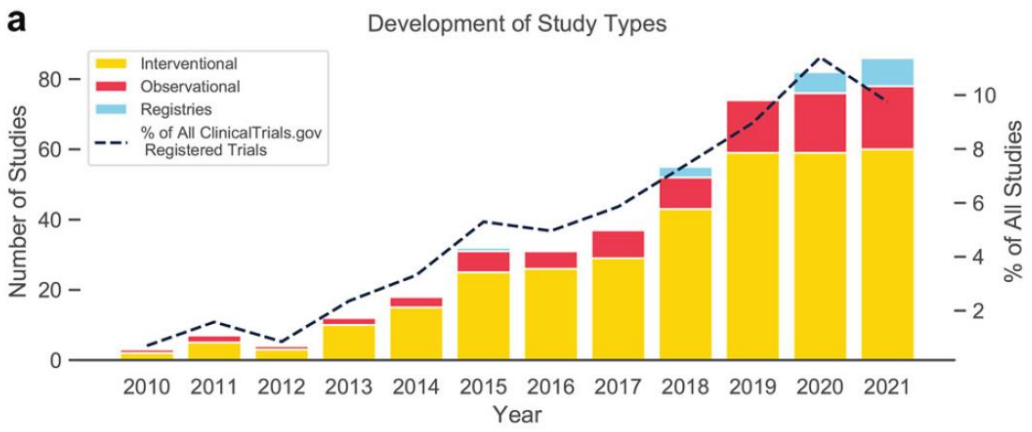
www.nature.com/npjdigitalmed

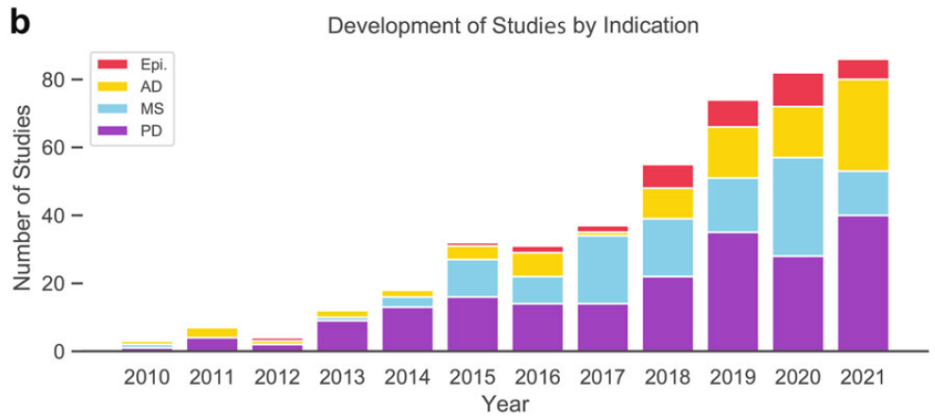
BRIEF COMMUNICATION OPEN

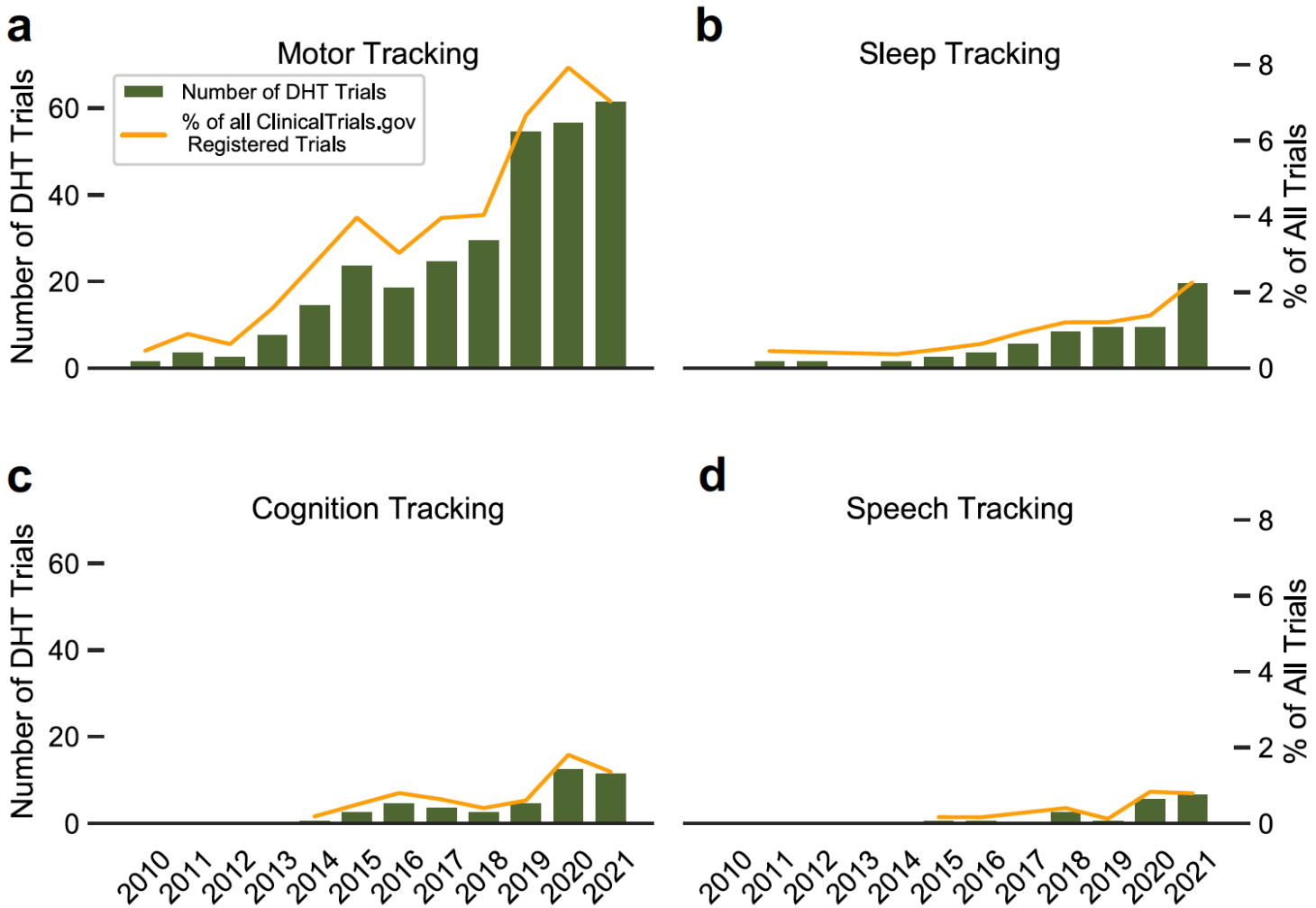
Check for updates

Evidence from ClinicalTrials.gov on the growth of Digital Health Technologies in neurology trials

Lars Masanneck[1,2], Pauline Gieseler[2], William J. Gordon[3,4,5], Sven G. Meuth[1] and Ariel D. Stern[2,6,7]✉






a
Motor Tracking
Number of DHT Trials
% of all ClinicalTrials.gov Registered Trials
Number of DHT Trials
% of All Trials
b
Sleep Tracking
c
Cognition Tracking
d
Speech Tracking
0
20
40
60
0
2
4
6
8
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021

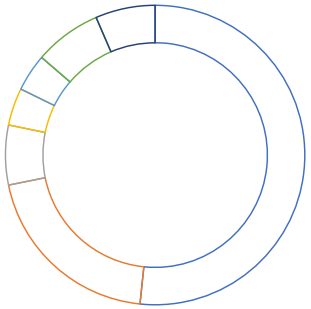
Systematic review of wearable technology in Rare Diseases

Neuromuscular Diseases

	Number of studies	Number of patients
DMD	18	550
ALS	15	2323
CMT	6	392
DM	4	142
FSHD	4	70
MG	2	60
SMA	1	81
SBMA	1	54
Dermato- myositis	3	79
Pompe disease	2	54
TOTAL	56	3605

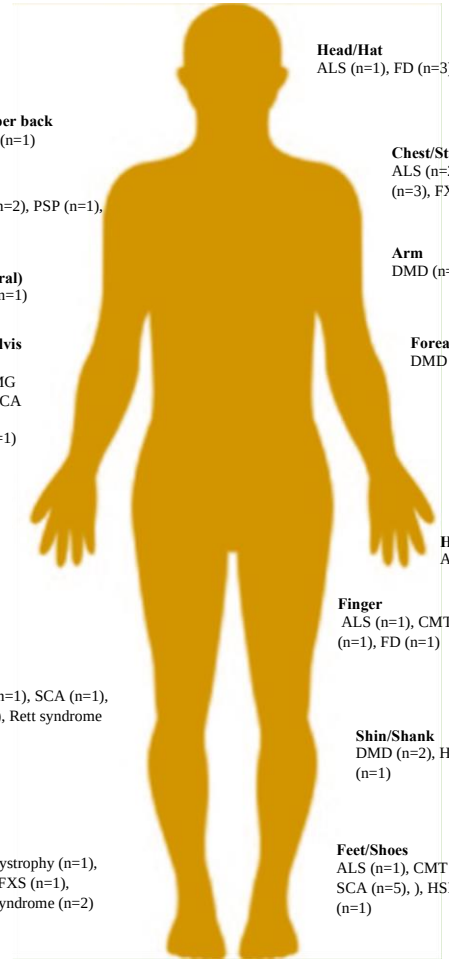
Poleur et al. in revision

Proportion of studies based on the number of sensors used



1 2 3 4 5 6 Unknown

Other
Wheelchair DMD (or trousers, n=1), SMA (n=1)
Bra/Belt/Pocket Pompe (n=1), HD (n=1)
Tee-shirt DMD (n=1)
Unknown ALS (n=1), HD (n=4), SBMA (n=1), Fabry (n=1), Narcolepsy (n=1), GM2 (n=1), Sarcoidosis (n=2)
Spoon FRDA (n=1)



Head/Hat
ALS (n=1), FD (n=3)

Upper back
HD (n=1)

Chest/Sternum
ALS (n=2), CMT (n=2), FSHD (n=2), HD (n=5), PSP (n=1), FD (n=1), SCA (n=3), FXS (n=2), PWS (n=1)

Trunk/Core/Torso/Thorax
DMD (n=2), ALS (n=2), HD (n=2), PSP (n=1), FRDA (n=1), Rett (n=1)

Arm
DMD (n=1), CMT (n=1), Sarcoidosis (n=1), Scleroderma (n=1)

Upper limb (general)
ALS (n=1), SCA (n=1)

Lower back/Waist/Lumbar area/Hip/Pelvis
DMD (n=1), ALS (n=2), CMT (n=1) myotonic dystrophy (n=2), FSHD (n=2), MG (n=2), HD (n=10), PSP (n=5), FD (n=1), SCA (n=6), FXS (n=2), Dermatomyositis (n=2), PWS (n=6), Rett syndrome (n=1), TSC (n=1)

Forearm
DMD (n=2), HD (n=2)

Wrist
DMD (n=7), ALS (n=1), myotonic dystrophy (n=1), FSHD (n=2), SMA (n=1), HD (n=8), PSP (n=2), SCA (n=4), FXS (n=1), FRDA (n=1), MPS (n=1), NPC (n=2), TSC (n=1)

Hands
ALS (n=1), FD (n=2), SCA (n=2)

Lower limb (general)
ALS (n=1) , SCA (n=1)

Finger
ALS (n=1), CMT (n=1), PSP (n=1), FD (n=1)

Thigh
CMT (n=1), HD (n=2), PSP (n=1), SCA (n=1), Sarcoidosis (n=1), PWS (n=1), Rett syndrome (n=3)

Shin/Shank
DMD (n=2), HD (n=1), PSP (n=1), SCA (n=1)

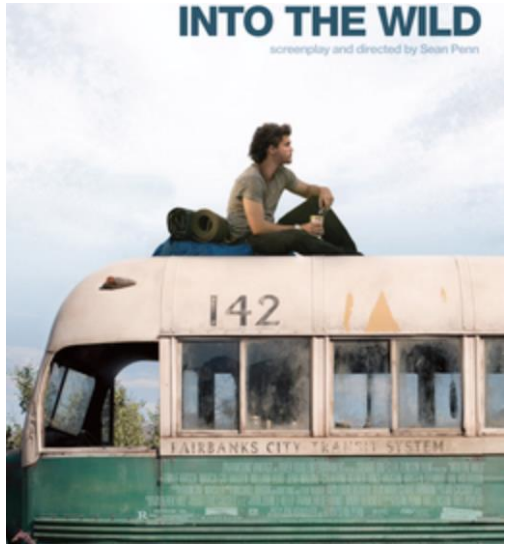
Ankle/Distal tibiae
DMD (n=5), CMT (n=2), myotonic dystrophy (n=1), FSHD (n=2), HD (n=2), SCA (n=1), FXS (n=1), Sarcoidosis (n=1), PWS (n=2), Rett syndrome (n=2)

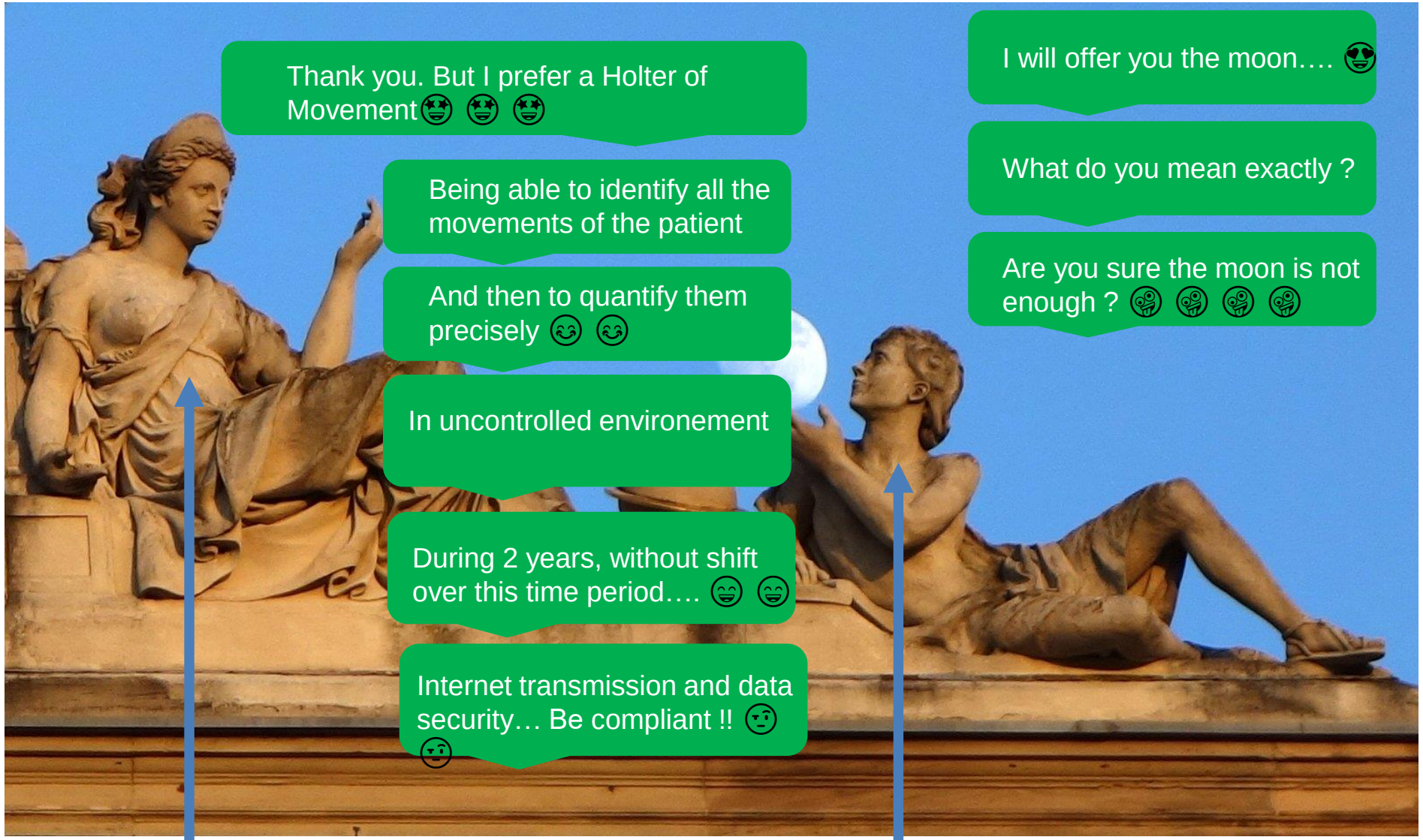
Feet/Shoes
ALS (n=1), CMT (n=2), HD (n=4), PSP (n=3), SCA (n=5),), HSP (n=3), FXS (n=1), FRDA (n=1)

So why are wearable devices not more used as primary outcome ??

What can I do with that ??

Clinical trial



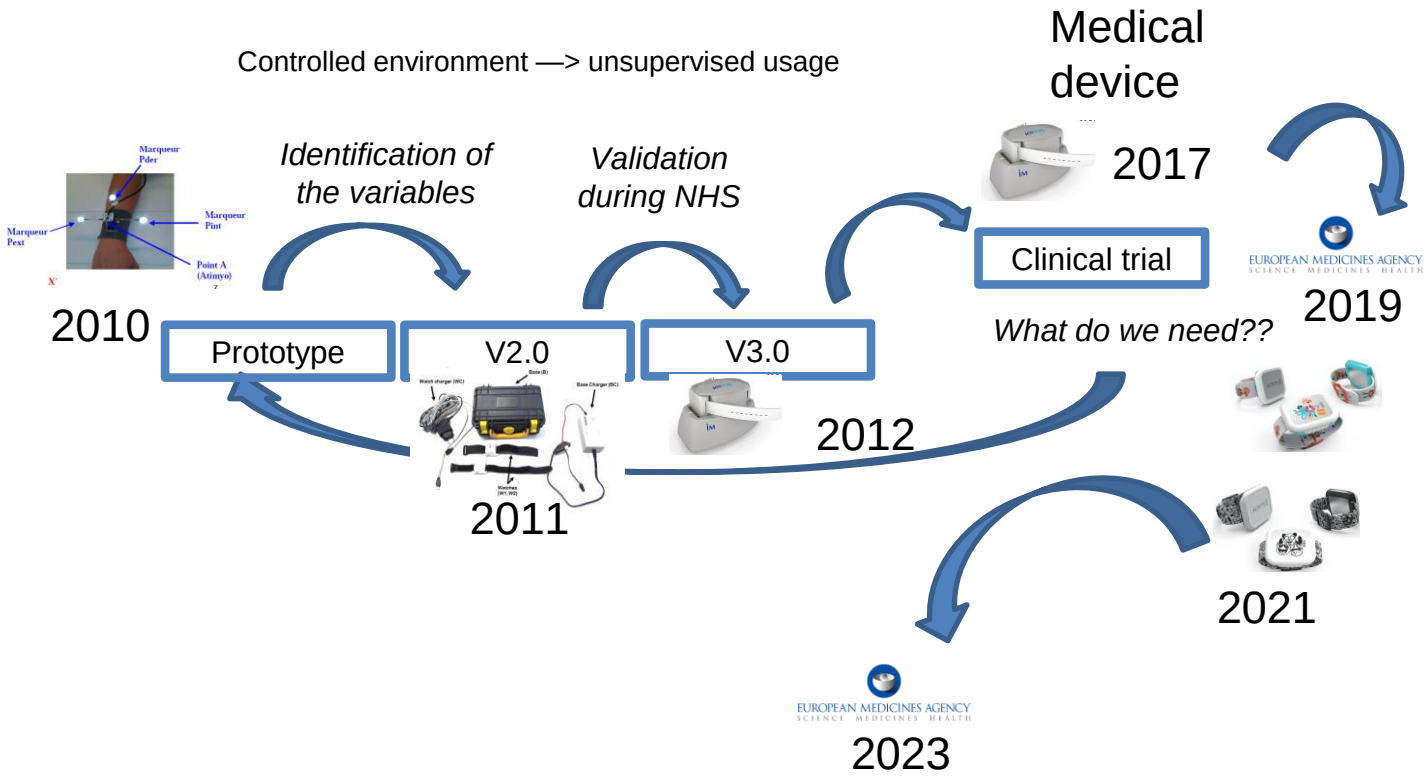


The doctor

The engineer

The long and winding road of hardware design

Technical development timeline



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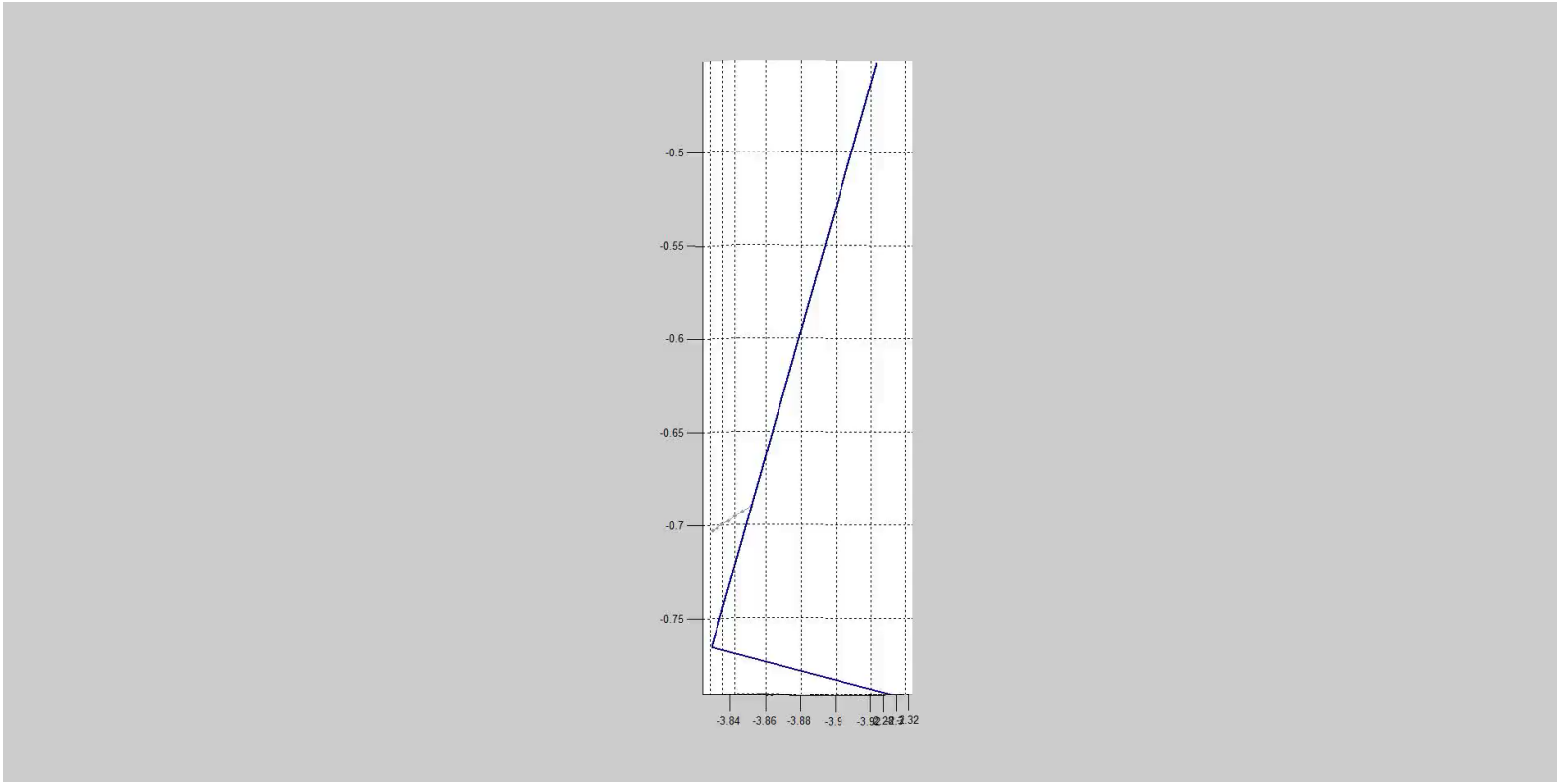
Gait analysis for ambulatory subjects

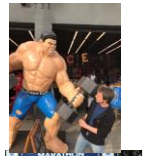


2 weeks

Mountain of data

Symptoms

Power



Fatigue

Activity

Falls

Ataxia

Abnormal movments

Objective

Signal of action

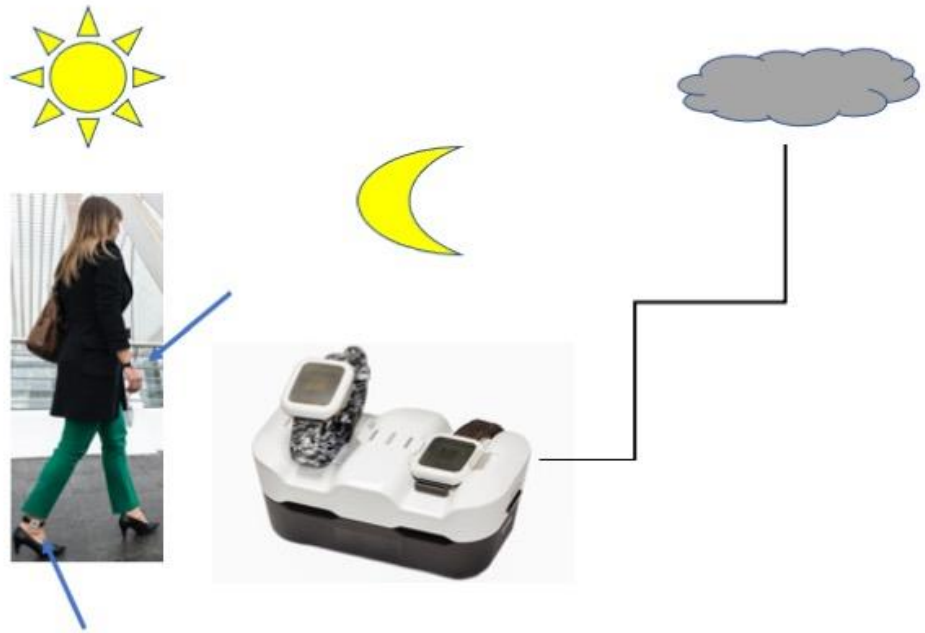
Pivotal trial

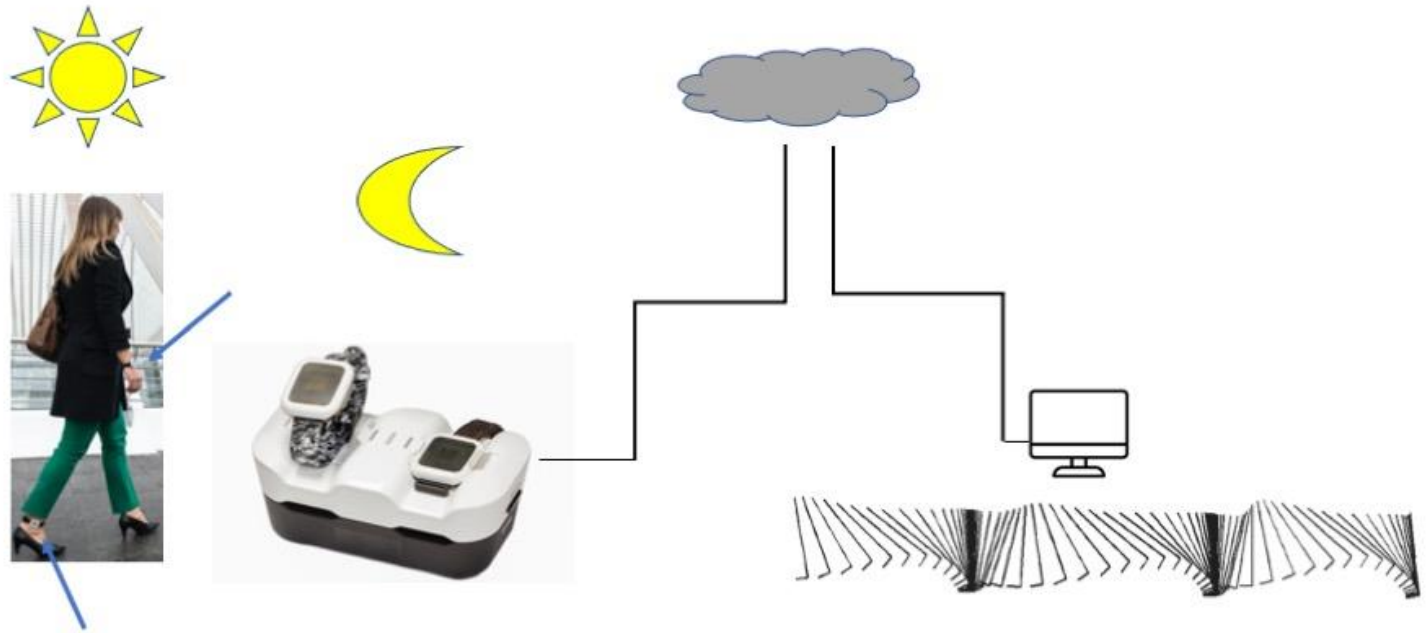
Payers

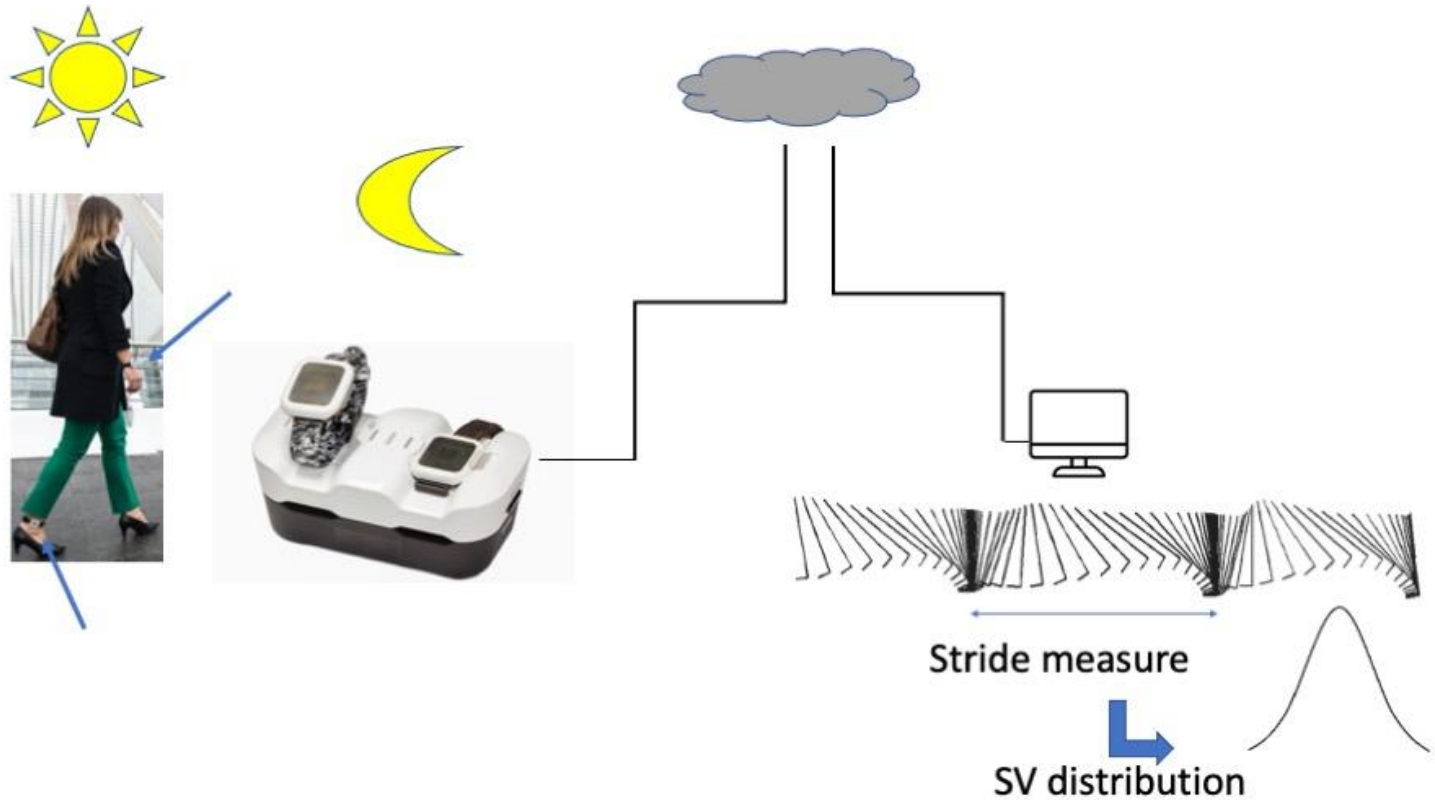
Patients

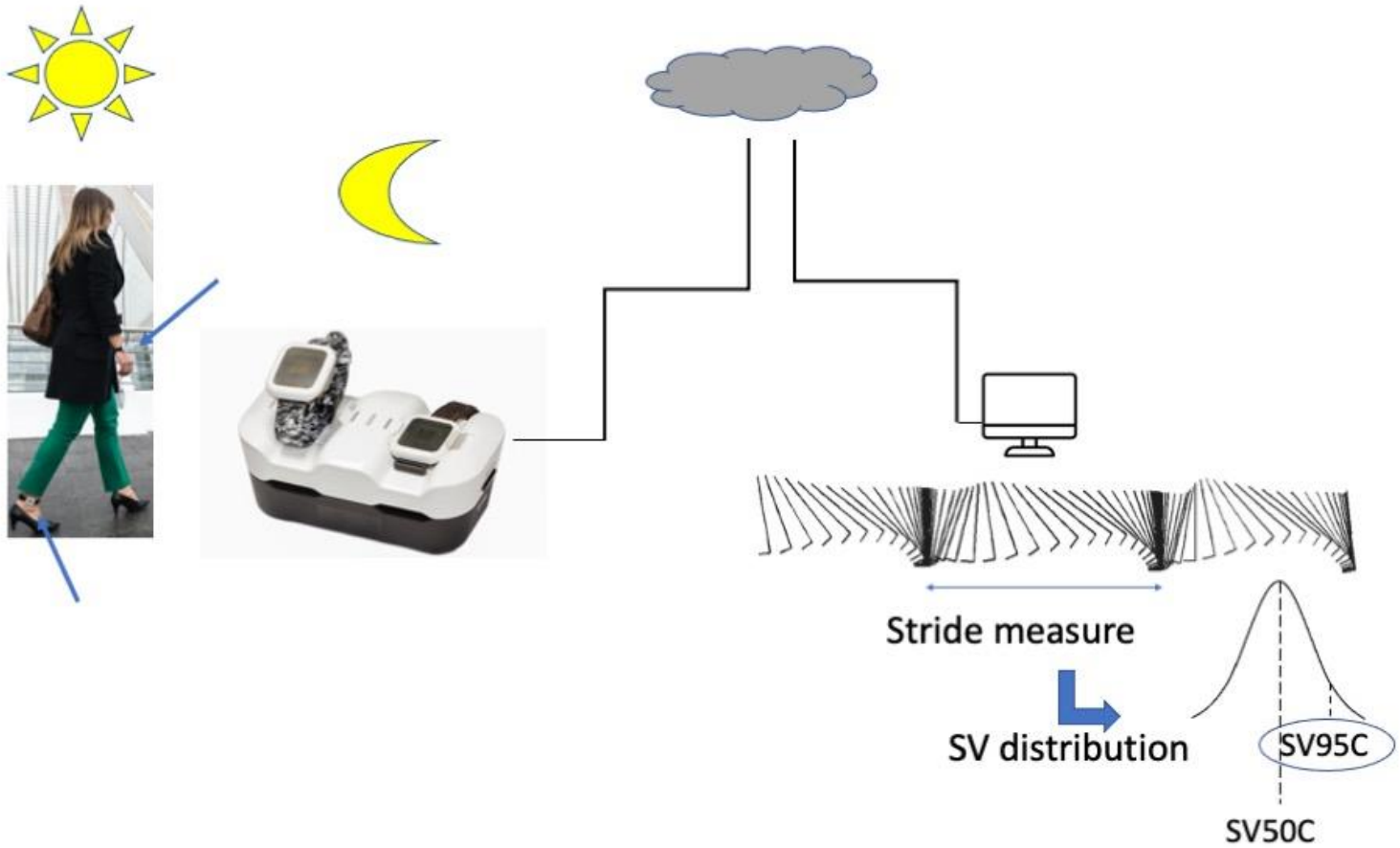
A validated outcome that you can enter into a database

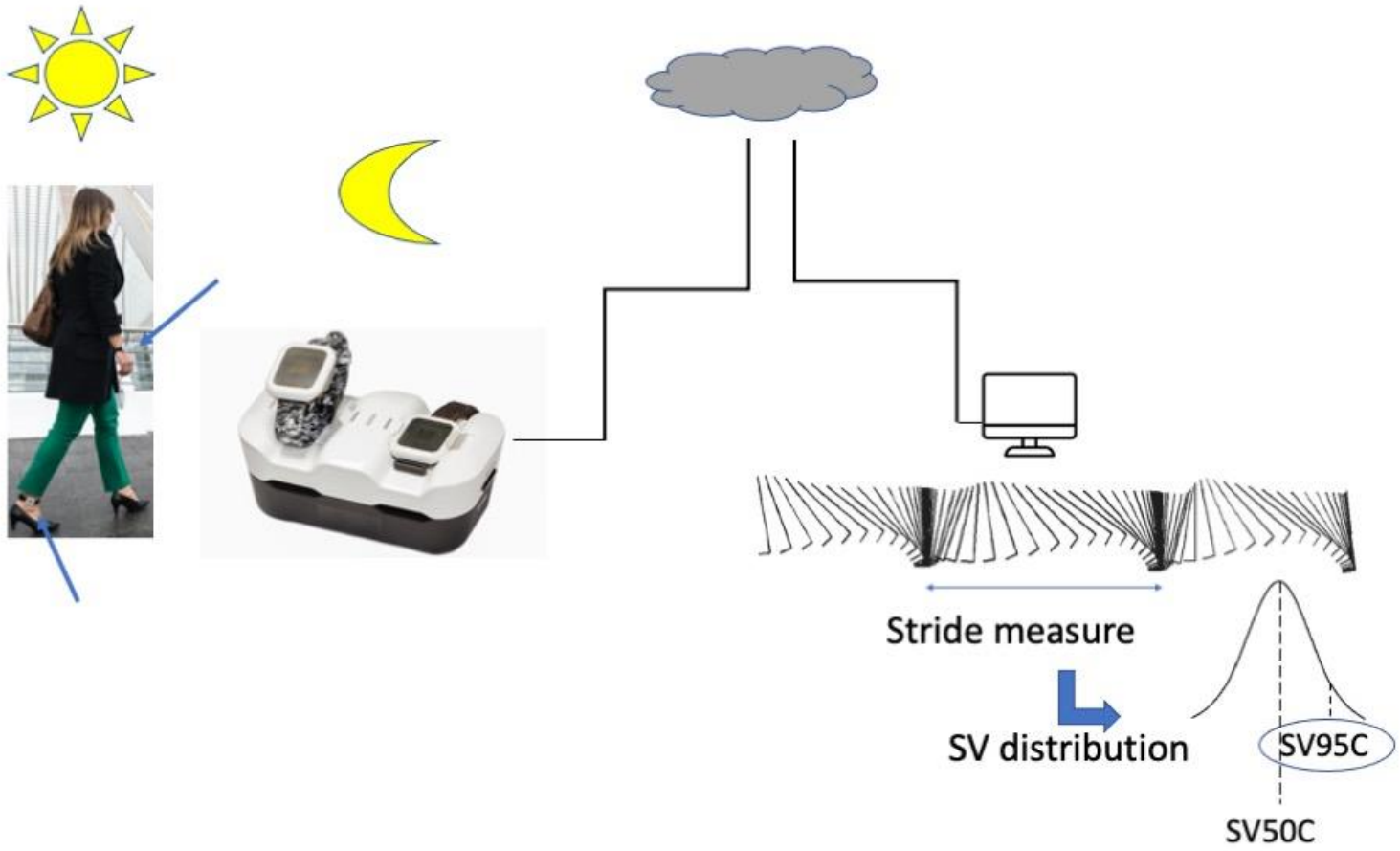
In DMD : SV95C






Stride measure
SV distribution

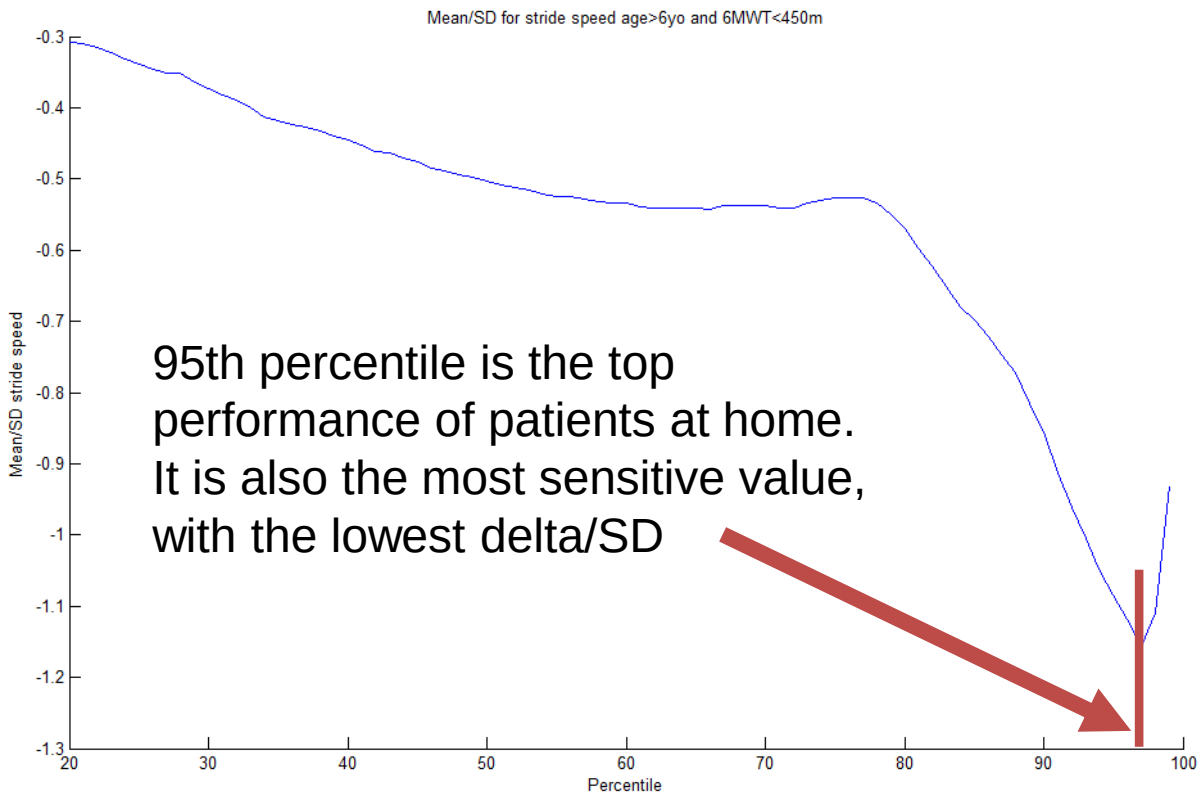

Stride measure
SV distribution
SV95C
SV50C



SV95C represents home-measured « top performance »

One of the first complain expressed by patients is not being able to play as others- not being able to follow others

Why 95th Centile ?



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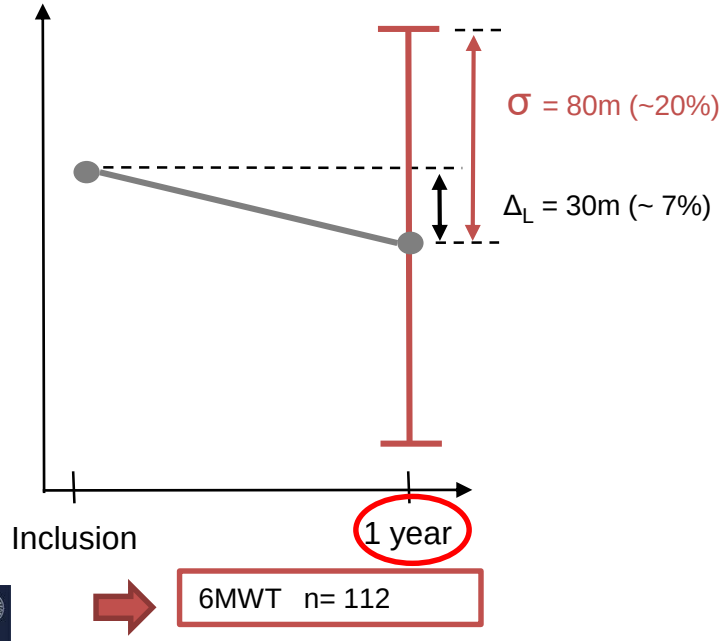
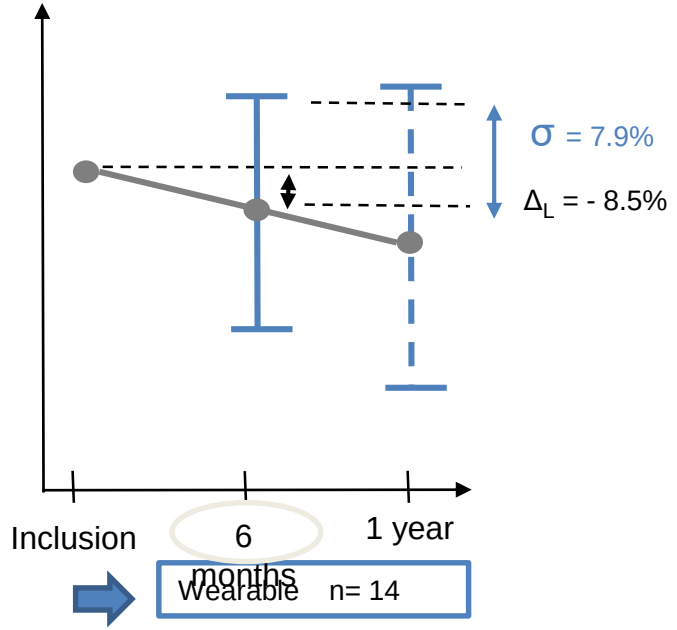
Number of patients to be included per arm in a placebo controlled trial

$$n = \frac{2\sigma^2}{\Delta_L^2}(z_{1-\alpha} + z_{1-\beta})^2$$

Risk α = probability to wrongly conclude to treatment efficacy
=> α : 5% Z= 1.96
Risk ß = probability to wrongly conclude to treatment inefficacy
=> ß : 20% Z= 0.842





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Variability of actimetry....

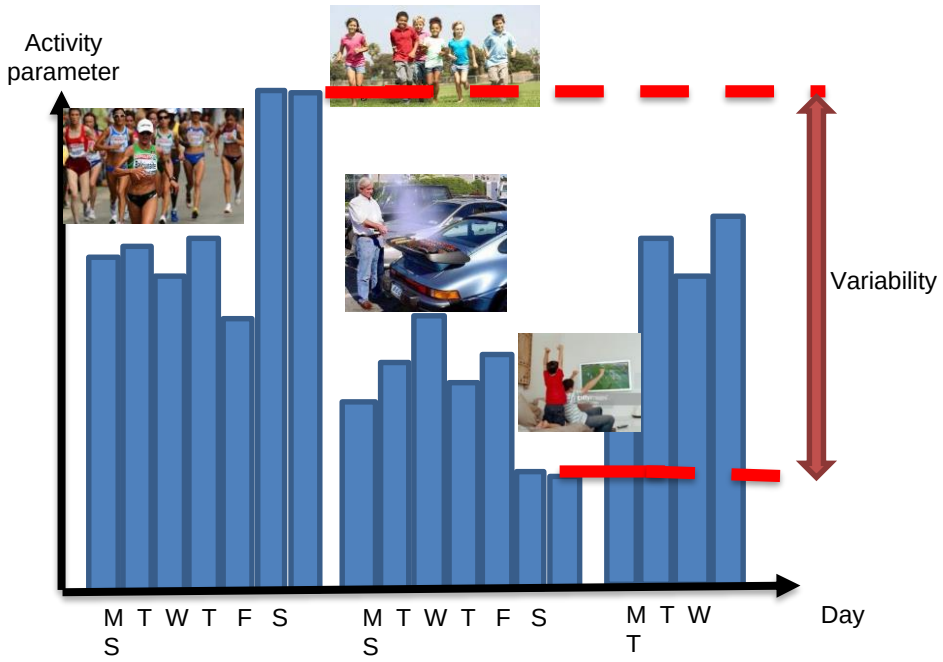
Theorem of Servais (Oxford 2021)

When it pours, British people walk less.
When it simply rains, they walk more

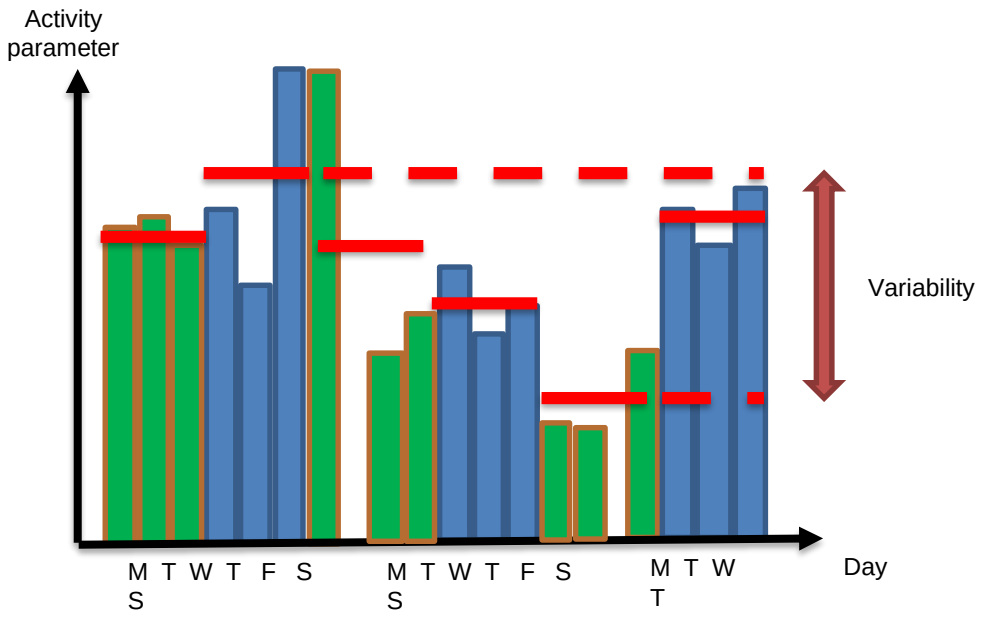
Theorem of Servais (Paris 2014)

When the French are on strike, they walk more

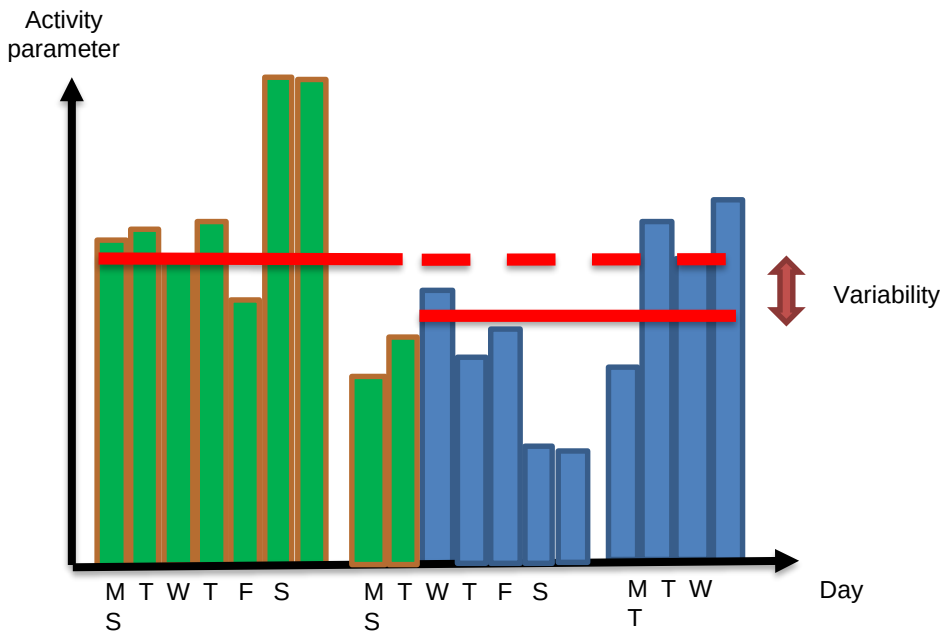
Variability measurements



Variability measurements

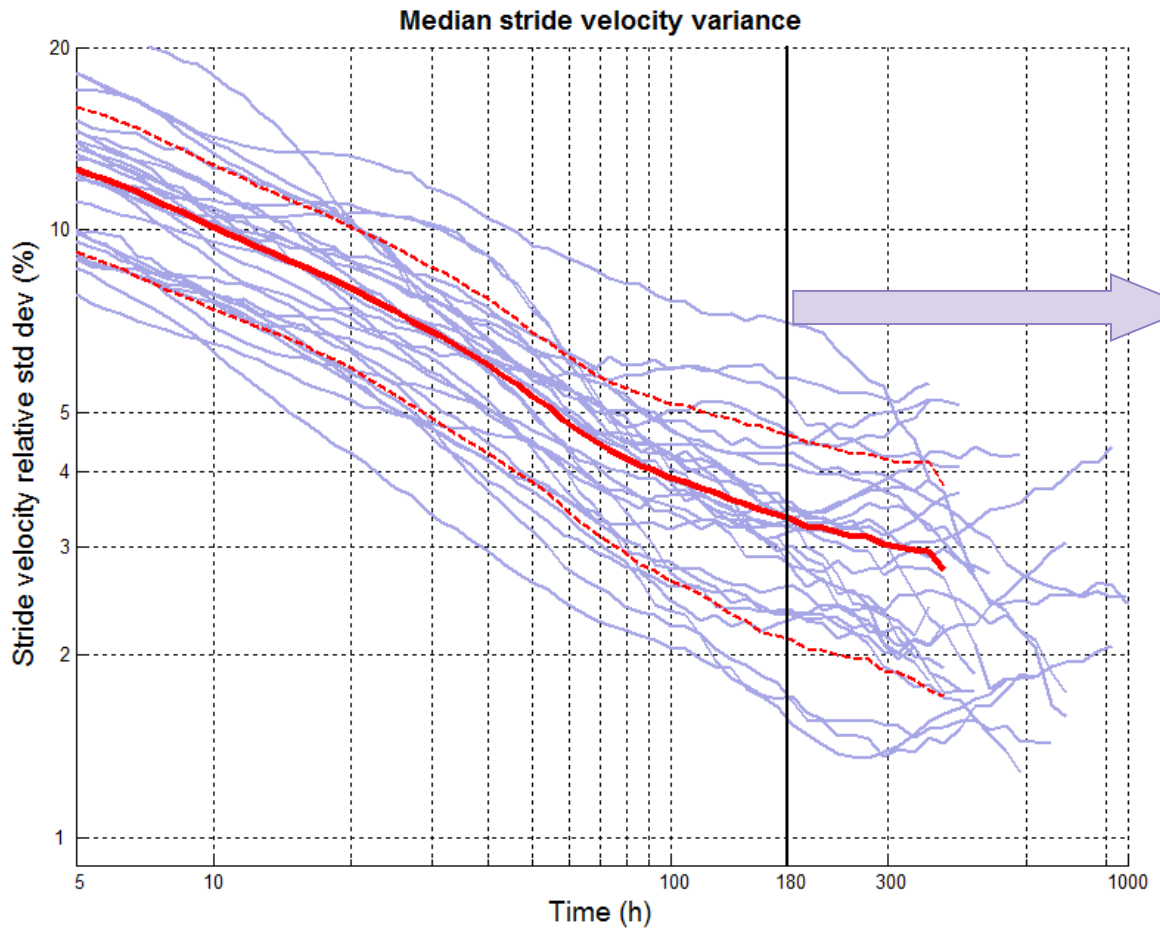


Variability measurements



Variability decreases with increasing length of monitoring

ACTIMYO HOME MONITORING



- Averaged variation stabilises at 3.3% after 180 hours (15 days) monitoring
- 15% variability currently "acceptable" for 6MWT

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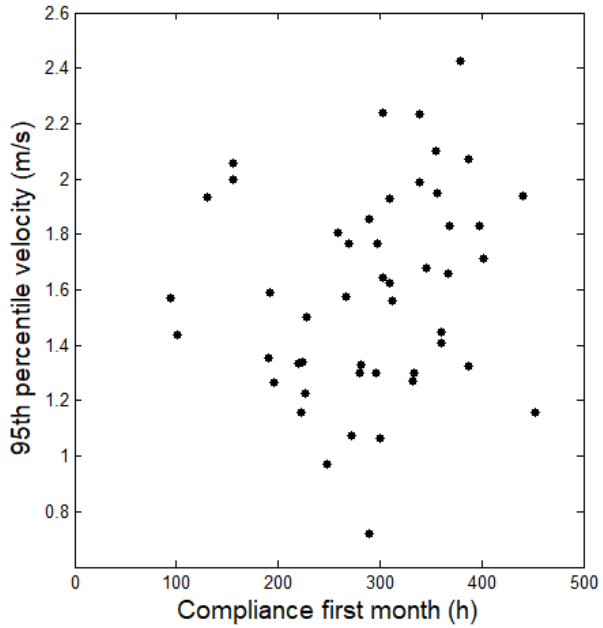
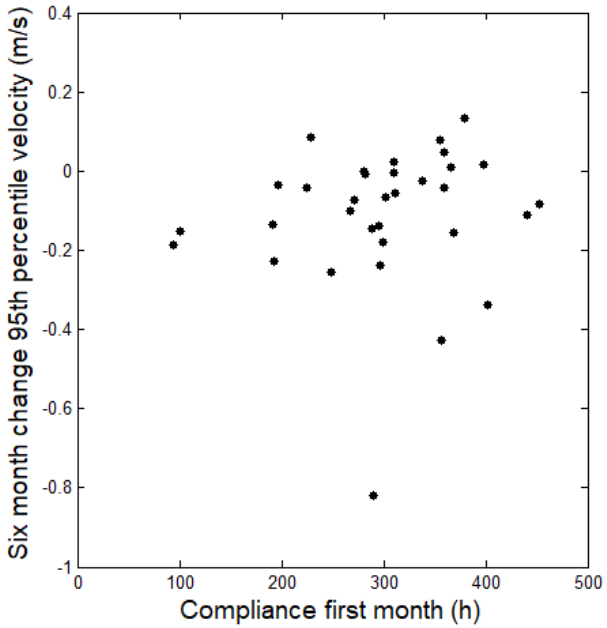
Influence of compliance on SV95C

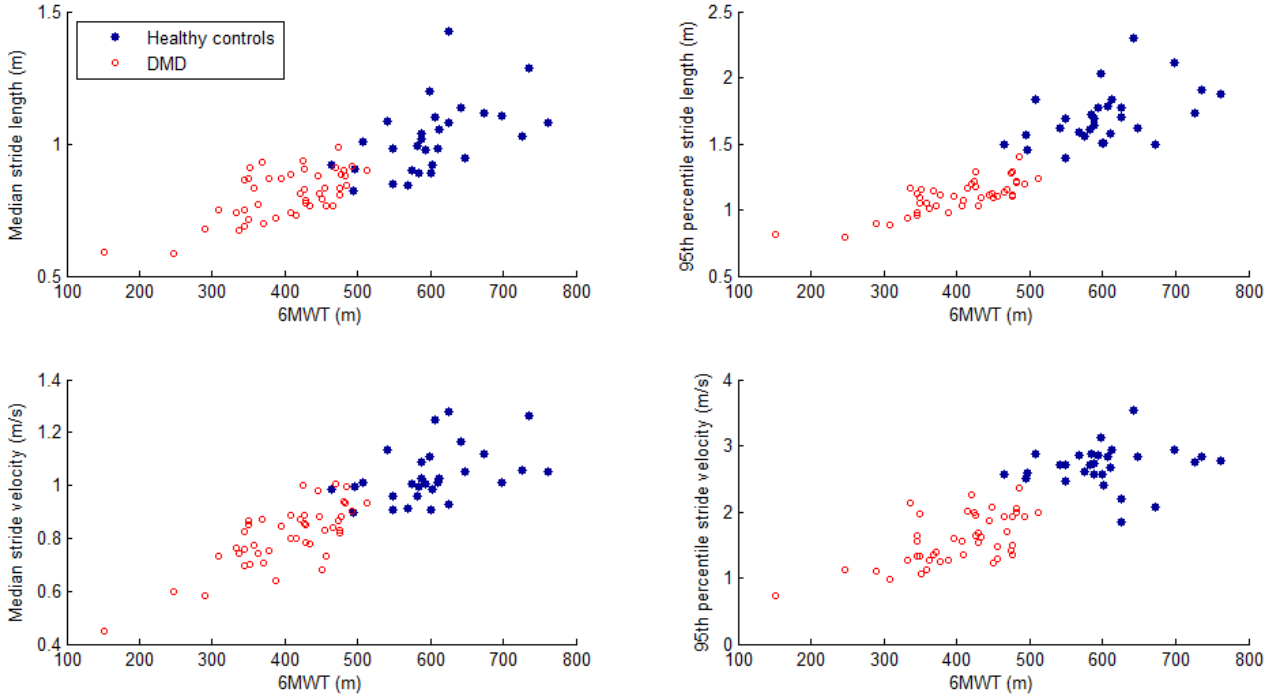




Absence of correlation between compliance and performance

Normative data in healthy age-matched controls

- DMD and healthy controls correlated with 6MWT



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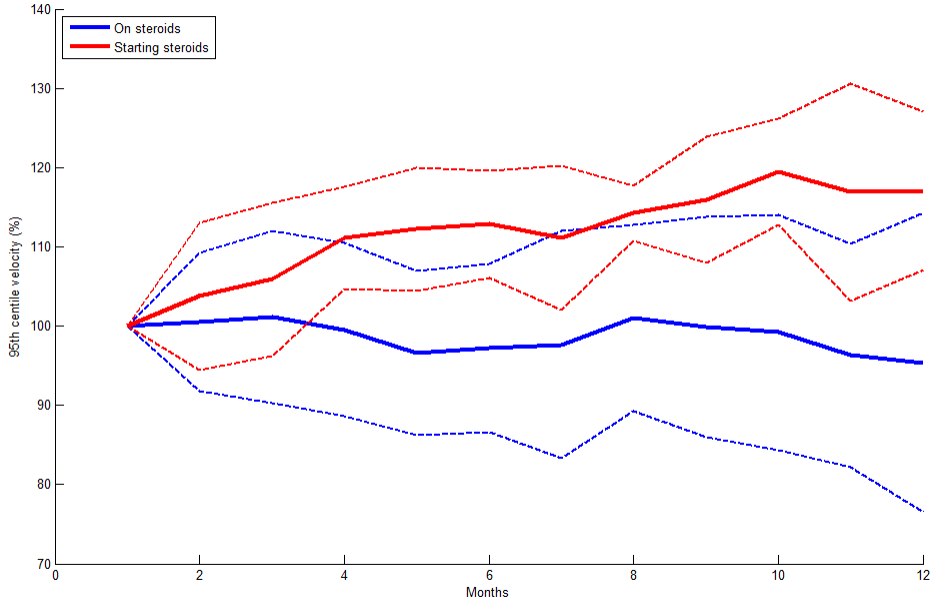
Sensitivity to positive Change : Patient starting steroid treatment



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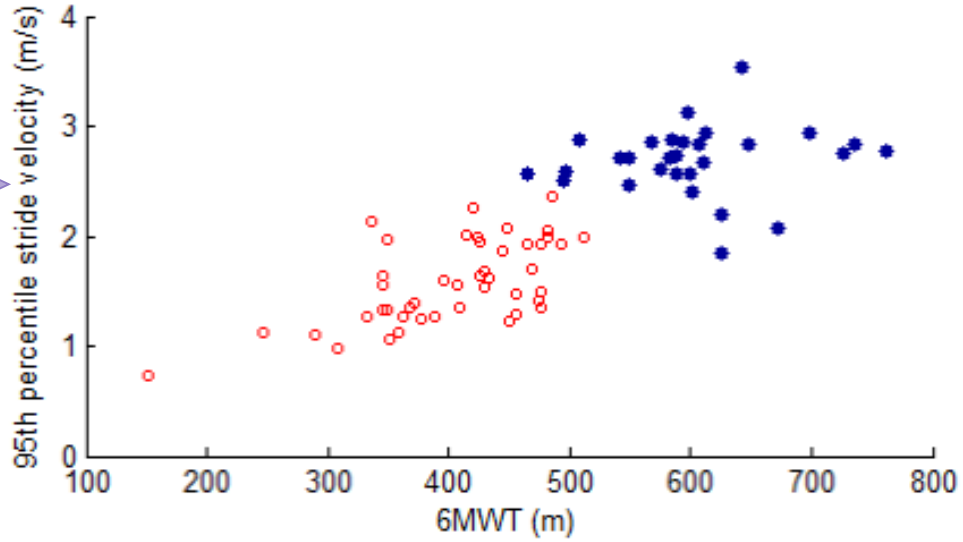
Correlation with different outcomes

		6MWT		NSAA		4SC	
ActiMyo® Variables	N	ρ	r	ρ	R	ρ	r
50th Percentile (median) stride length (m)	45	0,552**	0,649**	0,554**	0,607**	0,126	0,066
95th Percentile stride length (m)	45	0,679**	0,772**	0,779**	0,816**	-0,301*	-0,251
50th Percentile (median) stride velocity (m/s)	45	0,652**	0,758**	0,712**	0,724**	-0,161	-0,195
95th Percentile stride velocity (m/s)	**45**	**0,542****	**0,616****	**0,645****	**0,689****	**-0,547****	**-0,484****
Distance walked/hour	45	0,371*	0,436**	0,424**	0,435**	-0,304*	-0,313*



Minimally clinically important difference

	Mean	SD	Intra-correlation	MCID	Relative MCID
50th Percentile (median) stride length	0.825 m	0.087 m	0.957	0.0179 m	2.17%
95th Percentile stride length	1.101 m	0.129 m	0.951	0.0284 m	2.58%
50th Percentile (median) stride velocity	0.836 m/s	0.116 m/s	0.942	0.0278 m/s	3.33%
95th Percentile stride velocity	**1.578 m/s**	**0.391 m/s**	**0.937**	**0.0985 m/s**	**6.24%**
Distance walked/hour	162.6 m/h	87.9 m/h	0.839	35.3 m/h	21.7%

Muscular Dystrophy UK
MDUK Oxford Neuromuscular Centre
UNIVERSITY OF OXFORD

LIÈGE université

2019

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 April 2019
EMA/CHMP/SAWP/178058/2019
Committee for Medicinal Products for Human Use (CHMP)

Qualification opinion on stride velocity 95th centile as a secondary endpoint in Duchenne Muscular Dystrophy measured by a valid and suitable wearable device*

Draft agreed by Scientific Advice Working Party	12 April 2018
Adopted by CHMP for release for consultation	26 April 2018
Start of public consultation	21 September 2018
End of consultation (deadline for comments)	30 November 2018
Adopted by CHMP	26 April 2019

Keywords	Activity monitor, Duchenne Muscular Dystrophy (DMD), Real World Data, Stride Velocity, Ambulation

2023

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 February 2023

Case No.: EMA/SA/0000083386

Committee for Medicinal Products for Human Use (CHMP)

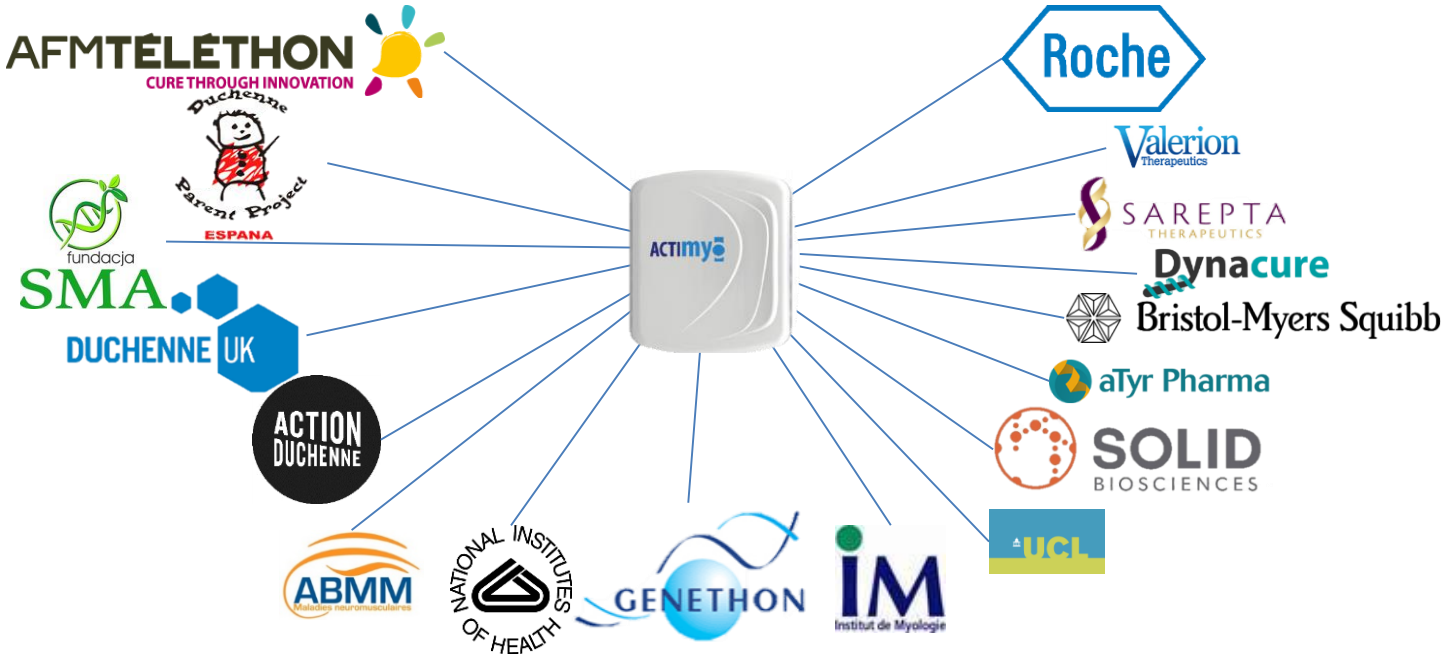
Draft Qualification Opinion for Stride velocity 95th centile as primary endpoint in studies in ambulatory Duchenne Muscular Dystrophy studies

Draft agreed by Scientific Advice Working Party (SAWP)	01 September 2022
Adopted by CHMP for release for consultation	15 September 2022[1]
Start of public consultation	28 February 2023[2]
End of consultation (deadline for comments)	10 April 2023

Comments should be provided using this template. The completed comments form should be sent to ScientificAdvice@ema.europa.eu

Keywords	Qualification of Novel Methodology, Duchenne Muscular Dystrophy studies, Digital Health Technology, efficacy endpoint, wearable sensor

CHMP qualification has been achieved thanks to the support of a broad community



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25

Number of sponsors

10

Number of conditions

DMD
SMA
FSHD
LGMD
ALS

Angelman
Dup15q
Sarcopenia
MS
Parkinson

60+

Participations in clinical trials

1 200 000 +

Hours recorded

Take home messages

1. Digital outcome has made its way in the regulatory landscape with the coming qualification of a digital outcome **as primary endpoint**…
2. …. Because it has the potential to dramatically **reduce the duration and the size of clinical trials** in a broad range of conditions

Key Learning The 3 D rule

1. The quality of the Device is key

2. The Development of interactions between engineers and MD is key

3. Early (high quality) Data collection

Key Question

1. How to make outcome measure develoment really attractive for industry/investors

2. How to deal with less common disease/Extension to diseases with similar phenotype (ex : LGMD)

3. Difference of processes between FDA and EMA makes qualification very time and energy consuming

4. How can a qualified outcome evoluate with time


The Liege CRMN Team
Olivier Schneider
Manon Huystincks
Fabian dal Farra
Laurane Mackels
Laurie Medard
Manon Duclos
Laura Buscemi
Charline Dubois
Aurore Daron
Stephanie Delstanche
Margaux
Poleur

Mélanie Annoussamy
1974-2023

Session 1: Considerations in Developing Rare Disease Endpoints: Digital Health Technology (DHT)

Moderator:

- **Michelle Campbell,** U.S. Food and Drug Administration

Panelists:

- **Damien Eggenspieler,** Sysnav
- **Hussein Ezzeldin,** U.S. Food and Drug Administration
- **Ami Mankodi,** U.S. Food and Drug Administration
- **Leonard Sacks,** U.S. Food and Drug Administration
- **Laurent Servais,** University of Oxford

Session 1: Considerations in Developing Rare Disease Endpoints: Digital Health Technology (DHT)

1. What are the biggest challenges stakeholders experience in developing DHTs for use in rare disease drug development? What are effective strategies for overcoming or minimizing the impact of those challenges?

2. What are the key opportunities regarding future development of DHTs for use in rare disease clinical research?

3. How can stakeholders (such as sponsors, regulators, and researchers) work together in the future to advance rare disease endpoints that involve the use of a DHT?

4. How can stakeholders best work with regulators to advance DHTs for use in rare disease drug development?

5. What else is needed to advance development and use of endpoints that involve use of a DHT in the rare disease space?

Session 2: Considerations in Developing Rare Disease Endpoints: Biomarker Surrogate Endpoints

2:15 – 3:05 pm ET

Biomarkers

- A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions.
- Biomarkers may include molecular, histologic, radiographic, or physiologic characteristics.
- A biomarker is not a measure of how an individual feels, functions, or survives.
- Categories of biomarkers include: susceptibility/risk, diagnostic, monitoring, prognostic, predictive, response, safety

BEST (Biomarkers, EndpointS, and other Tools) Resource: https://www.ncbi.nlm.nih.gov/books/NBK338448/

Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (Draft Guidance)

- Substantial evidence: evidence consisting of adequate and well-controlled (A&WC) investigations
  - Two A&WC clinical investigations
  - One large, multicenter A&WC clinical investigation
  - One A&WC clinical investigation plus confirmatory evidence

https://www.fda.gov/media/133660/download

Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (Draft Guidance)

- Endpoints
  - Clinical endpoint that reflects patient benefits (i.e., how patients feel, function, or survive)
  - Validated surrogate endpoint that has been shown to predict a specific clinical benefit

  Traditional approval

  - Intermediate clinical endpoint that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit
  - Surrogate endpoint that is reasonably likely to predict clinical benefit

  Accelerated approval

https://www.fda.gov/media/133660/download

Pathways to Integrate Biomarkers into Drug Development and Practice

Note: These pathways do not exist in isolation and many times parallel efforts are underway within or between pathways. All share common core concepts, are data-driven, and involve regulatory assessment and outcomes based on the available data.

FDA Drug Development Tools Website

Facilitating Biomarker Development: Strategies for Scientific Communication, Pathway Prioritization, Data-Sharing, and Stakeholder Collaboration; Published June 2016, Duke-Margolis Center for Health Policy

Considerations in Developing Rare Disease Endpoints: Surrogate Endpoints: IgA Nephropathy as an example

Patrick H. Nachman, MD, FASN

Director, Division of Nephrology and Hypertension

June 7, 2023

UNIVERSITY OF MINNESOTA

Driven to Discover®

Disclosures

- UMN participated in including one of the trials mentioned in this presentation, and currently participates in clinical trials of IgAN,.

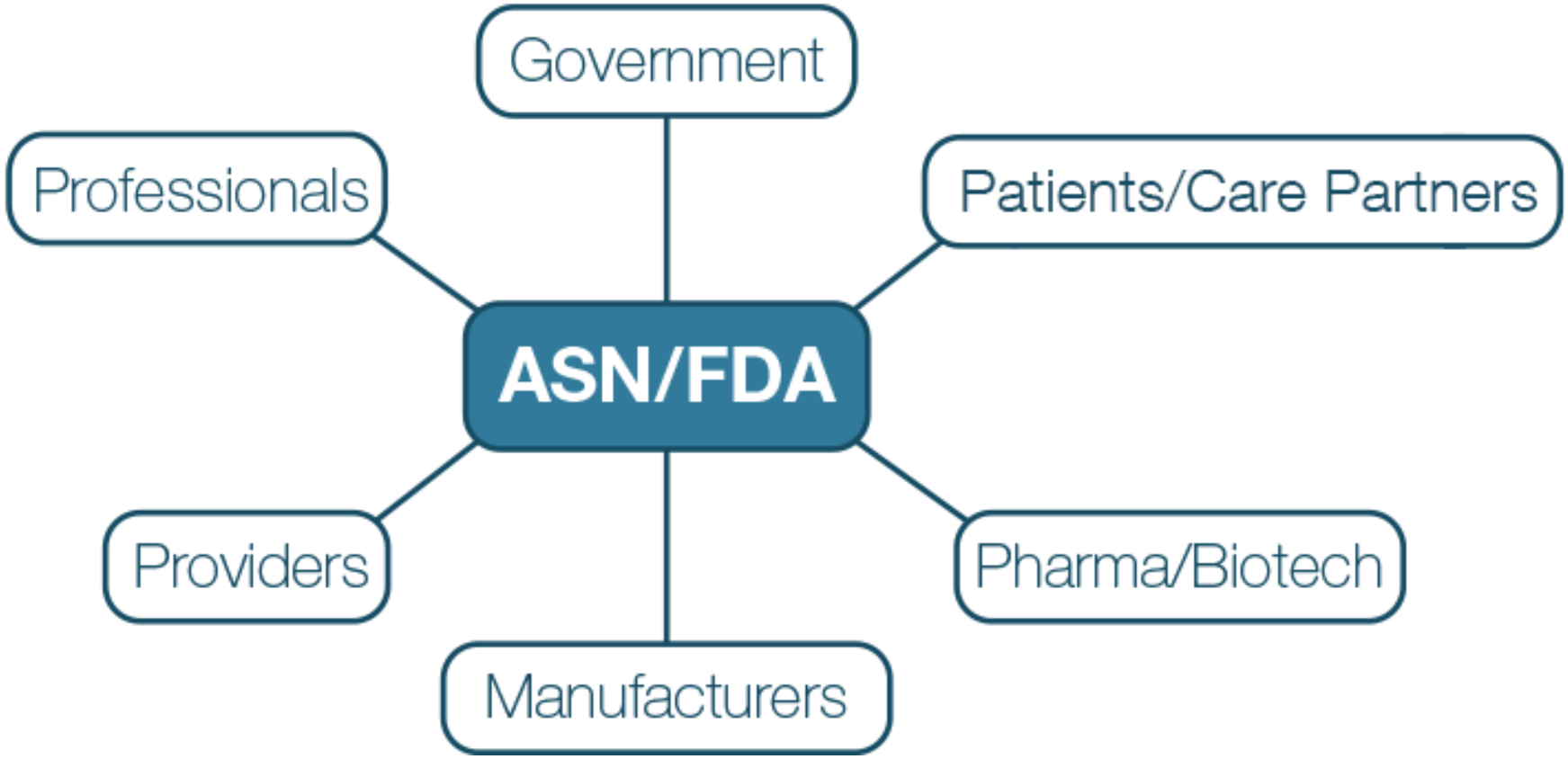
- I have No financial relationship with clinical trial sponsors pertinent to this presentation.

Outline

- Introduction of the Kidney Heath Initiative
- Assessment of Proteinuria Reduction as Surrogate Endpoint in IgA Nephropathy
- Knowledge Gaps (Limitations) and Future Directions


KHI
KIDNEY HEALTH INITIATIVE

KHI Stakeholders



Courtesy Melissa West, KHI, ASN

Identifying Surrogate Endpoints for Clinical Trials in IgA Nephropathy

Workgroup Meeting

July 12, 2016

Ethnicity and Renal Survival in IgAN

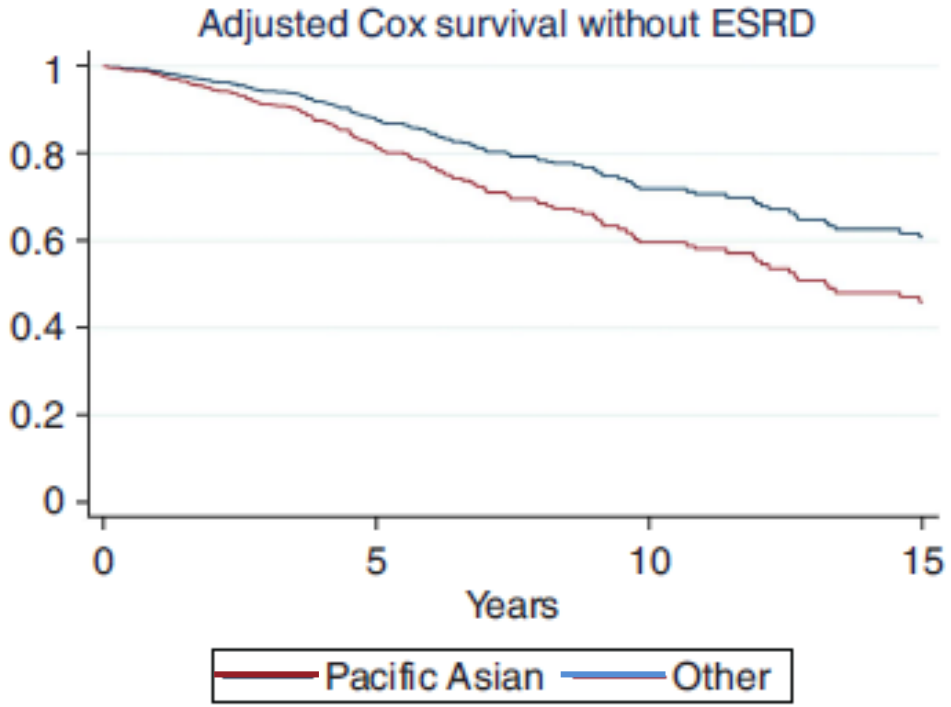


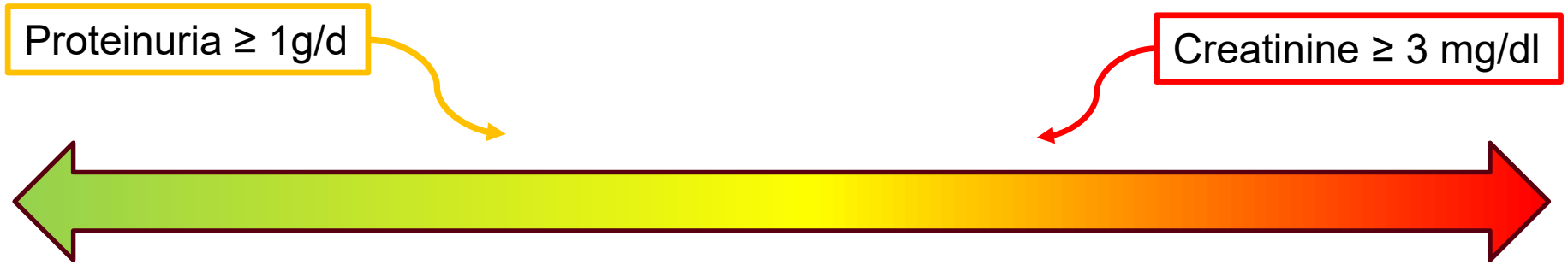
Figure 3 | The adjusted Cox proportional hazards survival curves for the risk of end-stage renal disease (ESRD) across the Pacific Asian origin and other groups ($P = 0.01$), based on the multivariable model shown in Table 4.

Table 4 | Result of a multivariable Cox proportional hazard model for the risk of ESRD

	HR	95% CI	*P*-value
Pacific Asian versus other origin	1.56	1.10, 2.22	0.01
Age (per year)	0.98	0.96, 0.99	<0.001
Male sex	0.90	0.66, 1.22	0.5
eGFR at biopsy (per ml/min/17.3 m^2)	0.95	0.94, 0.96	<0.001
MAP (per mm Hg)[a]	1.03	1.02, 1.05	<0.001
Proteinuria (per g/day)[a]	1.16	1.12, 1.21	<0.001
Use of ACEi or ARB[a]	0.99	0.72, 1.36	0.9
Use of immunosuppression[a]	1.36	0.95, 1.96	0.09

Barbour SJ. *et al.* Kidney Int 2013, 84: 1017-1024

Spectrum of Disease Progression (target patient populations for clinical trials)



Low risk of progression

Supportive therapy only

Risk of Progression over many years.

Intervention desired.

Need surrogate endpoint for ESKD

Rapid progression

Point Of No Return?

Identifying Surrogate Endpoints for IgA Nephropathy

Unmet Need: Therapies that can improve renal outcomes in IgAN.

Given the time course for disease progression and size of affected population, endpoints such as progression to ESKD or a marked loss of kidney function may not be feasible.

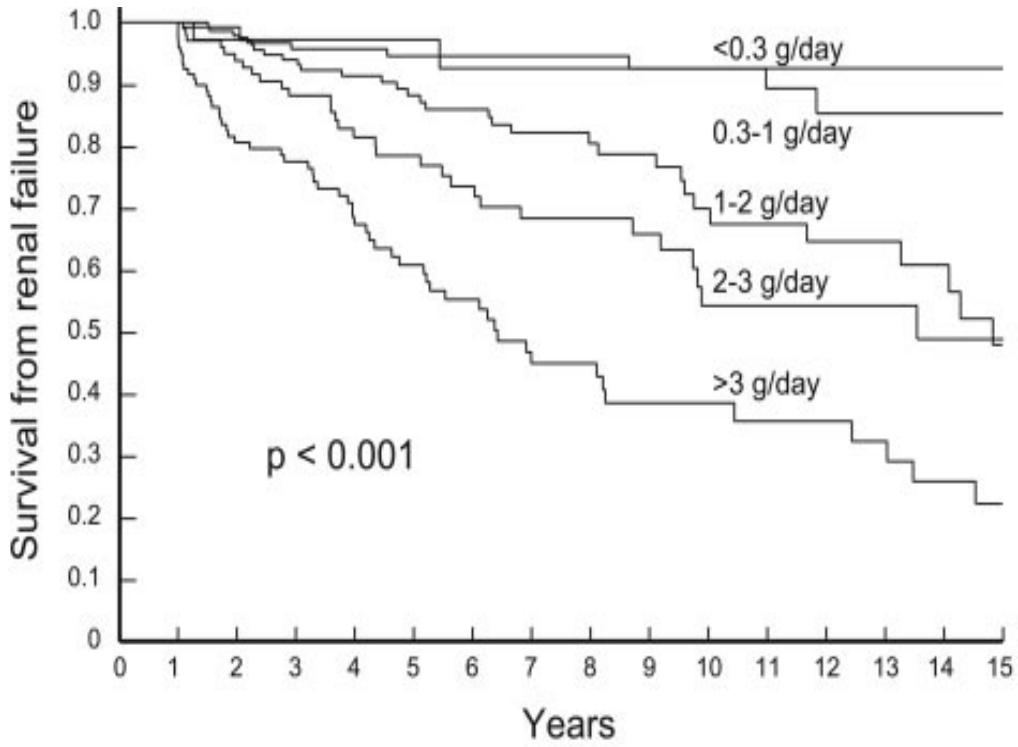
Project: Convene multi-disciplinary team (industry, academics, regulators) to discuss and determine candidate surrogate endpoint(s) in IgAN.

Biologic plausibility of causation:

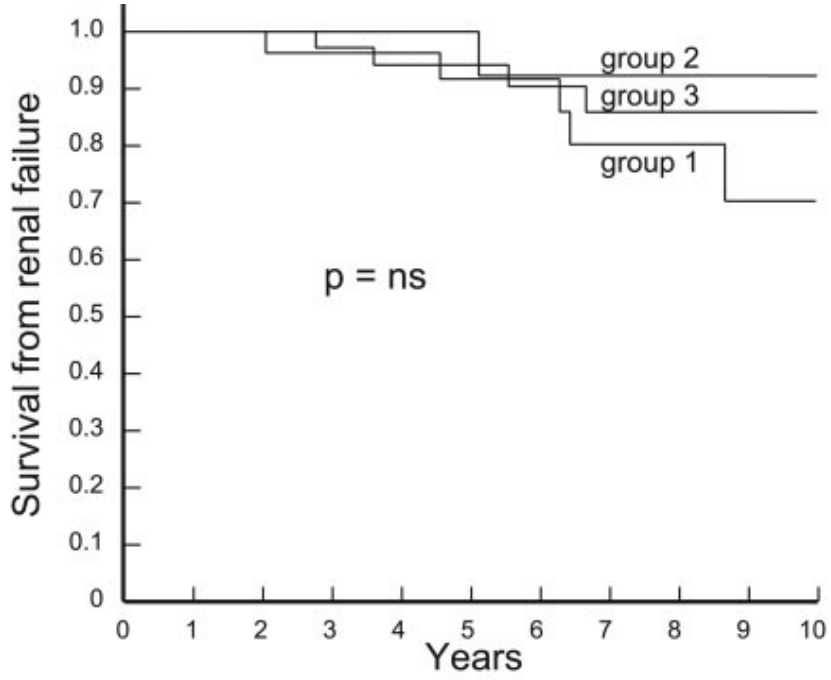
- There are a number of *in vitro* studies linking proteinuria with tubular damage.
- There are limited *in vivo* data mechanistically linking proteinuria with kidney damage.
- Several studies link specific molecules with kidney damage.
- There are limited data SPECIFIC to IgAN linking proteinuria with kidney damage.
- The degree of proteinuria associated with poor renal outcomes differs significantly between proteinuric diseases.
  - The degree of persistent proteinuria associated with progressive kidney function decline is significantly lower in IgAN than other kidney diseases (≤1g/day vs ≥ 3g/day in FSGS or MN)

Data in support of proteinuria reduction as surrogate endpoint from cohort studies?

Remission of Proteinuria and Prognosis



<0.3 g/day	37	22	8	1
0.3-1 g/day	134	79	35	11
1-2 g/day	145	79	28	10
2-3 g/day	105	50	18	4
>3 g/day	120	44	13	6



Group 1	29	18	6
Group 2	21	13	2
Group 3	39	26	10

partial remission (≤1 g/d) associated with similar outcome regardless of peak.

Peak proteinuria:

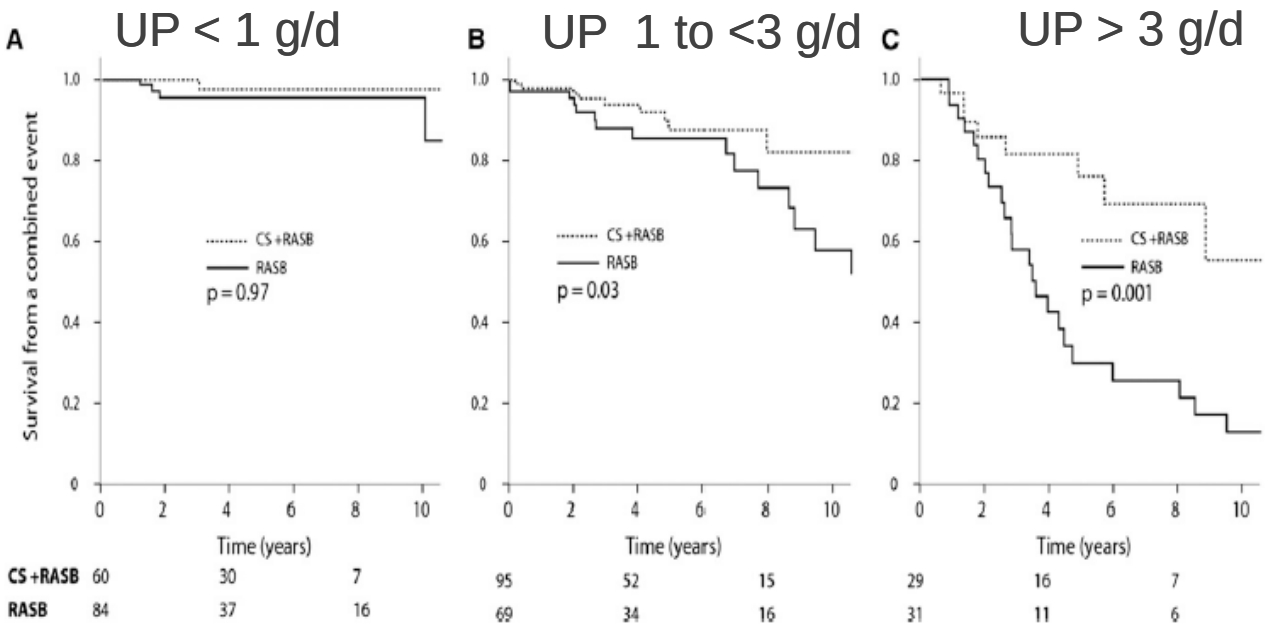
Group 1, 1- 2 g/d

Group 2, 2- 3 g/d;

Group 3, >3 g/d.

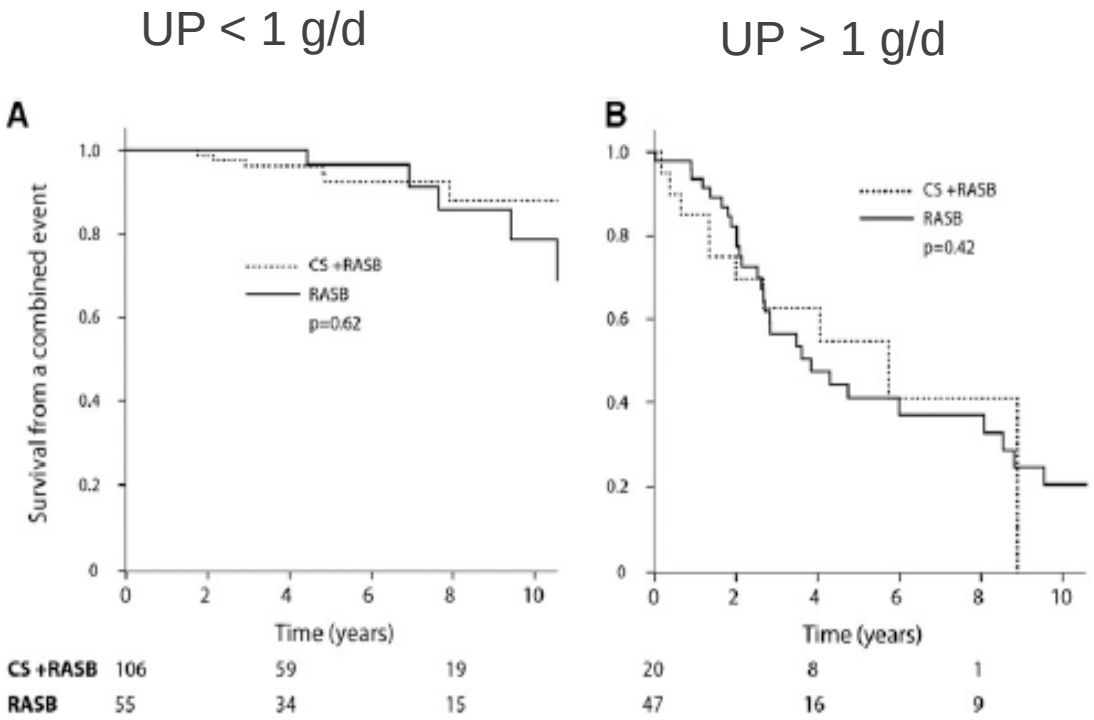
Reich HN et al J Am Soc Nephrol 2007;18:3177-3183

VALIGA – derived study of RAS Blockade ±Steroids



Response to treatment based on time-average proteinuria before treatment

Kidney survival based on achieving proteinuria < 1 g/d in response to treatment



Tesar V et al. J Am Soc Nephrol 2015;26:2248-58

What data from clinical trials?

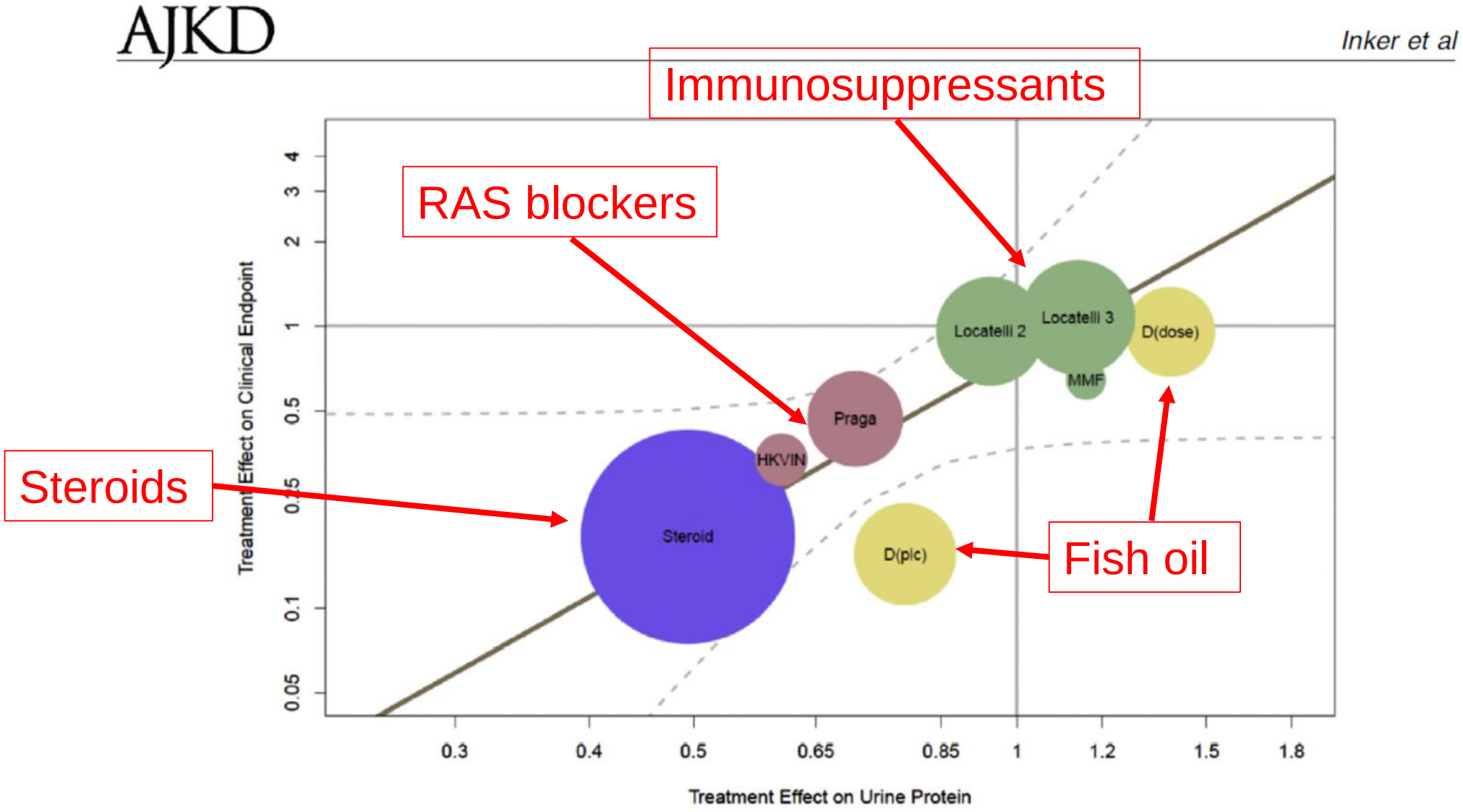
AJKD

Original Investigation

Early Change in Urine Protein as a Surrogate End Point in Studies of IgA Nephropathy: An Individual-Patient Meta-analysis

Lesley A. Inker, MD, MS,[1] Hasi Mondal, MPH,[1] Tom Greene, PhD,[2] Taylor Masaschi, BA,[1] Francesco Locatelli, MD,[3] Francesco P. Schena, MD,[4] Ritsuko Katafuchi, MD,[5] Gerald B. Appel, MD, PhD,[6] Bart D. Maes, MD,[7] Philip K. Li, MD,[8] Manuel Praga, MD,[9] Lucia Del Vecchio, MD,[3] Simeone Andrulli, MD,[3] Carlo Manno, MD,[4] Eduardo Gutierrez, MD,[9] Alex Mercer, PhD,[10] Kevin J. Carroll, PhD,[11] Christopher H. Schmid, PhD,[12] and Andrew S. Levey, MD[1]

Bayesian Mixed-Effect Regression Model



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intensive Supportive Care plus Immunosuppression in IgA Nephropathy

Thomas Rauen, M.D., Frank Eitner, M.D., Christina Fitzner, M.Sc., Claudia Sommerer, M.D., Martin Zeier, M.D., Britta Otte, M.D., Ulf Panzer, M.D., Harm Peters, M.D., Urs Benck, M.D., Peter R. Mertens, M.D., Uwe Kuhlmann, M.D., Oliver Witzke, M.D., Oliver Gross, M.D., Volker Vielhauer, M.D., Johannes F.E. Mann, M.D., Ralf-Dieter Hilgers, Ph.D., and Jürgen Floege, M.D., for the STOP-IgAN Investigators*

ABSTRACT

The effect of treatment on proteinuria reduction was NOT associated with a demonstrably beneficial effect on kidney function

N Engl J Med 2015; 373: 2225-36

JAMA | Original Investigation

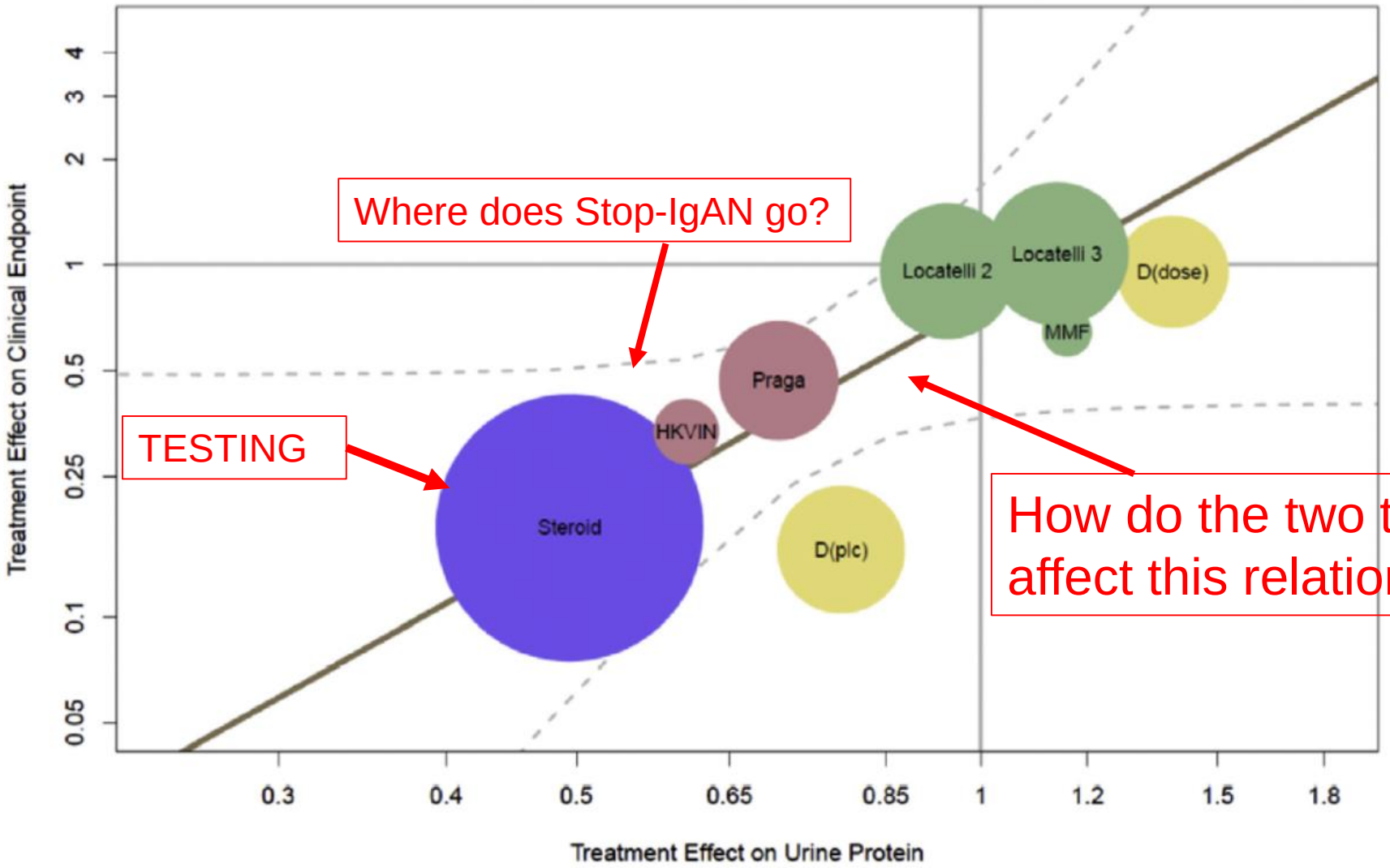
Effect of Oral Methylprednisolone on Clinical Outcomes in Patients With IgA Nephropathy

The TESTING Randomized Clinical Trial

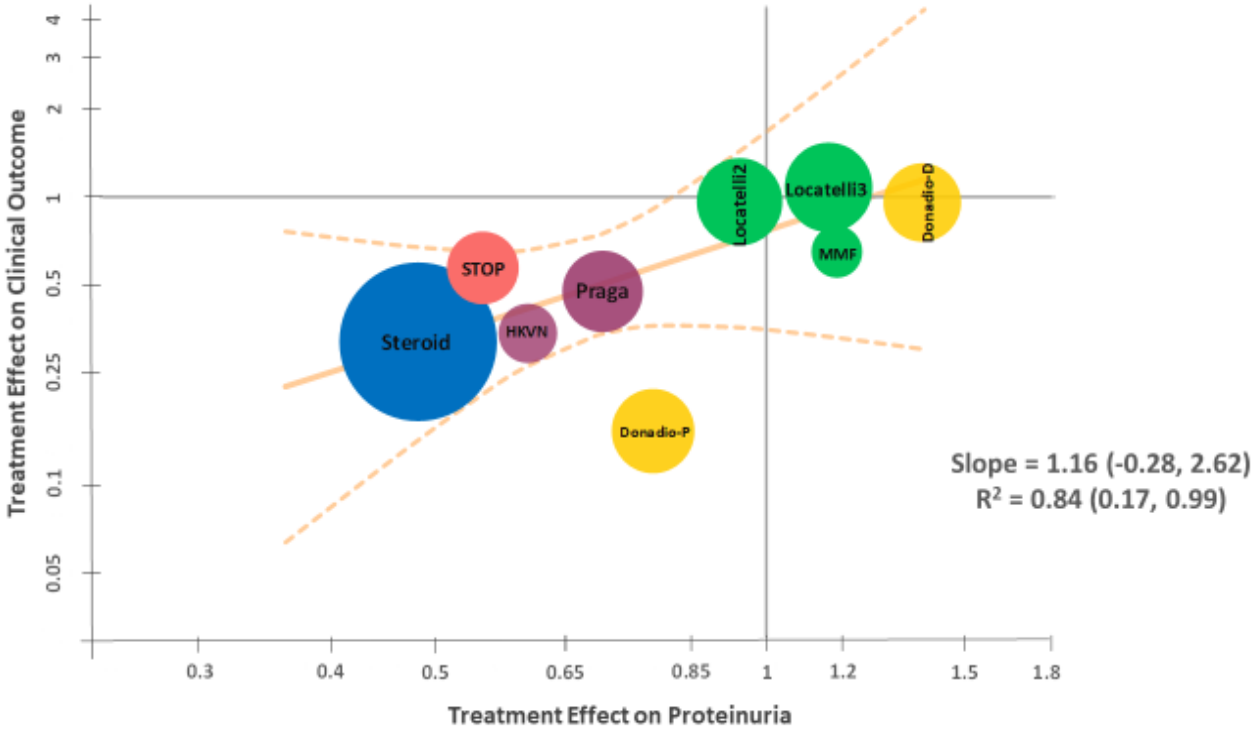
Jicheng Lv, MD; Hong Zhang, PhD; Muh Geot Wong, PhD; Meg J. Jardine, PhD; Michelle Hladunewich, MD; Vivek Jha, MD; Helen Monaghan, PhD; Minghui Zhao, MD; Sean Barbour, MD; Heather Reich, MD; Daniel Cattran, MD; Richard Glassock, MD; Adeera Levin, FRCPC; David Wheeler, FRCP; Mark Woodward, PhD; Laurent Billot, MSc; Tak Mao Chan, MD; Zhi-Hong Liu, MD; David W. Johnson, MD; Alan Cass, FRACP; John Feehally, MD; Jürgen Floege, MD; Giuseppe Remuzzi, MD; Yangfeng Wu, MD; Rajiv Agarwal, MD; Hai-Yan Wang, MD; Vlado Perkovic, PhD; for the TESTING Study Group

The effect of treatment on proteinuria reduction WAS associated with a beneficial effect on kidney function

JAMA. 2017;318(5):432-442.


Where does Stop-IgAN go?
TESTING
How do the two trials affect this relationship?
Steroid
HKVIN
Praga
D(pic)
Locatelli 2
Locatelli 3
MMF
D(dose)
Treatment Effect on Clinical Endpoint
0.05
0.1
0.25
0.5
1
2
3
4
0.3
0.4
0.5
0.65
0.85
1
1.2
1.5
1.8
Treatment Effect on Urine Protein

Updated the regression model to include the results of Stop-IgAN and TESTING
→ The graded relationship between the effect of treatment on proteinuria reduction and on clinical outcome is confirmed.



Thompson A et al. CJASN

SUMMARY

- Persistent proteinuria is a strong risk factor for the progression of kidney dysfunction.
- No uniform definition of proteinuria reduction for use as surrogate endpoint.
- Meta-analysis of intervention trials: treatment effect on the change in proteinuria is predictive of treatment effect on composite renal endpoint (ESKD or doubling of SCr or death).

Proteinuria reduction as a reasonably likely surrogate end point for a treatment's effect on progression to ESKD in IgAN.

Feature CJASN ePress. Published on January 22, 2019 as doi: 10.2215/CJN.08800718

Proteinuria Reduction as a Surrogate End Point in Trials of IgA Nephropathy

Aliza Thompson,[1] Kevin Carroll,[2] Lesley A. Inker,[3] Jürgen Floege,[4] Vlado Perkovic,[5] Sonia Boyer-Suavet,[6] Rupert W. Major,[7] Judith I. Schimpf,[4] Jonathan Barratt,[8] Daniel C. Cattran,[9] Barbara S. Gillespie,[10] Annamaria Kausz,[11] Alex W. Mercer,[12] Heather N. Reich,[9] Brad H. Rovin,[13] Melissa West,[14] and Patrick H. Nachman[15]

Implementing the Kidney Health Initiative Surrogate Efficacy Endpoint in Patients With IgA Nephropathy (the PROTECT Trial)

Jonathan Barratt[1], Brad Rovin[2], Ulysses Diva[3], Alex Mercer[4] and Radko Komers[5]; on behalf of the PROTECT Study Design Group

[1]Department of Cardiovascular Sciences, University of Leicester and Leicester General Hospital, Leicester, UK; [2]Department of Medicine, Ohio State University Wexner Medical Center, Columbus, Ohio, USA; [3]Biometrics, Retrophin, Inc., San Diego, California, USA; [4]Clinical Drug Development, JAMCO Pharma Consulting AB, Stockholm, Sweden; and [5]Nephrology, Retrophin, Inc., San Diego, California, USA

www.kidney-international.org clinical trial

Results from part A of the multi-center, double-blind, randomized, placebo-controlled NeflgArd trial, which evaluated targeted-release formulation of budesonide for the treatment of primary immunoglobulin A nephropathy

see commentary on page 258
OPEN

Jonathan Barratt[1], Richard Lafayette[2], Jens Kristensen[3], Andrew Stone[4], Daniel Cattran[5], Jürgen Floege[6], Vladimir Tesar[7], Hernán Trimarchi[8], Hong Zhang[9], Necmi Eren[10], Alexander Paliege[11] and Brad H. Rovin[12]; for the NeflgArd Trial Investigators[13]

Kidney International February 2023

Sparsentan in patients with IgA nephropathy: a prespecified interim analysis from a randomised, double-blind, active-controlled clinical trial

*Hiddo J L Heerspink, Jai Radhakrishnan, Charles E Alpers, Jonathan Barratt, Stewart Bieler, Ulysses Diva, Jula Inrig, Radko Komers, Alex Mercer, Irene L Noronha, Michelle N Rheault, William Rote, Brad Rovin, Howard Trachtman, Hernán Trimarchi, Muh Geot Wong, Vlado Perkovic, for the PROTECT Investigators**

The Lancet April 2023

Both products received FDA approval based on the Accelerated Pathway
Both studies are in the prespecified/predesigned confirmatory phase

The results of the confirmatory phase will provide valuable information on how well the “reasonably likely” surrogate endpoint predicts clinical benefit

Limitations:
Why Focus on Proteinuria?

http://first-the-trousers.com/hello-world/

Knowledge gaps warranting future studies:

- The relationship between treatment effects on proteinuria and treatment effects on patient and kidney outcome is best supported for the proteinuria and eGFR* levels from which the data is derived.

Biomarkers in IgAN: Candidate for Surrogate Endpoint?

Association/Correlation with:	Gd-IgA1	Sd-IgA1	IgG anti-Gd IgA1	IgA anti-Gd IgA1	sCD89-IgA	fibronectin-IgA	Serum C3	Tissue C3	Serum IgA/C3	Copeptin	
IgAN diagnosis	+		+	+	-	+	-		+		
baseline histology						+	-	+	+		
baseline proteinuria	+		+				-		-	+	
baseline eGFR							-		-	+	
prognosis (↓eGFR or ESKD)	+	+	+	+	+		+	+	+	+	
disease activity	-		-		-						
risk of relapse post transplant	+		+		+						

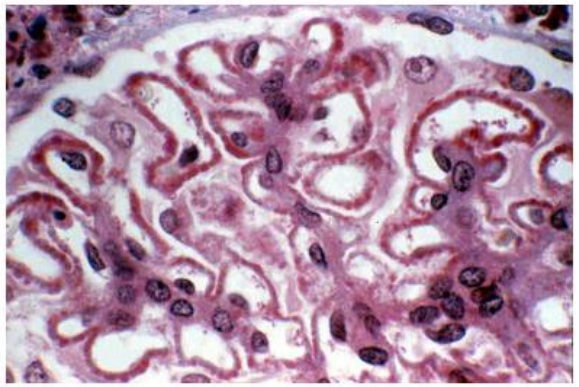
Future directions: We have come a long way, but

- Ultimately, surrogate endpoints should be applicable to the management of individual patients (Is my patient responding to the treatment?)
- Identifying better – more specific – markers of disease activity, especially “complete remission”
- How do we obtain and **share** data on specific biomarkers from clinical trials to analyze whether they can serve as surrogate endpoints (or component of)

MEMBRANOUS NEPHROPATHY SCIENTIFIC WORKSHOP

JAN 14, 2023

Possible Uses of Anti-PLA2R in Membranous Nephropathy Clinical Trials



Summary

- Work of surrogate endpoint for clinical trial has helped with the design of new trials
- The use of reasonably likely surrogate endpoint was applied to two clinical trials -> leading to approval through the accelerated pathway
- Conversely, the results of the confirmatory phases of these trials will inform on the validity/robustness of the surrogate endpoint
- More work should be pursued for the analysis of other, better, disease-specific surrogate endpoints

KHI IgA Nephropathy Workgroup

Workgroup Co-Chairs:

Aliza Thompson (FDA/CDER, USA)

Patrick Nachman (U. of Minnesota, USA)

Workgroup members:

Jonathan Barrat (U. Leicester, UK.)

Sonia Boyer* (CHU Nice, France)

Kevin Carroll (KJC Statistics, UK.)

Daniel Cattran (U. Toronto, Canada)

Jurgen Floege (U. Aachen, Germany)

Barbara Gillespie (Covance, USA)

Lesley A. Inker (Tufts U., USA)

Annamaria Kausz (Allena Pharm., USA)

Rupert Major* (U. Leicester, UK)

Alex Mercer (JAMCO Consulting, Sweden)

Workgroup members (cont'd):

Vlado Perkovic (George Institute, AUS)

Heather Reich (U. of Toronto, Canada)

Brad Rovin (Ohio State U., USA)

Judith Schimpf* (U. Aachen, Germany)

KHI Board of Directors Liaison

Ronald J. Falk (U. North Carolina, USA)

KHI Staff:

Melissa West
KHI Project Director

Ryan Murray
KHI Senior Project Associate

Elle Silverman, Meghan Alain
KHI Project Associate

Session 2: Considerations in Developing Rare Disease Endpoints: Biomarker Surrogate Endpoints

Moderator:

- **Michael Pacanowski,** U.S. Food and Drug Administration

Panelists:

- **Patrick Nachman,** University of Minnesota
- **Lynley K. Thinnes,** Travere
- **Aliza Thompson,** U.S. Food and Drug Administration

Session 2: Considerations in Developing Rare Disease Endpoints: Biomarker Surrogate Endpoints

1. What are the biggest challenges your respective stakeholder communities experience in developing biomarkers to be used in drug development for rare diseases? What are effective strategies for overcoming or minimizing the impact of those challenges?
2. What does "reasonably likely to predict clinical benefit" mean in terms of evidence from your perspective? How does a company or the community make a case that a biomarker may be reasonably likely to predict clinical benefit (is mechanism and pathobiology alone sufficient)? What distinguishes those biomarkers that are fully validated and able to support traditional approval? How does your respective community view uncertainty?
3. How do we ensure that robust, high-quality data to facilitate endpoint development are generated from natural history studies (or even clinical trials)? How might current approaches and infrastructure for data collection and analysis be improved to benefit biomarker development in the rare disease space? What are special considerations for hard to access tissues where sampling may be limited?
4. How can stakeholders work together to advance rare disease biomarker development? What are some of the key opportunities regarding future development of biomarkers for use in rare disease clinical research?

Break

3:05 pm – 3:20 pm ET

Session 3: Considerations in Developing Rare Disease Endpoints: Clinical Outcome Assessment (COA)

3:20 – 4:10 pm ET

Patient-Focused Drug Development Guidance Series

Guidance 1: Collecting Comprehensive and Representative Input

Guidance 2: Methods to Identify What is Important to Patients

Guidance 3: Selecting, Developing or Modifying Fit-for-Purpose Clinical Outcome Assessments

Guidance 4: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision Making

https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

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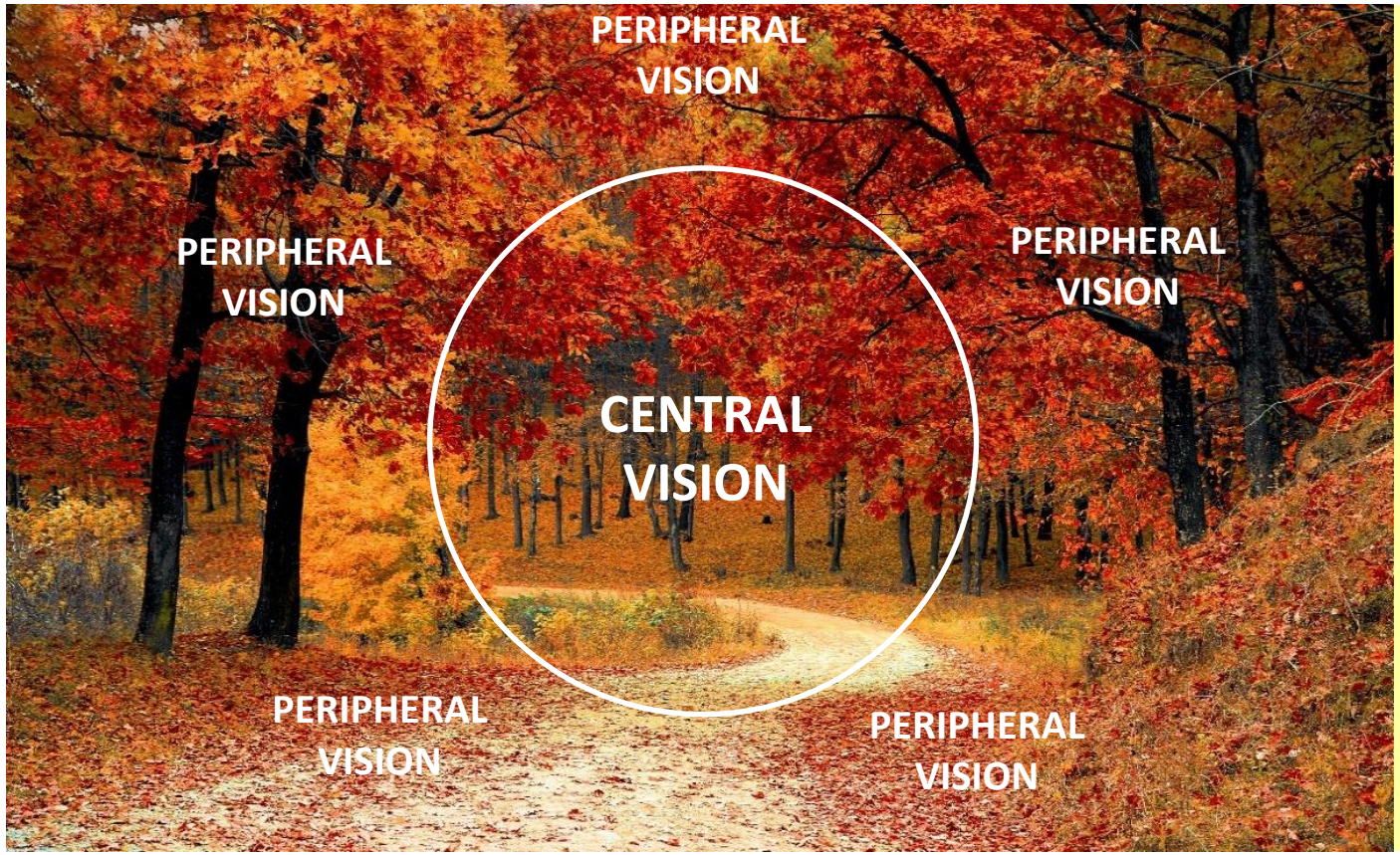
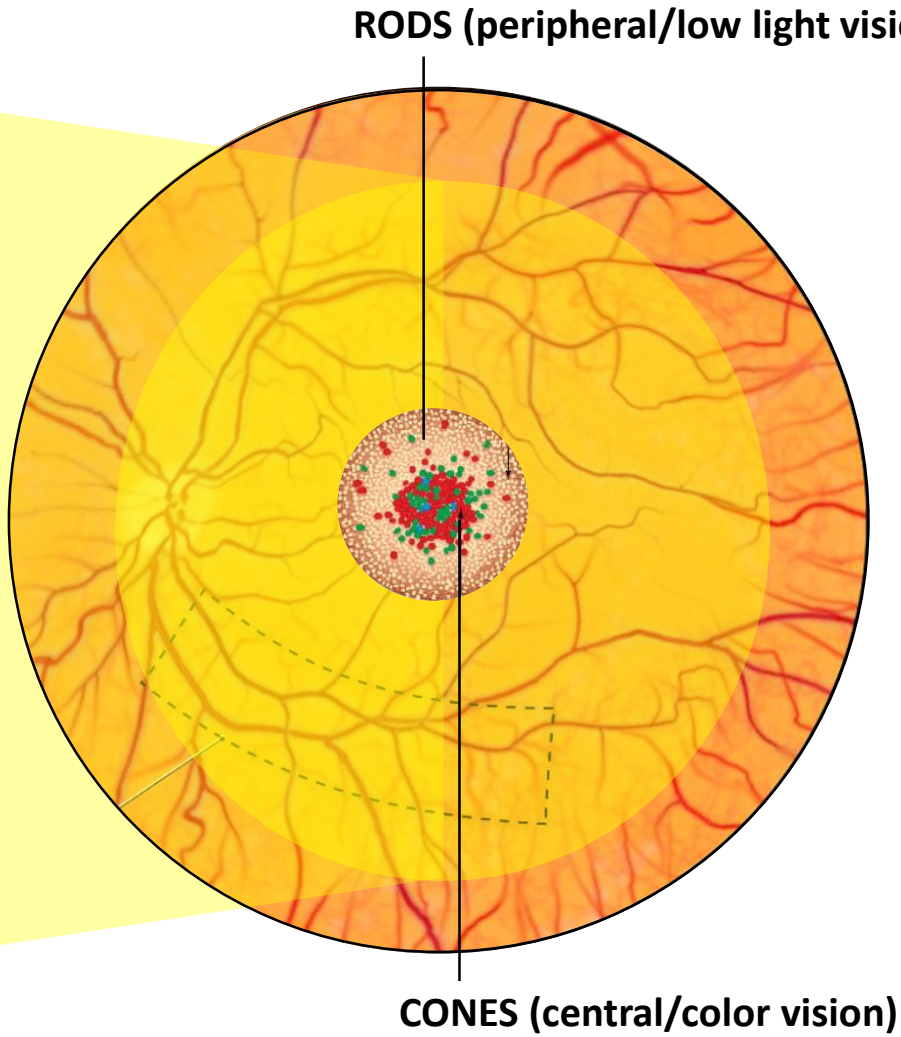
N-RPE65-US-490100-2

HOW VISION WORKS

ROLE OF PHOTORECEPTORS

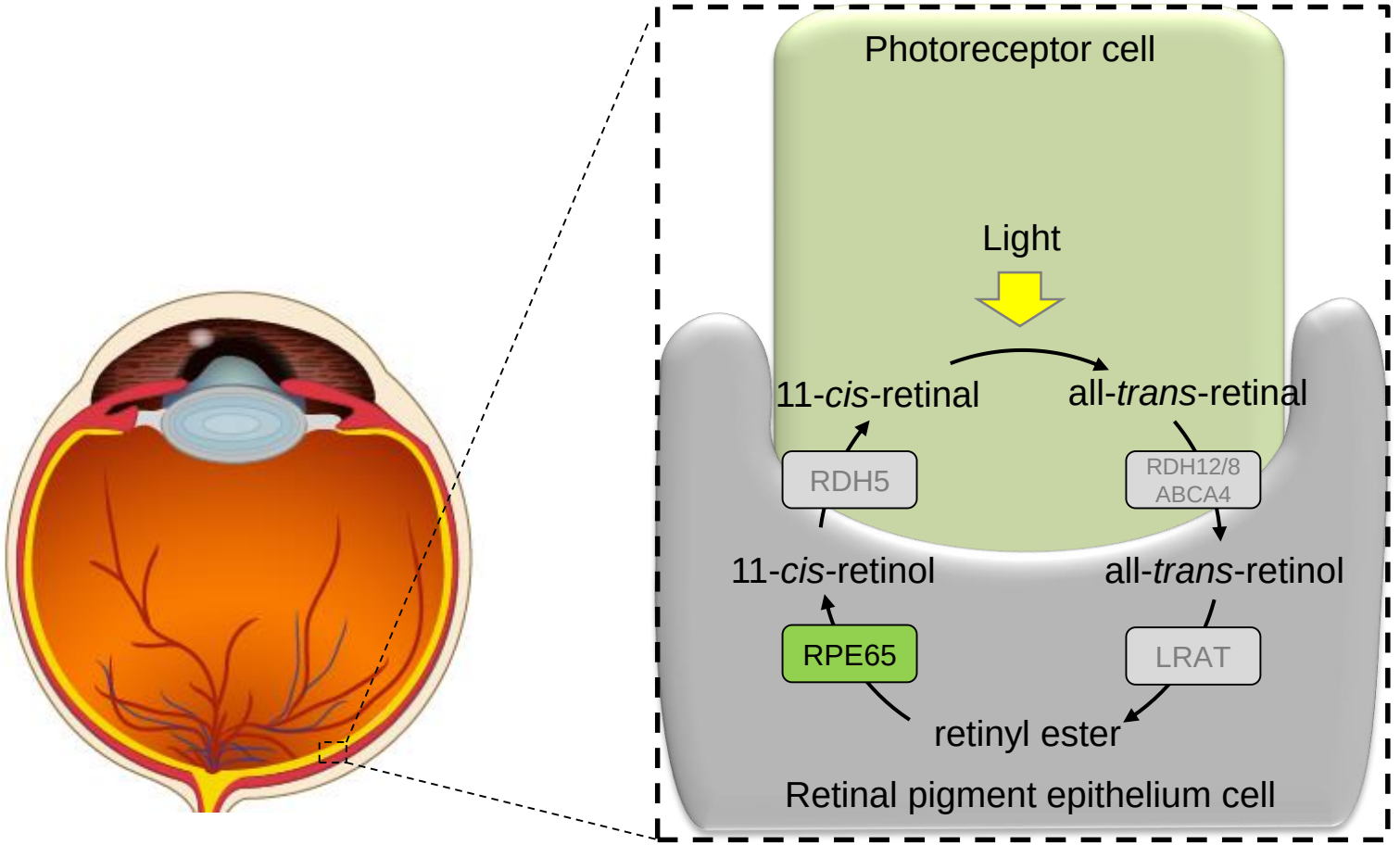




Information for Healthy Vision: How the Eye Works. National Eye Institute. https://www.nei.nih.gov/learn-about-eye-health/healthy-vision/how-eyes-work Accessed June 6, 2023.

ROLE OF RPE65 IN THE VISUAL CYCLE

- The *RPE65* gene encodes a protein, RPE65[1,2]
  - RPE65 is a critical component in the visual cycle
  - RPE65 is necessary for vitamin A metabolism in photoreceptor cells
- Mutations in the *RPE65* gene lead to vision loss due to loss of function (or death) of RPE cells and eventual degeneration of photoreceptors[2,3]



1. Gu et al. *Nat Genet.* 1997;17:194-197. **2.** Weleber et al. *Invest Ophthalmol Vis Sci.* 2011;52:292-302. **3.** Palczewski et al. *Invest Ophthalmol Vis Sci.* 2014;55:6651-6672.
ABCA4, ATP-binding cassette family A transporter member 4;
LRAT, lecithin retinol acyltransferase; RDH, retinol dehydrogenase.

BIALLELIC *RPE65* MUTATION–ASSOCIATED RETINAL DYSTROPHY

VISION LOSS

- Symptoms increasingly limit an affected individual's ability to independently navigate the environment, especially under suboptimal light[1-3]

Photoreceptor Cells	Impairment in Biallelic *RPE65* Mutation–Associated Retinal Dystrophy[1-3]
Rods	Decreased light sensitivity Diminished visual field Nyctalopia Nystagmus Poor adaptation to suboptimal light situations
Cones	Inability to resolve finer central detail

1. Thompson et al. *Invest Ophthalmol Vis Sci.* 2000;41:4293-4299. **2.** Weleber et al. *Invest Ophthalmol Vis Sci.* 2011;52:292-302. **3.** Lorenz et al. *Invest Ophthalmol Vis Sci.* 2000;41:2735-2742.

BIALLELIC *RPE65* MUTATION–ASSOCIATED RETINAL DYSTROPHY

VISUAL FUNCTION ASSESSMENTS

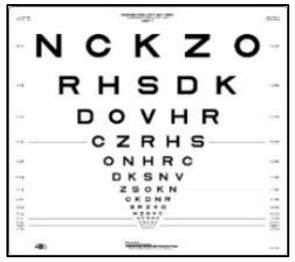
Photoreceptor Cells	Available Assessments	Measured Parameter
Rods[1]	Visual field testing - peripheral Full-field light sensitivity threshold test Electroretinogram - rod response	Peripheral visual field Light detection Electrical activity in response to light
Cones[1]	Visual field testing - central Full-field light sensitivity threshold test with chromatic stimuli Electroretinogram - cone response Visual acuity	Center of visual field Light detection Electrical activity in response to light Central vision

- None of the existing individual assessments fully capture the range of visual impairments in biallelic *RPE65* mutation–associated retinal dystrophy[2]
- A novel assessment is needed to measure a patient's ability to navigate under different environmental lighting conditions[2]

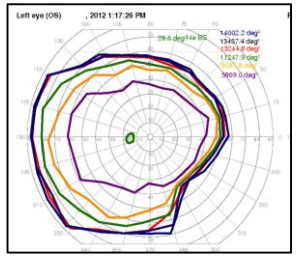
1. Roman et al. *Exp Eye Res.* 2005;80:259-272. **2.** Data on file, Spark Therapeutics, Inc.

VISUAL FUNCTION VS. FUNCTIONAL VISION

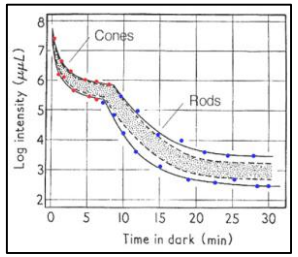
Visual Function



Visual Acuity



Visual Fields



Contrast, Light/Dark Adaptation

Integration

Functional Vision

Reading

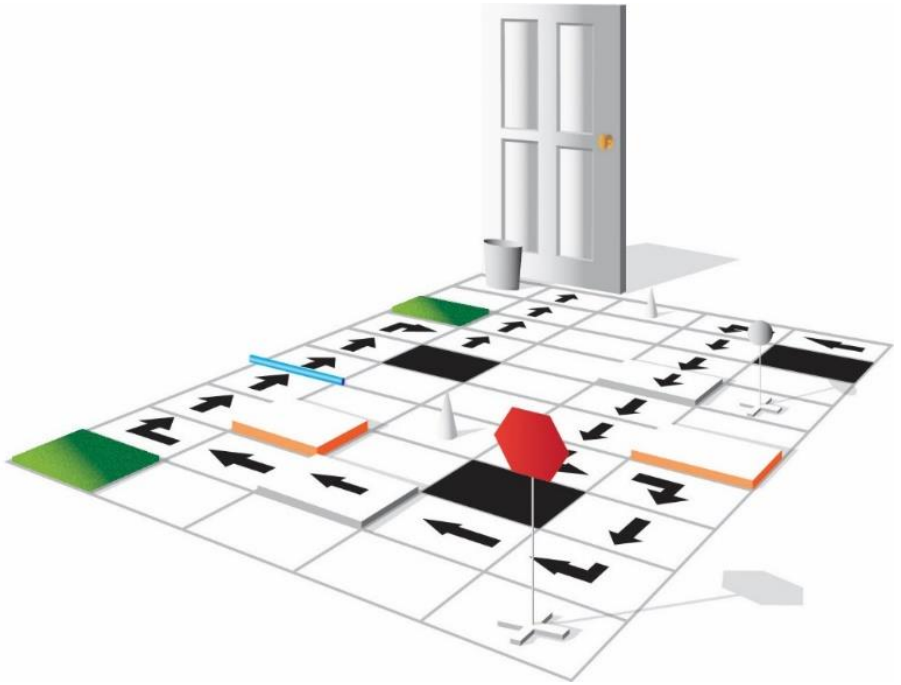
Mobility/ Navigation

MULTI-LUMINANCE MOBILITY TEST (MLMT)^{SM}

A NOVEL MEASURE OF FUNCTIONAL VISION, WHICH REFERS TO THE ABILITY TO CONDUCT VISUALLY DEPENDENT ACTIVITIES OF DAILY LIVING INDEPENDENTLY

- Developed at CHOP by the sponsor of voretigene neparvovec-rzyl clinical trials with input from the FDA
- Designed to provide clinically meaningful assessment of functional vision and evaluate potential changes in functional vision over time, including after intervention
- Measures functional, ambulatory vision at light levels encountered during activities of daily living

MLMT^{SM} course layout



1 of 12 standardized configurations

CHOP, Children's Hospital of Philadelphia; FDA, US Food and Drug Administration

Chung et al. *Clin Experiment Ophthalmol*. 2017, doi: 10.1111/ceo.13022.

MULTI-LUMINANCE MOBILITY TEST (MLMT^{SM})

PHASE 3, PRIMARY EFFICACY ENDPOINT

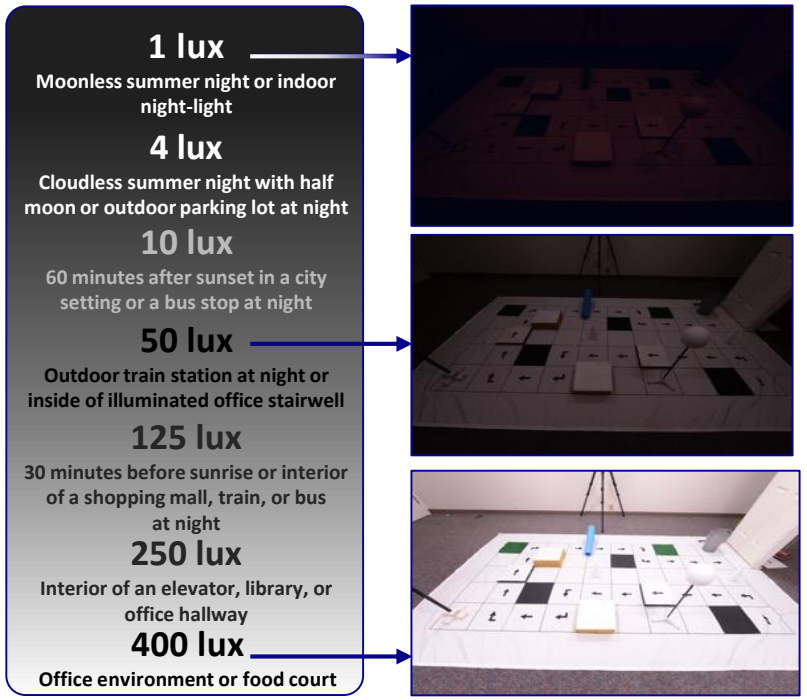
MLMT^{SM}

- Subjects were observed while navigating a course with obstacles of varying height under different levels of illumination[1-3]
- After 40 minutes of dark adaptation, subjects completed a configuration of the course with one eye patched, completed a new configuration with the other eye patched, and completed a third configuration using both eyes[1]
- This process was repeated until failing and passing light level thresholds were identified for each eye-patched condition[1]
- Subjects were graded based on accuracy and speed[1]
  - Passing was defined as completion of the course at the specified lux level with fewer than 4 errors and within 3 minutes[1]

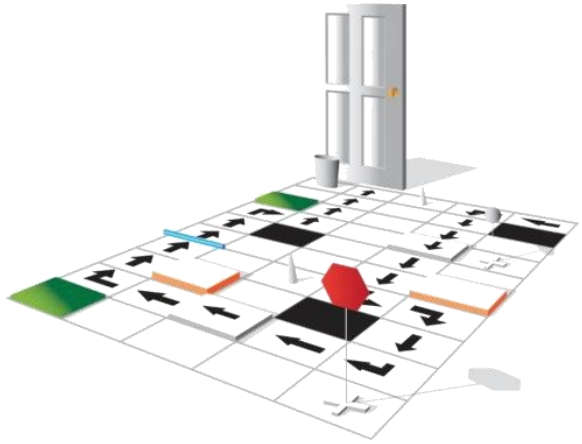
Lux levels

- To quantify subject performance over time, an MLMT^{SM} score change was calculated by assigning score codes to each lux level[3]
- The score change is the difference between the score of the lowest lux level passed at baseline and Year 1[3]

Light levels with examples[2,3,a]



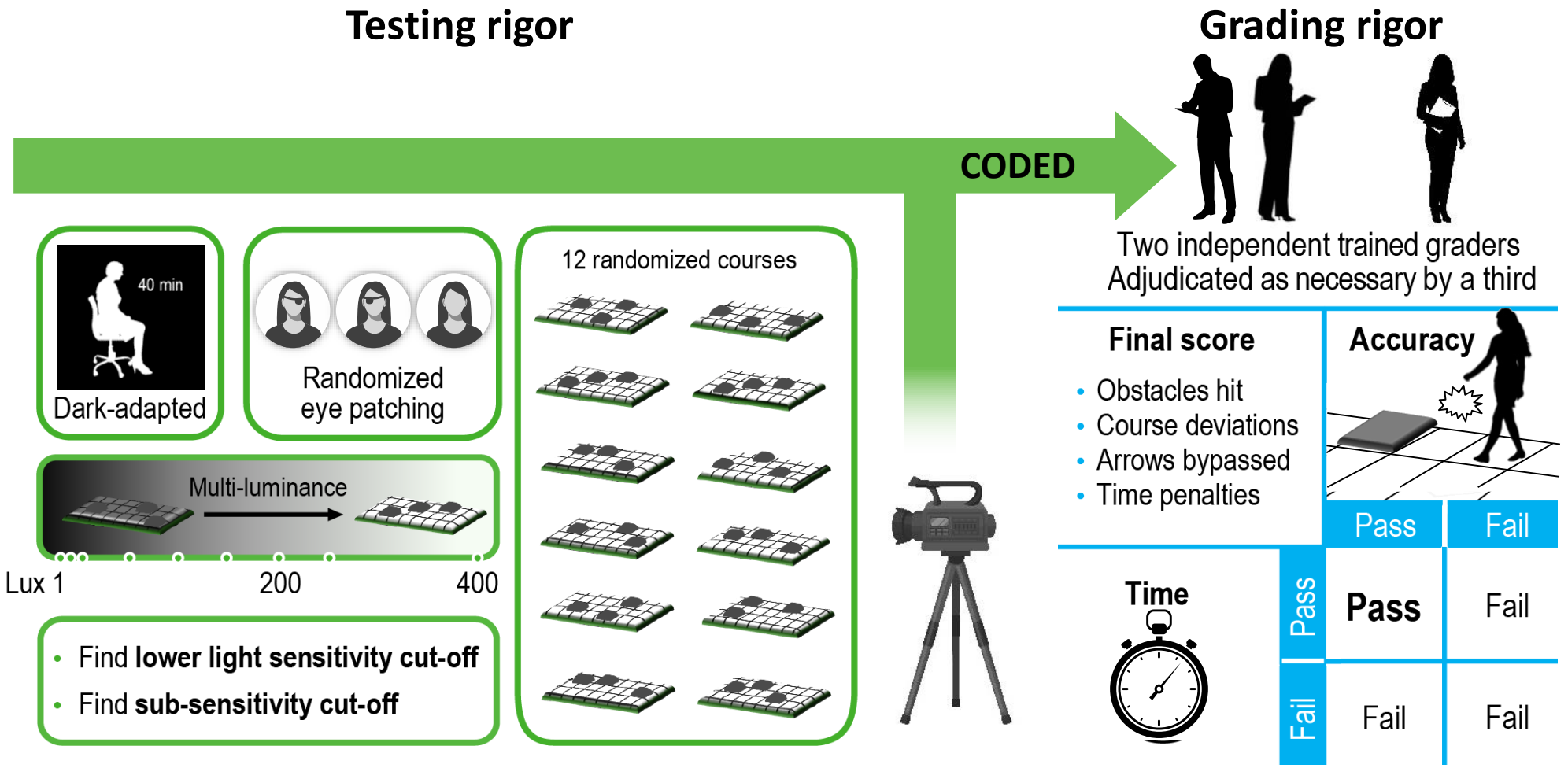
MLMT^{SM} course layout (1 of 12 standardized templates)[1-3]



[a]NIST-calibrated, Extech model #EA33 light meter used to both provide light examples and set light levels for MLMT^{SM}.

1. Russell et al. *Lancet*. 2017;390:849-860. **2.** Chung et al. *Clin Experiment Ophthalmol*. 2018;46(3):247-259.
3. LUXTURNA [package insert]. Philadelphia, PA: Spark Therapeutics, Inc., 2022.

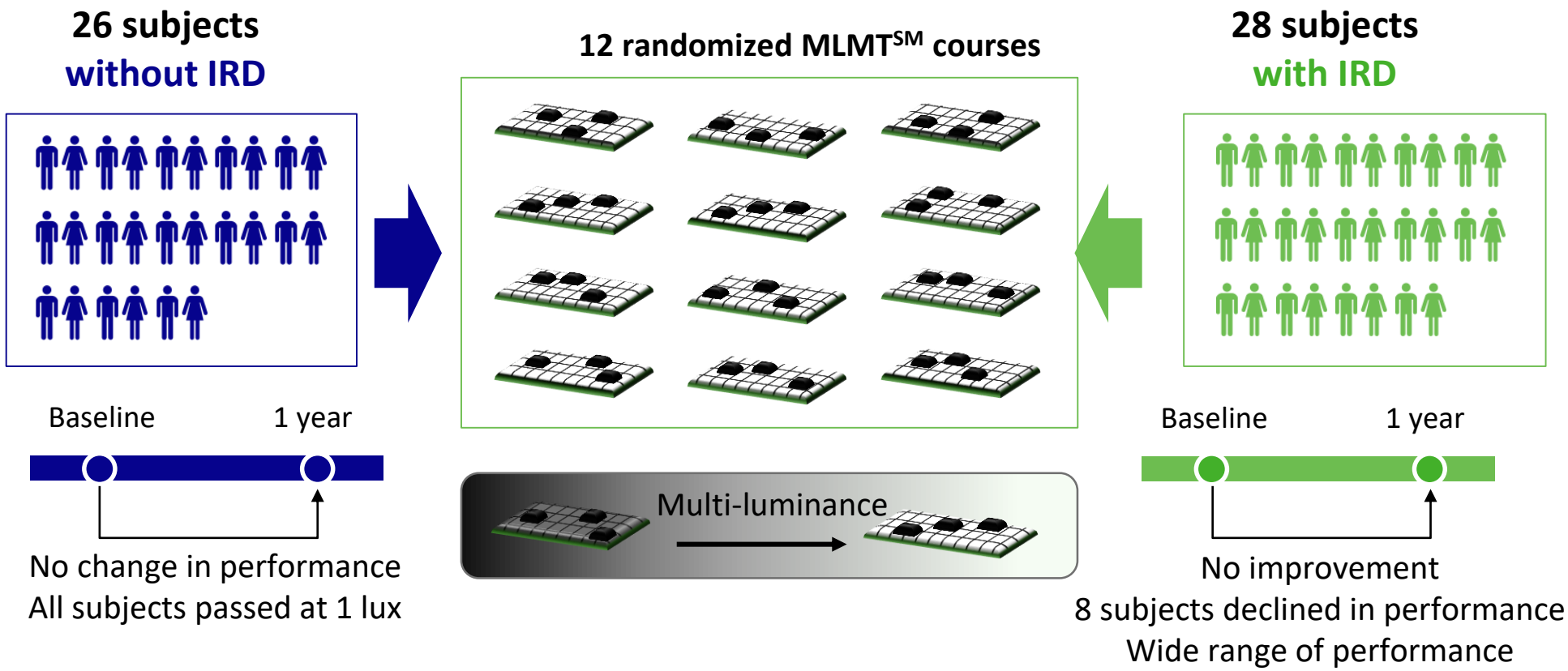
MLMT^{SM} ASSESSMENT



Chung et al. *Clin Experiment Ophthalmol*. 2017, doi: 10.1111/ceo.13022.

MLMT[SM] VALIDATION STUDY

DESIGNED TO ASSESS CONSTRUCT AND CONTENT VALIDITY



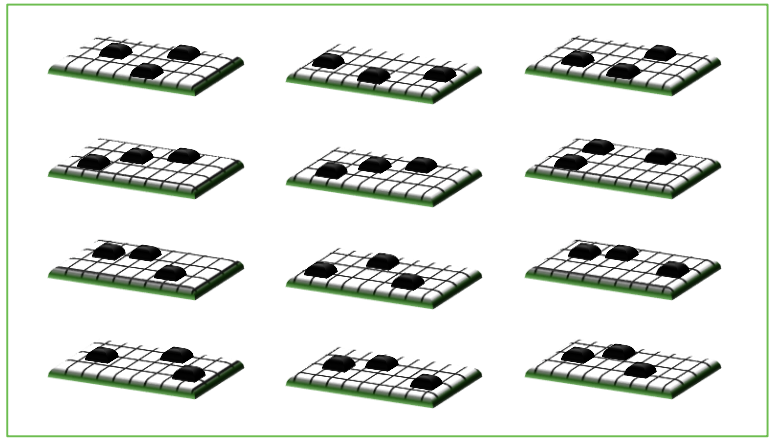
IRD, inherited retinal dystrophy.

Chung et al. *Clin Experiment Ophthalmol*. 2017, doi: 10.1111/ceo.13022.

MLMT[SM] VALIDATION STUDY

KEY FINDINGS AND CONCLUSIONS

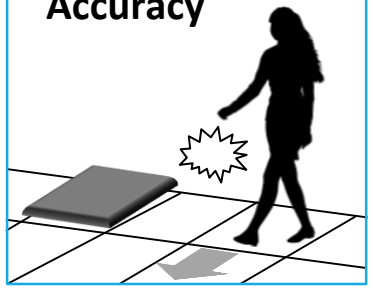
12 randomized MLMT[SM] courses are of comparable difficulty



The scoring system is highly reproducible

Time

Accuracy

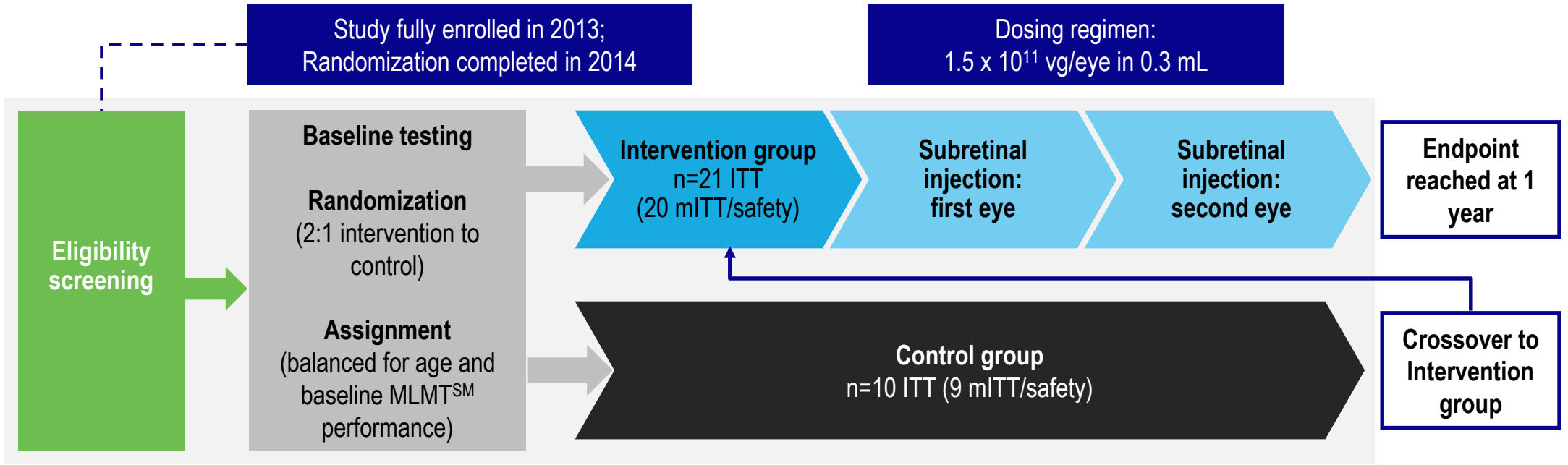


Clinical assessment needs met

- Accuracy score relates to visual acuity, visual field, and quality of life, the latter measured by a visual function questionnaire
- Distinguish visually impaired and normally sighted subjects
- Identify a range of functional vision ability of low vision patients
- Assess changes in functional vision over time

Chung et al. *Clin Experiment Ophthalmol*. 2017, doi: 10.1111/ceo.13022.

LUXTURNA® (VORETIGENE NEPARVOVEC-RZYL) PHASE 3: TRIAL DESIGN



Key inclusion criteria:

- ≥3 years of age
- Confirmed *RPE65* mutations
- Sufficient viable retinal cells (can be confirmed by OCT)

Endpoints:

- Primary: MLMT^{SM} performance (bilateral)
- Secondary: FST testing, MLMT^{SM} (assigned first eye), visual acuity

FST, full-field light sensitivity threshold; ITT, intent-to-treat; mITT, modified intent-to-treat; MLM^{SM}, Multi-Luminance Mobility Test; OCT, optical coherence tomography; vg, vector genome.

Russell et al. *Lancet*. 2017;390:849-860.

PHASE 3 RESULTS

CHANGES IN FUNCTIONAL VISION AS ASSESSED BY MLMT^{SM}

Efficacy Outcomes	LUXTURNA (n=21)	Control (n=10)	Difference (LUXTURNA Minus Control)	*P* Value
MLMT^{SM} score change for bilateral eyes, median (min, max)	2 (0, 4)	0 (-1, 2)	2	0.001
MLMT^{SM} score change for first-treated eye, median (min, max)	2 (0, 4)	0 (-1, 1)	2	0.003

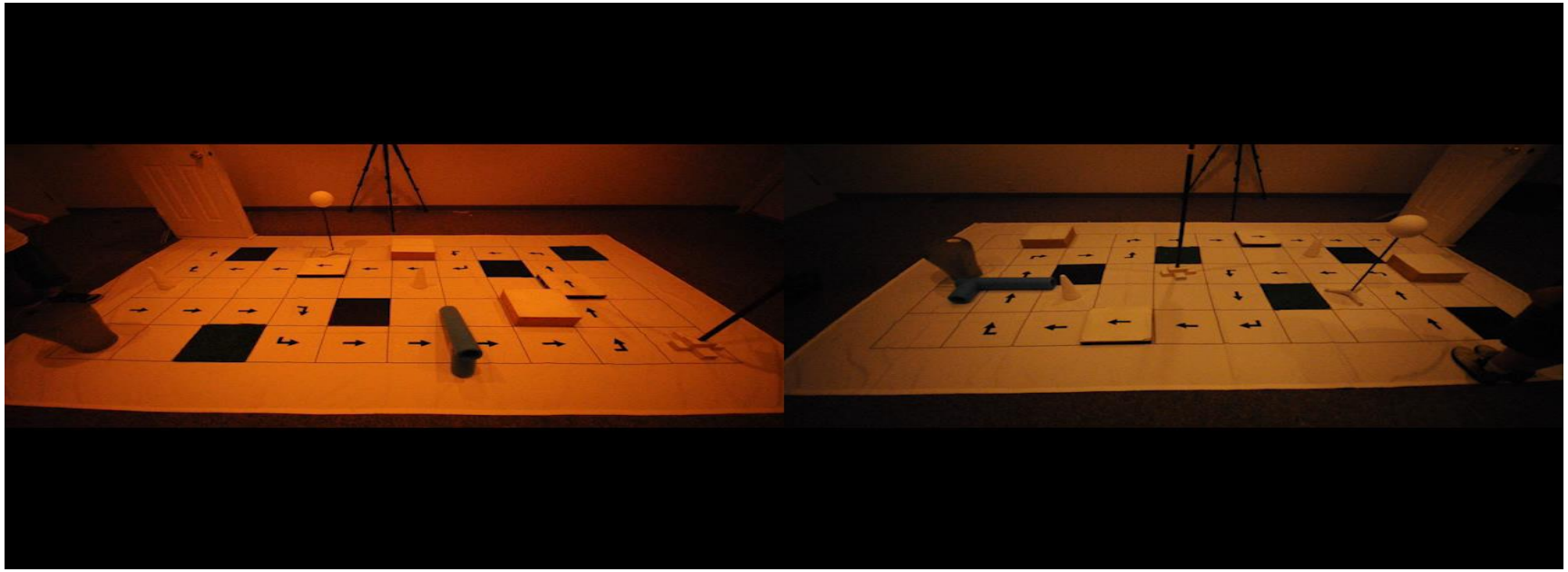
MLMT^{SM}, Multi-Luminance Mobility Test^{SM}.

LUXTURNA [package insert]. Philadelphia, PA: Spark Therapeutics, Inc., 2022.

TRIAL PARTICIPANT MLMT^{SM} VIDEOS (BILATERAL TESTING)

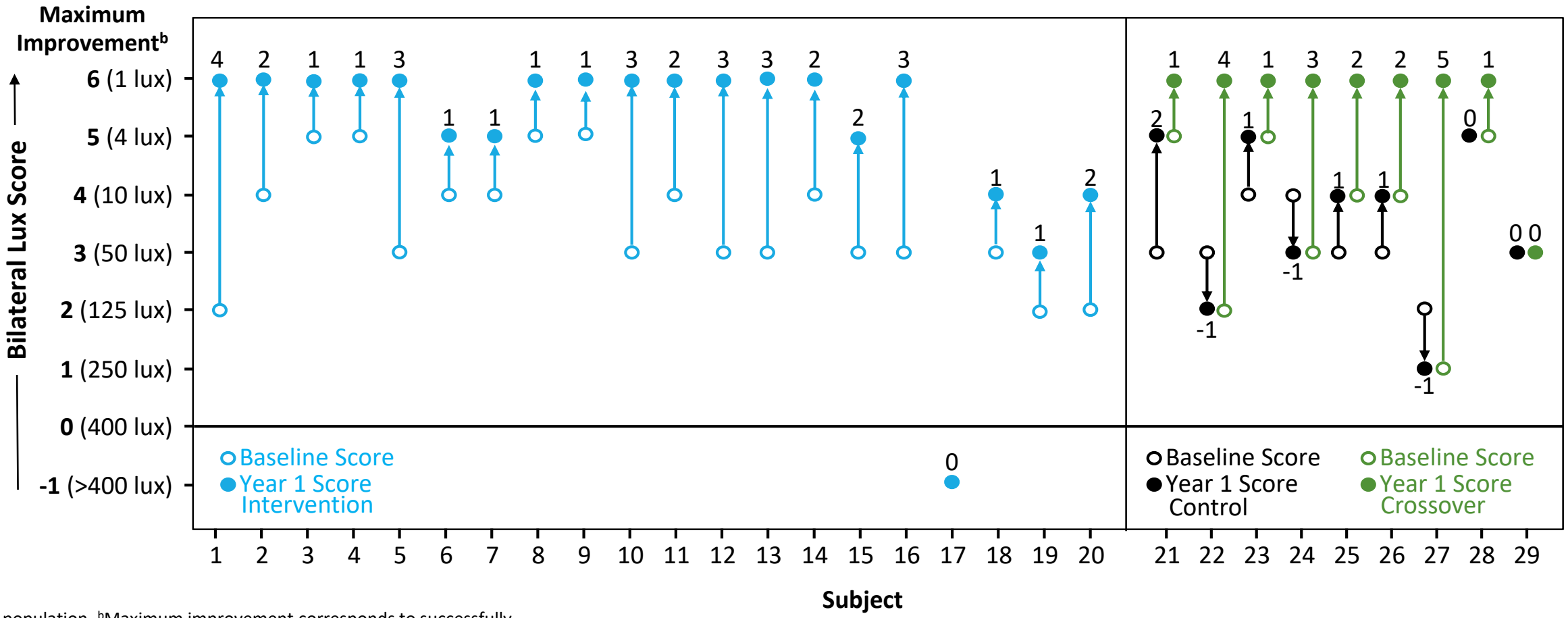
Baseline visit at 1 lux (**Fail**)

1-year visit after LUXTURNA administration at 1 lux (**Pass**)



Note: The videos are representative of a clinical trial participant with a clinically meaningful bilateral MLMT^{SM} score change of 2 from baseline. The subject's baseline passing light level was 10 lux and Year 1 passing light level was 1 lux.
Light meter: National Institute of Standards and Technology-calibrated, Extech model #EA33 light meters used to provide examples and to set/verify specified light levels used for mobility testing
The camera used automatically adjusts the level and temperature of the light that it captures. Because of this feature, there may be slight variations in hue when filming at low light levels (eg, 1 lux).
Both videos were filmed in low-light environments.
Data on File. Study 301 MLMT^{SM} Video Library. 2017. Spark Therapeutics, Inc. Philadelphia, PA.

BILATERAL MLMT[SM] LUX SCORES AT BASELINE AND YEAR 1 BY SUBJECT[1,a]



[a]mITT population. [b]Maximum improvement corresponds to successfully navigating under a moonless summer night, which may improve critical parts of daily life, such as crossing the street at night.[2]

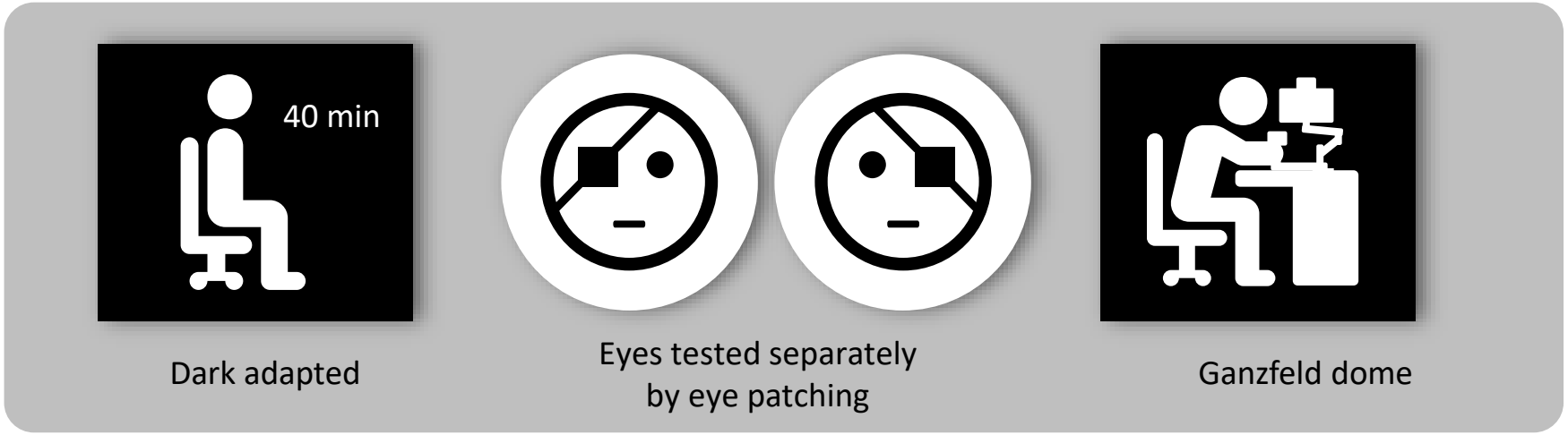
mITT, modified intent-to-treat; MLMT, Multi-Luminance Mobility Test.

1. LUXTURNA [package insert]. Philadelphia, PA: Spark Therapeutics, Inc., 2022.

2. Chung et al. *Clin Experiment Ophthalmol*. 2017. : doi:10.1111/ceo.13022.

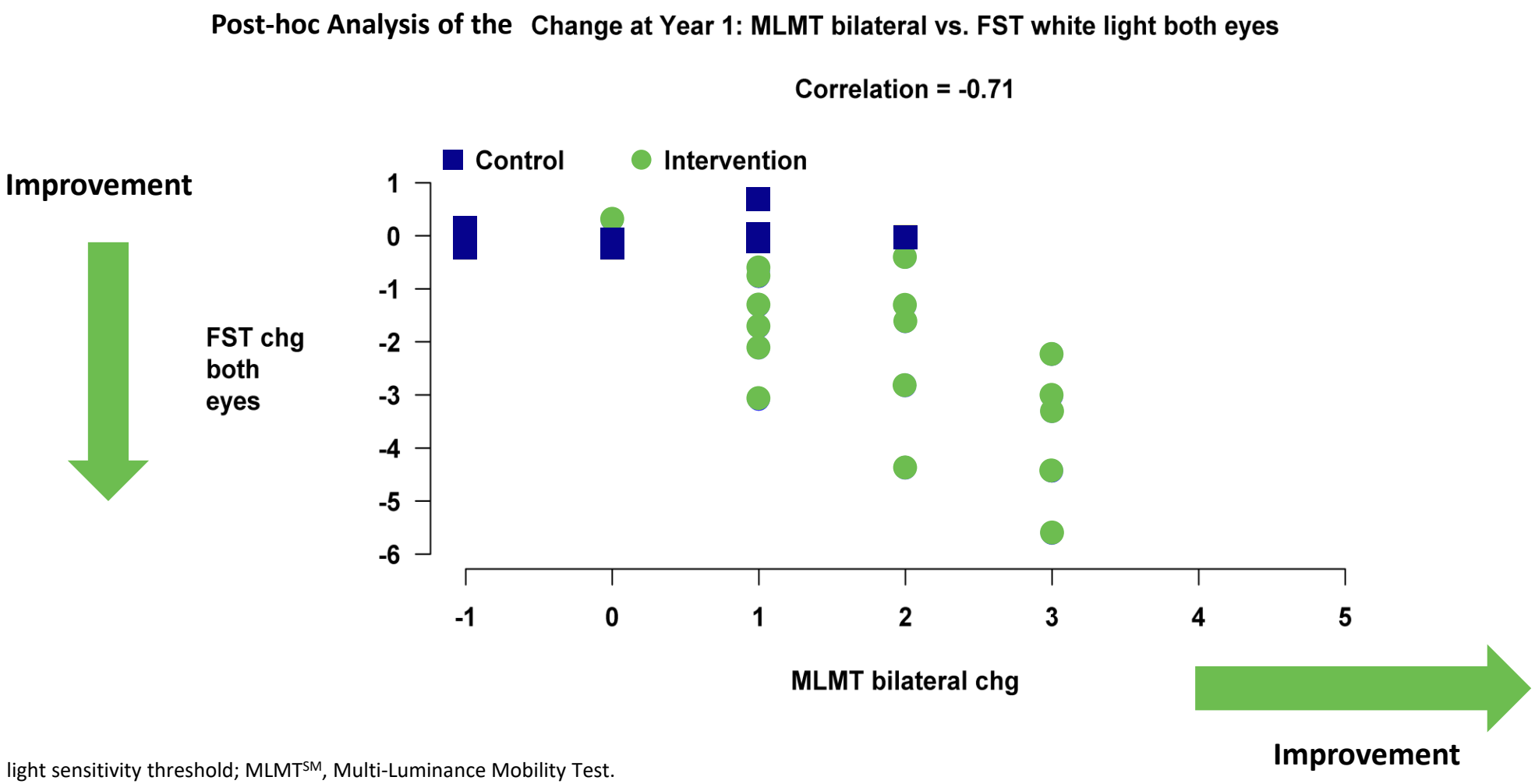
FULL-FIELD LIGHT SENSITIVITY THRESHOLD (FST) TEST

- Provides a physiological test of retinal function that is relevant to the visual deficits experienced by patients with inherited retinal dystrophy[1]
- Measures the lowest illumination detectable over the entire visual field[1]
  - Sensitivity to light is measured over a >5 log unit range[2]
  - An algorithm calculates the minimum luminance at which the subject perceives light for each eye[1]



1. Roman et al. *Exp Eye Res.* 2005;80:259-272. **2.** Bennett et al. *Lancet.* 2016;388:661-672.

CHANGE AT YEAR 1: MLMT^{SM} BILATERAL VS. FST BOTH EYES, CORRELATION= –0.71



FST, full-field light sensitivity threshold; MLMT^{SM}, Multi-Luminance Mobility Test.

Maguire AM, et al. Ophthalmology. 2019 Sep;126(9):1273-1285. doi: 10.1016/j.ophtha.2019.06.017. Epub 2019 Jun 22. PMID: 31443789.

We don’t follow footsteps. We create the path.

Session 3: Considerations in Developing Rare Disease Endpoints: Clinical Outcome Assessment (COA)

Moderator:

- **Naomi Knoble,** U.S. Food and Drug Administration

Panelists:

- **Yuqun "Abigail" Luo,** U.S. Food and Drug Administration
- **Lindsey Murray,** Critical Path Institute
- **David Rousso,** Spark Therapeutics
- **Lei Xu,** U.S. Food and Drug Administration

Session 3: Considerations in Developing Rare Disease Endpoints: Clinical Outcome Assessment (COA)

1. What are some of the biggest challenges stakeholders experience in developing and using COAs for rare disease research? What are effective strategies for overcoming or minimizing the impact of those challenges?
2. How can sponsors identify existing COAs that may be reused or modified for new applications? How can researchers and sponsors benefit from the broader sharing of data around the utility of existing COAs?
3. How can stakeholders, including patients/advocates, work together to advance the use of COAs in rare disease drug development?
4. What are some of the key opportunities regarding future development of COAs for use in rare disease clinical research?
5. What else is needed to advance the development and use of COAs in the rare disease space?

Session 4: Considerations in Developing Rare Disease Endpoints: Multiple Endpoints, with a Focus on Multicomponent Endpoints

4:10 – 4:55 pm ET

Endpoint Types and Definitions

Kathleen Fritsch, Ph.D., Master Mathematical Statistician
FDA/CDER/Division of Biometrics III
Rare Disease Endpoint Advancement Workshop
June 7, 2023

Endpoint Definition

- A precisely defined variable intended to reflect an outcome of interest that is statistically analyzed to address a particular research question
- Typically, you need to specify the
  - Type of assessments
  - Timing of those assessments
  - Assessment tools used
  - How multiple assessments within an individual will be combined

(Source: BEST (Biomarkers, EndpointS, and other Tools) Resource)

Types of Clinical Trial Assessments

- Outcomes or events (e.g., death, stroke, venous thromboembolism)
- Signs or symptoms (e.g., pain, dyspnea (difficulty breathing), erythema (redness))
- Performance measures (e.g., distance walked)
- Biomarkers

The first 3 categories are examples of ‘clinical outcomes’ that can support ‘clinical benefit’ and describe or reflect how an individual ‘feels, functions, or survives’

Role of the Key Endpoints

- Primary Endpoints – the endpoint(s) that establish the effects of the drug and will be the basis for concluding that the study meets its objective
- Secondary Endpoints – additional meaningful outcomes that further characterize the investigational product's effects
- Primary and secondary endpoint findings are typically communicated to healthcare providers and patients in product labeling

Managing Multiple Assessments

- Multiple (Simple) Distinct Endpoints
  - Define individual endpoint for each assessment
- Multicomponent Endpoints
  - More than one assessment combined into a single ‘score’ for an individual subject
  - Many options for combining assessments
- Composite Endpoints
  - Special case for a set of adverse outcomes/events you would like to delay or prevent

Multiple Distinct Endpoints

- Define 2 or more individual endpoints
- Useful when condition can be characterized by a limited number of (relatively distinct) assessments (e.g., pain, nausea)
- Advantage: clinical interpretation is straightforward
- Disadvantage: may need many endpoints (could lead to larger sample size)
- Example: Acne has 3 co-primary endpoints.
  - Change in inflammatory lesions
  - Change in non-inflammatory lesions
  - Success on an Investigator's Global Assessment

Multicomponent Endpoint

- Within-subject combination of 2 or more assessments. Useful for
  - Conditions with variable presentation across patients
  - Conditions which are challenging to characterize with a single assessment (e.g., activities of daily living assessment)
  - Conditions where an individual needs to experience improvement on multiple disease elements to be considered to have clinically meaningful improvement
- Can be sum scores, responder definitions, or other meaningful combinations
- Advantage: allows you to combine related assessments into a single endpoint
- Disadvantage: may be harder to interpret/identify which components are impacted by the treatment (or whether any are negatively impacted)
- Conclusion is on the overall effect, not on any of the individual components
  - Assessment of the individual components is usually important, but formal testing should only be conducted if the trial is specifically designed to evaluate them, and the components are meaningful and fit for purpose on their own

Multicomponent Endpoint Examples

- Example 1 (Sum Score): Montgomery-Asberg Depression Rating Scale (MADRS) for major depressive disorder
  - 10 items scored from 0 to 6 (apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulty, lassitude, inability to feel, pessimistic thoughts, suicidal thoughts)
  - Total score ranges from 0 to 60, with higher scores indicating more severe depression
- Example 2 (Responder Definition): Complete cure in onychomycosis of the toenail
  - Responder must have: 0% clinical involvement of the target toenail AND negative results on 2 types of mycological lab tests

Composite Endpoint

- Historically, Major Adverse Cardiovascular Events (MACE) endpoints were called ‘composite’ endpoints
  - Example: incidence of myocardial infarction OR stroke OR death during the trial (analysis evaluates the time to first event)
- MACE has a unique construction compared to multicomponent endpoints
  - Objective to prevent or delay occurrence of clinically important and related events rather than an objective of improving a set of signs/symptoms/performance assessments
- Cardiovascular community developed recommendations and expectations for analyzing ‘composite’ endpoints (i.e., MACE) that did not necessarily translate to multicomponent endpoints
  - For example, individual components for composite should always be examined and reported (see if any important components trend in the wrong direction)
- Consequently, the term ‘composite endpoint’ is primarily applied to MACE and the term ‘multicomponent endpoint’ is applied to symptomatic conditions to avoid confusion regarding recommendations for analysis methods and handling of individual components

Summary

- Endpoints should align with study objectives
- Objectives should guide choice between ‘simple’ or multicomponent endpoints rather than sample size or analytical convenience
- The appropriateness of ‘simple’ vs. multicomponent endpoints will depend on the complexity of the condition, the inter-relatedness of the assessments, and the interpretability of a proposed multicomponent score

Resources

- BEST (Biomarkers, EndpointS, and other Tools) Resource

https://www.ncbi.nlm.nih.gov/books/NBK338448/#IX-E

- Guidance for industry “Multiple Endpoints in Clinical Trials” (October 2022)

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/multiple-endpoints-clinical-trials-guidance-industry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Rare Disease Drug Development: Multiple Endpoints Considerations

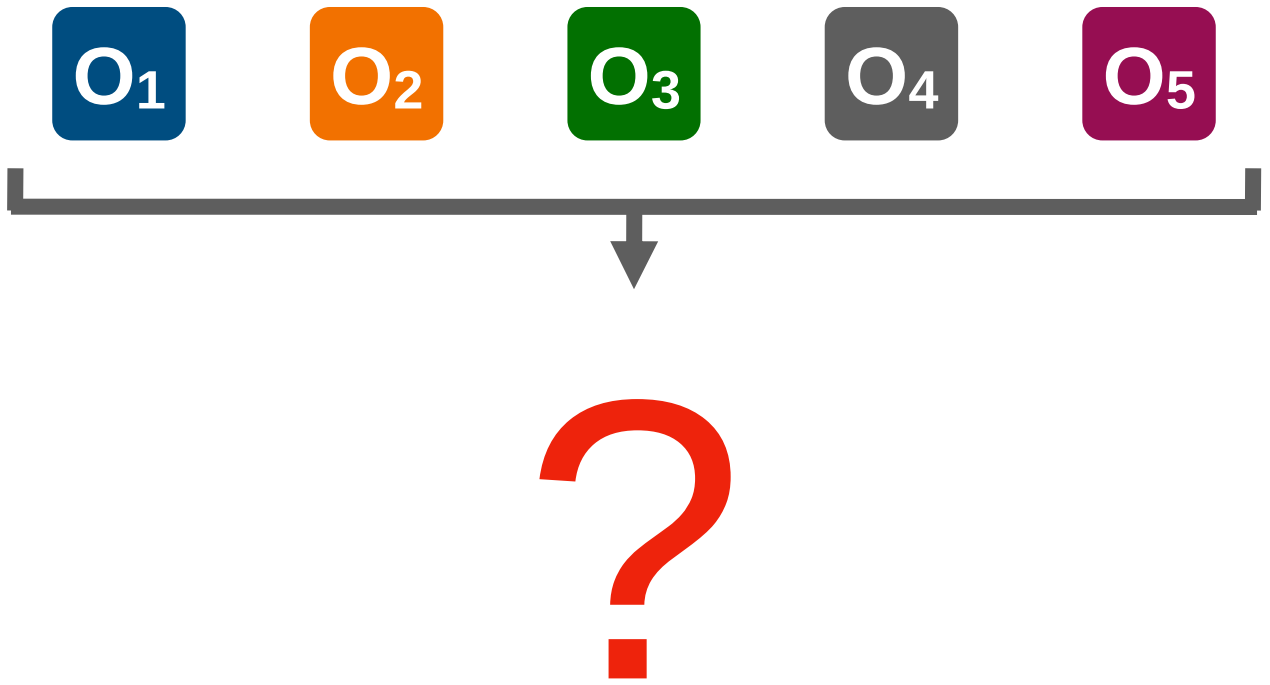
Lili Garrard, PhD
Master Scientist and Technical Lead
Patient-Focused Statistical Scientists
CDER/OTS/Office of Biostatistics/Division of Biometrics III

Endpoint Development is Hard…Especially in Rare Disease Drug Development

- Challenging to assess a single concept of interest across all patients due to heterogeneity within a disease
- No perfect endpoint strategy when a disease affects multiple aspects of feeling and functioning
  - Maybe necessary to consider several different aspects to adequately assess benefit
  - Should consider the strengths and limitations of various approaches
  - When possible, evaluate several different endpoints in earlier studies to inform endpoint selection for later studies

Heterogeneity In Diseases

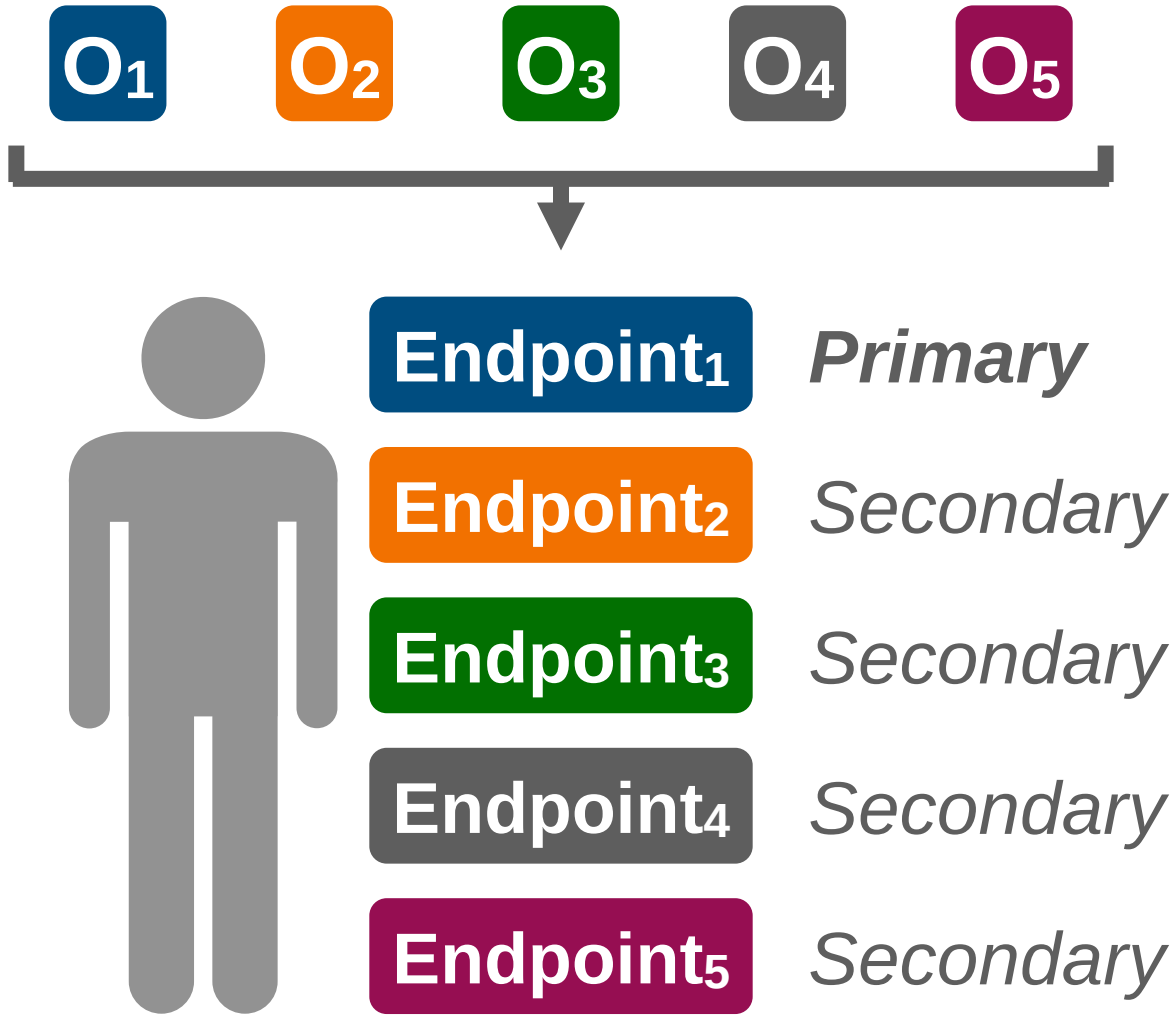
Multiple outcome variables associated with a disease



Heterogeneity In Diseases

Multiple outcome variables associated with a disease

Construct separate endpoints for each aspect of health



Heterogeneity In Diseases

Multiple outcome variables associated with a disease

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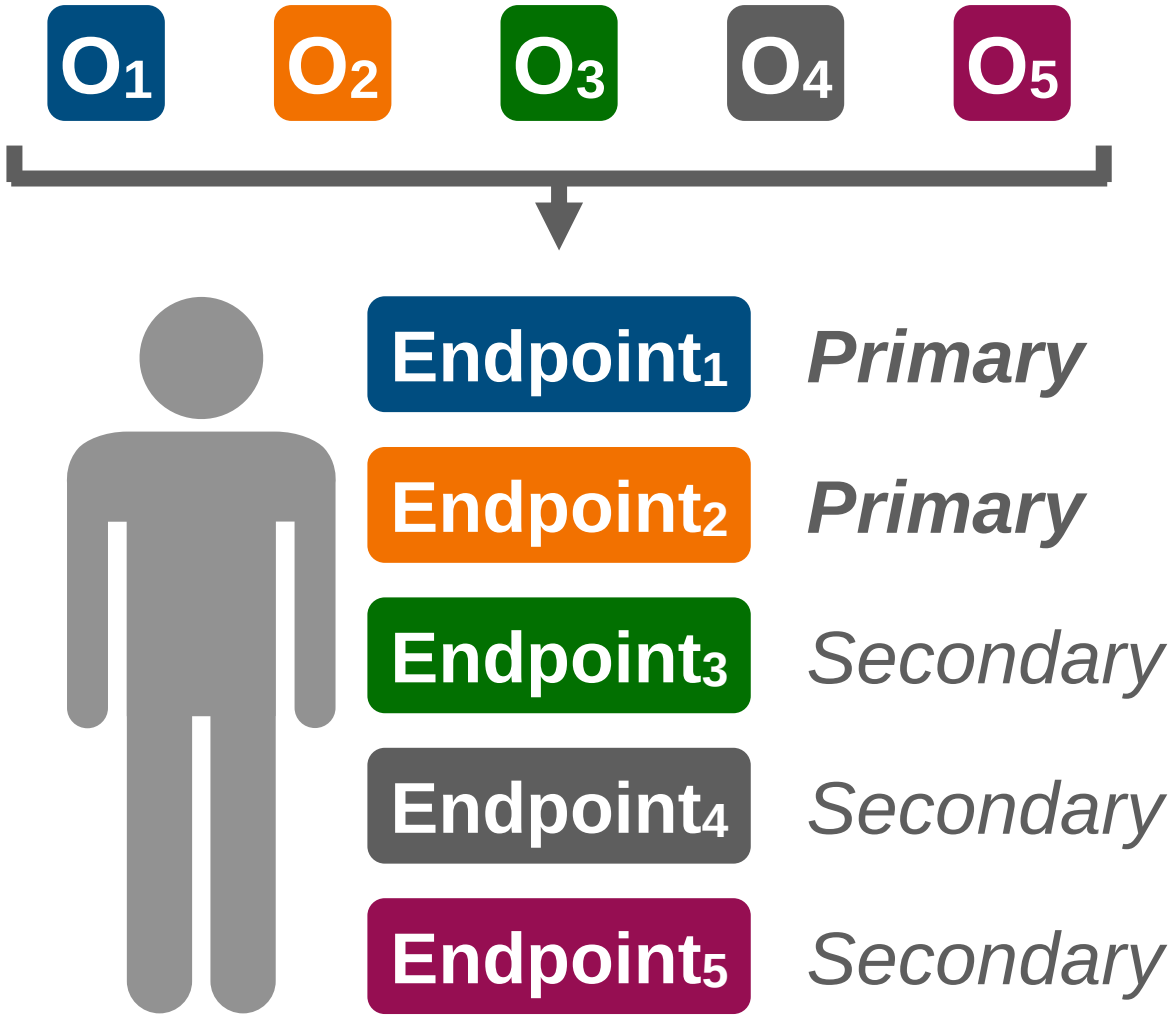
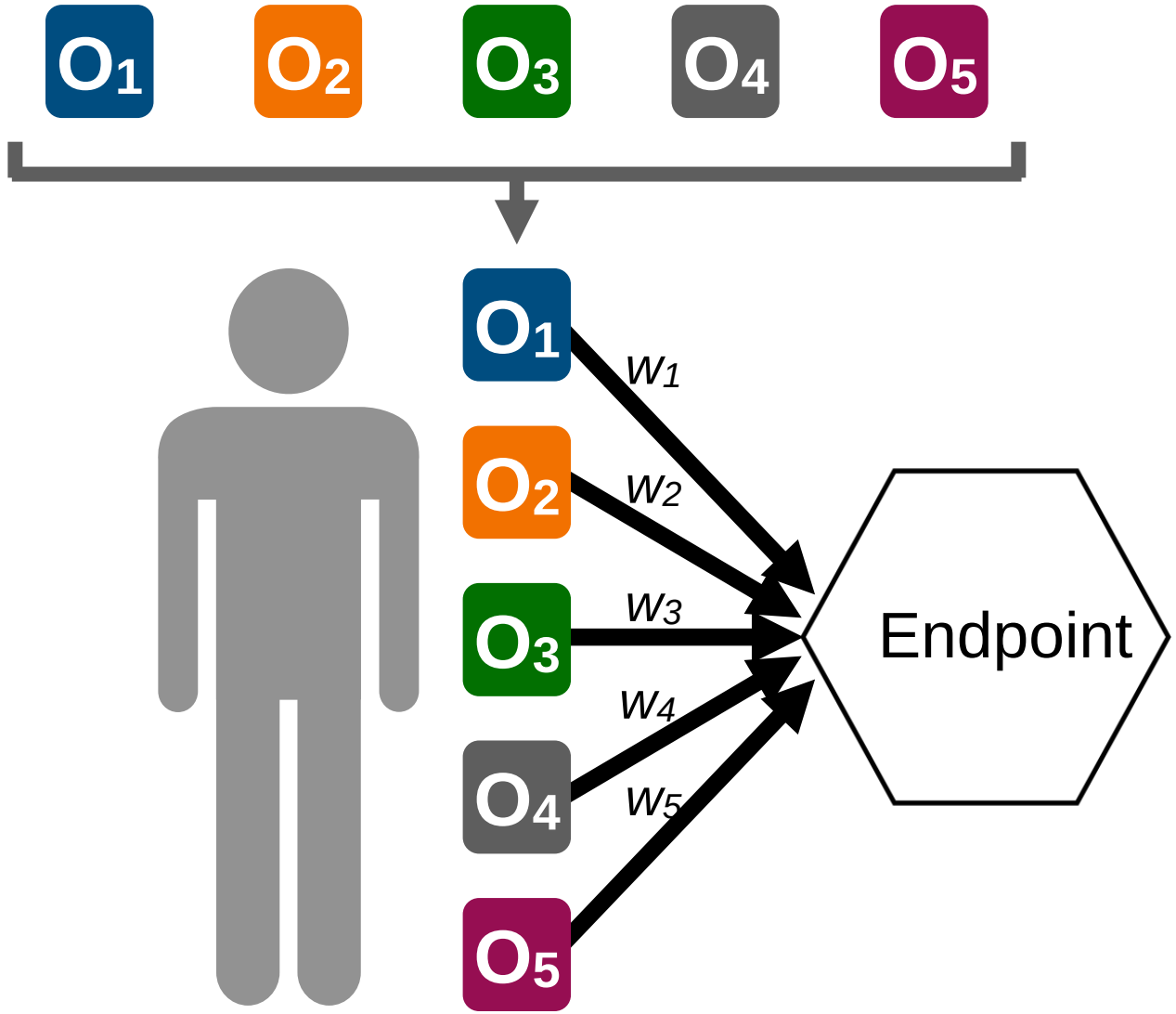


Separate Endpoints For Each Aspect of Health

- Strength: Clarity about which aspect of health is affected by medical product
- Challenges
  - Aspect(s) of health affected by medical product not always known ahead of time
  - Depending on role of endpoints, multiplicity adjustments might be needed, resulting in larger sample size
  - If patients differ in aspect of health affected, then treatment effect for any one endpoint will be diluted

Heterogeneity In Diseases

Multiple outcome variables associated with a disease



Construct a multi-component endpoint

"[A] within-subject combination of two or more components"

Multi-Component Endpoint

- Need to carefully consider the interpretation of the overall endpoint
  - Selection of individual components is critical. Some considerations include, but not limited to:
    - Clinical importance
    - Whether different components trend in the same direction within a subject
    - How each individual component will be measured
    - How will interpretation be impacted when combining different types of components? E.g., Combing biomarker- and clinical outcome assessment (COA)-based components into a multi-component endpoint
  - Scoring method for the overall endpoint and each component, including the weighting scheme, if applicable

Endpoint Development is Hard…Especially in Rare Disease Drug Development

- There is no perfect endpoint strategy when a disease affects multiple aspects of feeling and functioning, so sponsors should choose the best for their context of use
  - Provide a well-justified rationale to support the proposed endpoint, for example
    - Strengths and limitations of the proposed endpoint
    - Why the proposed endpoint is important to patients and/or caregivers
    - If a multi-component endpoint, justification for components included and the algorithm for combining them into the endpoint
  - Interpretation is key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Department of Population Health Sciences
Duke University School of Medicine

Rare Disease Drug Development
Multicomponent Endpoints

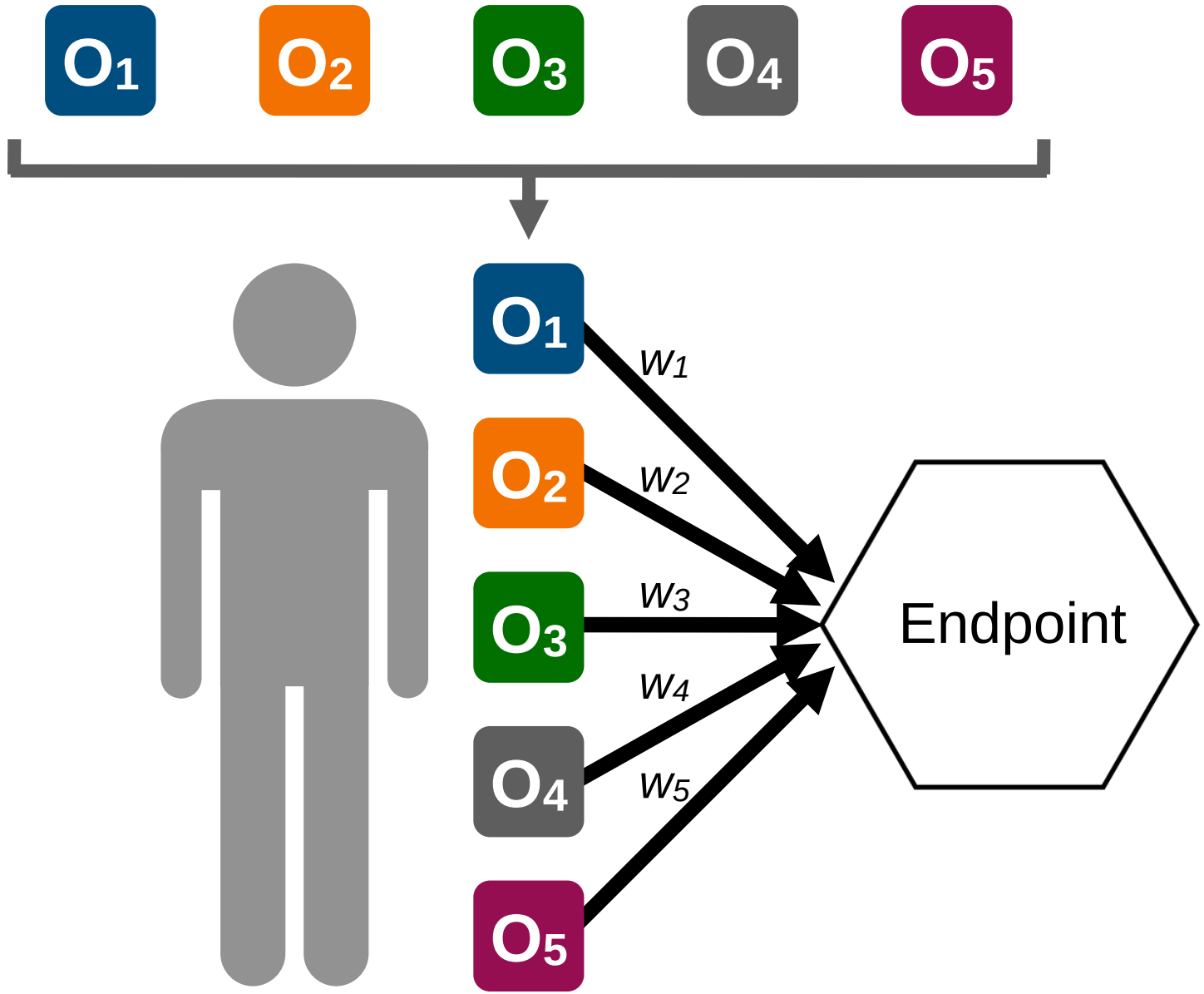
Kevin Weinfurt, PhD
James B. Duke Distinguished Professor
Department of Population Health Sciences
Duke University School of Medicine
Special Governmental Employee, FDA/CDER

Center for Health Measurement
person centered • evidence driven

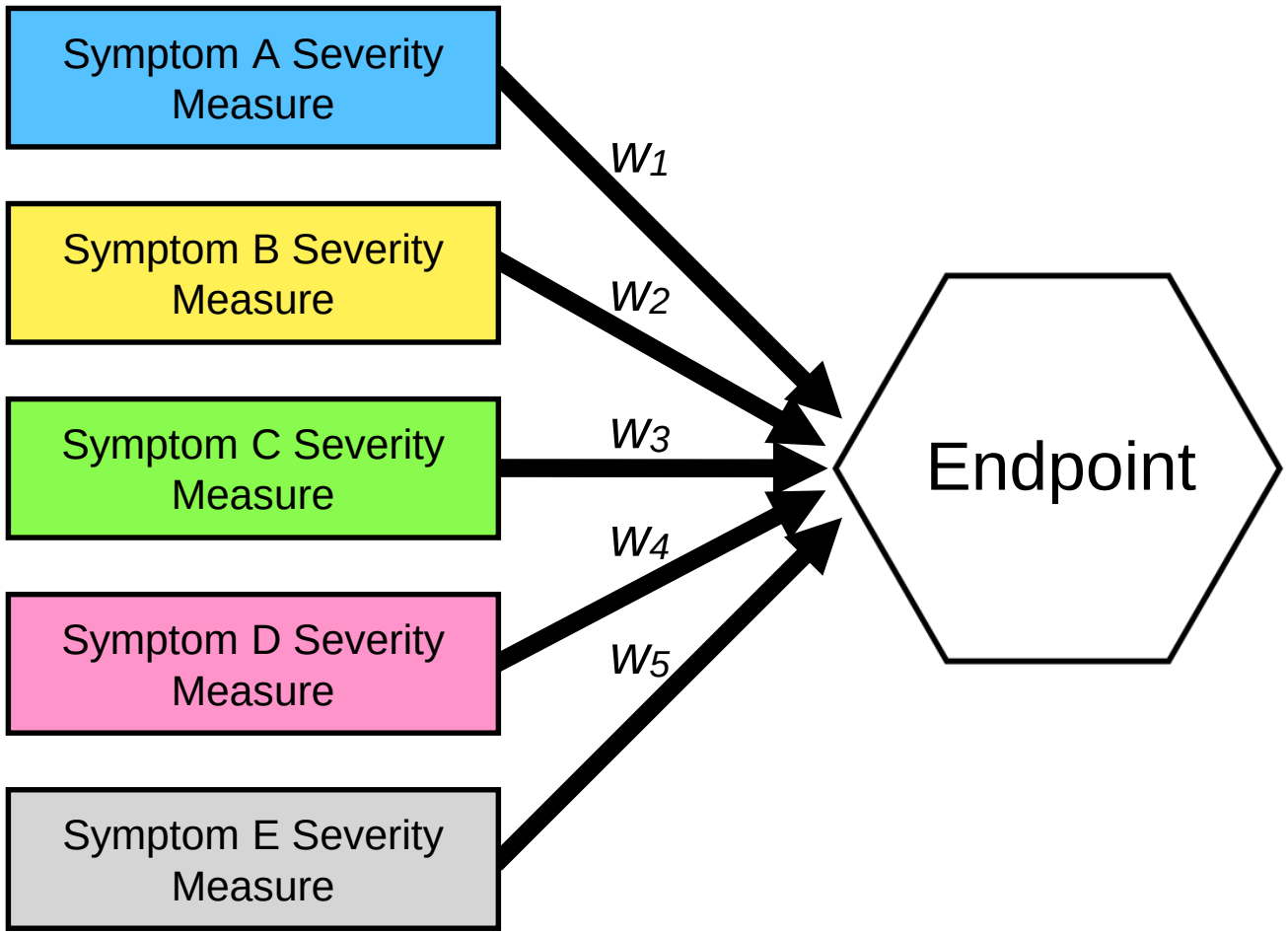
Multiple outcome variables associated with a disease

Construct a multi-component endpoint

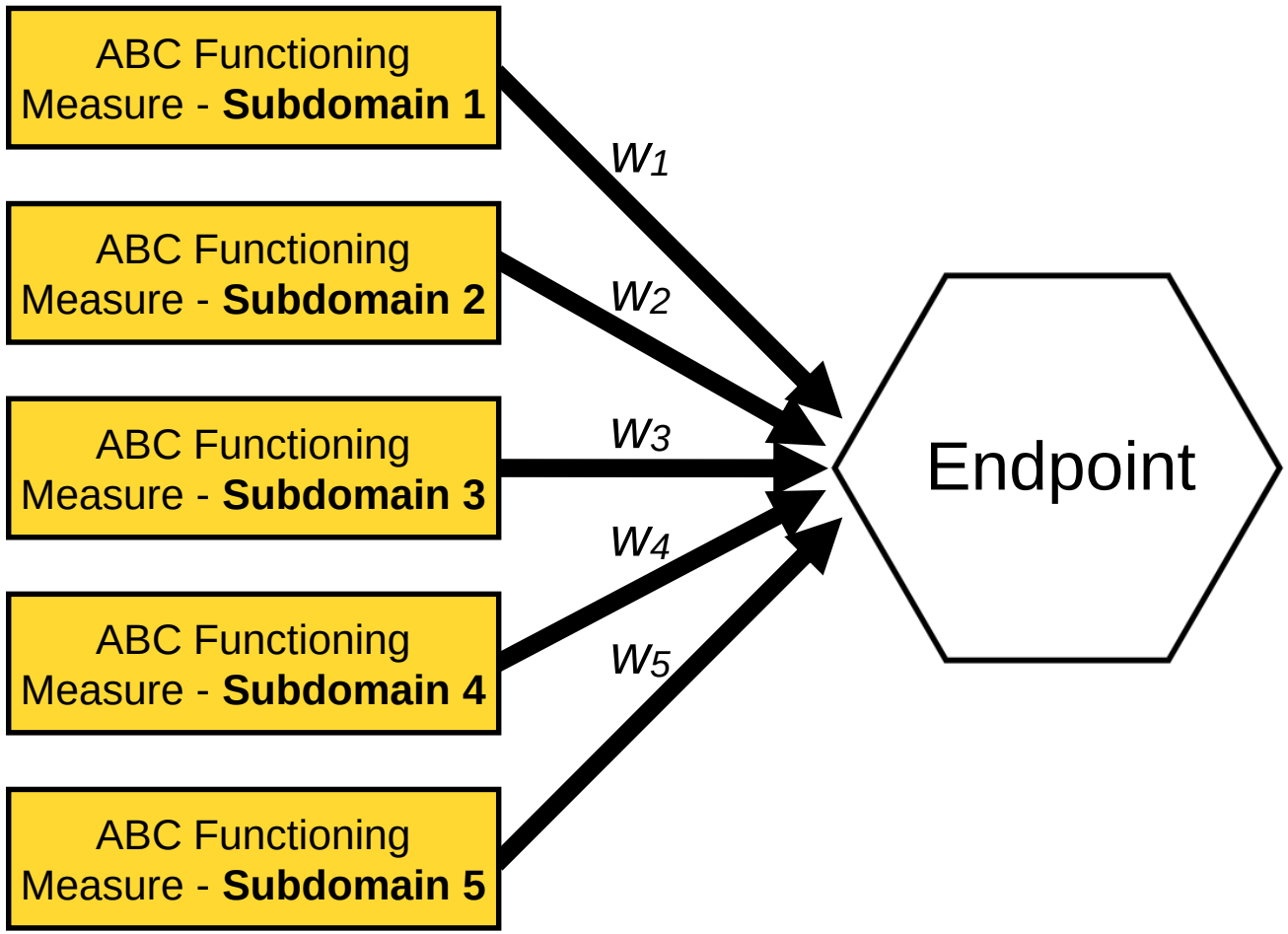
"[A] within-subject combination of two or more components"



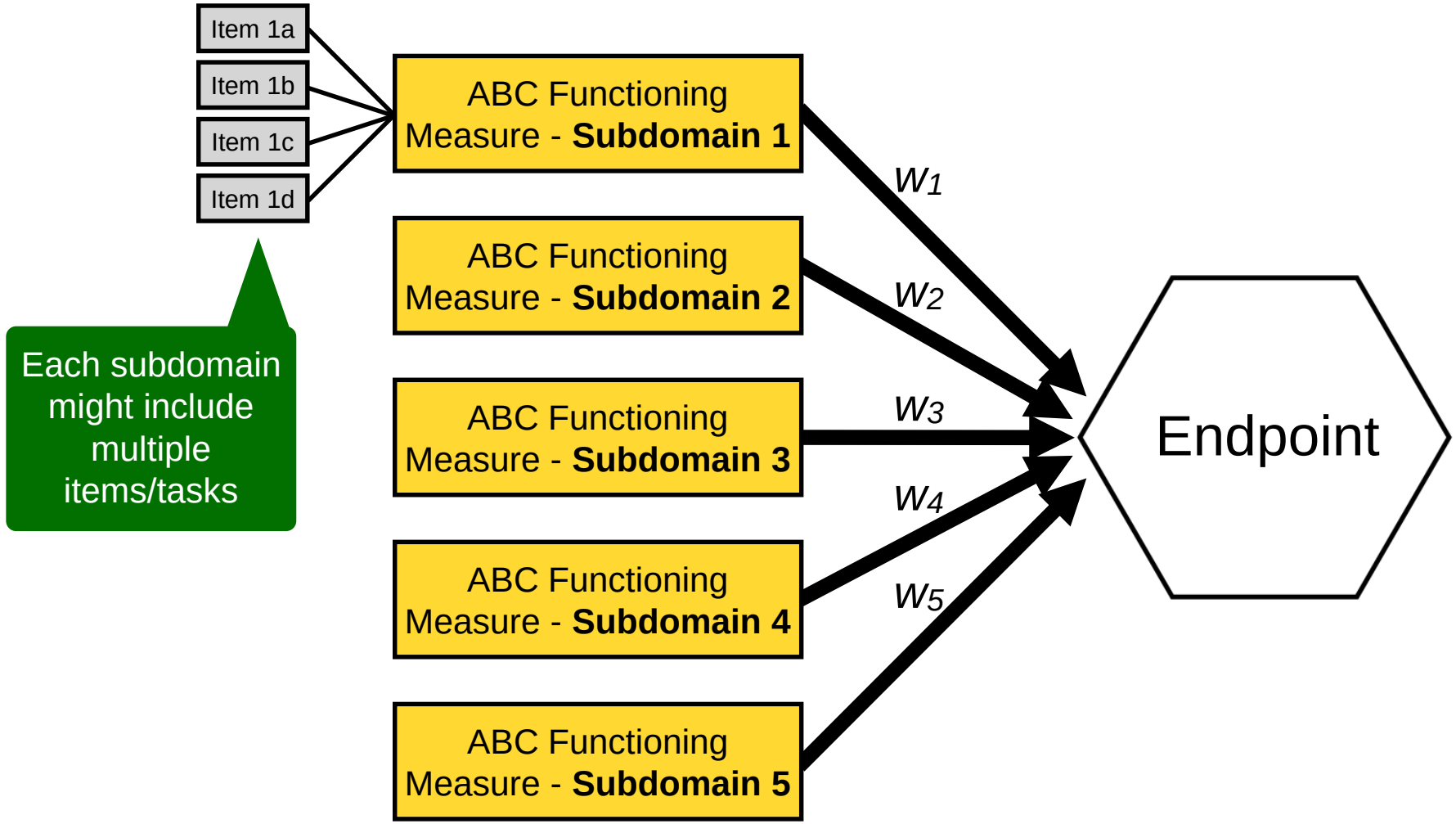
Option 1: Each component could be the score from a different COA



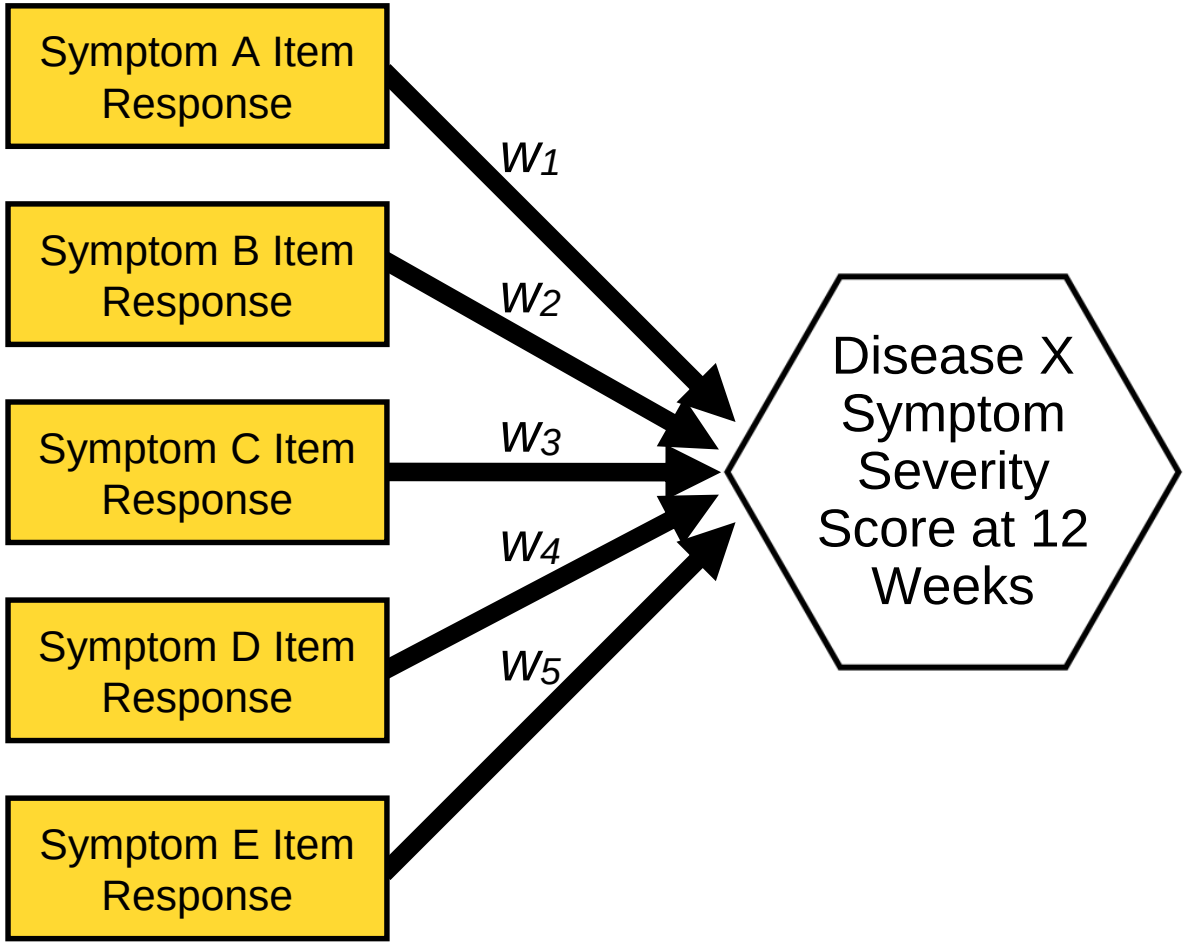
Option 2: Each component could be the score from a subdomain of a single, multidimensional COA



Option 2: Each component could be the score from a subdomain of a single, multidimensional COA

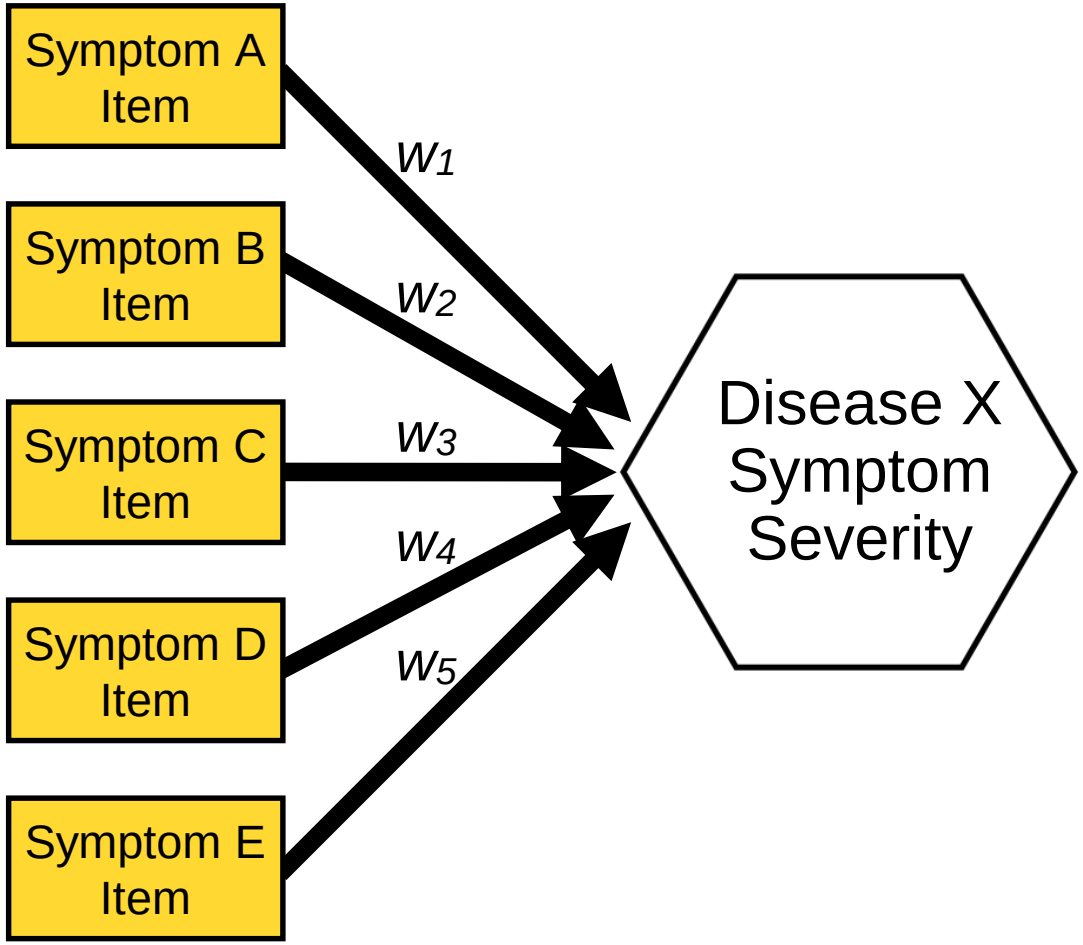


Option 3: Each component could be the response to an item/task from a single COA

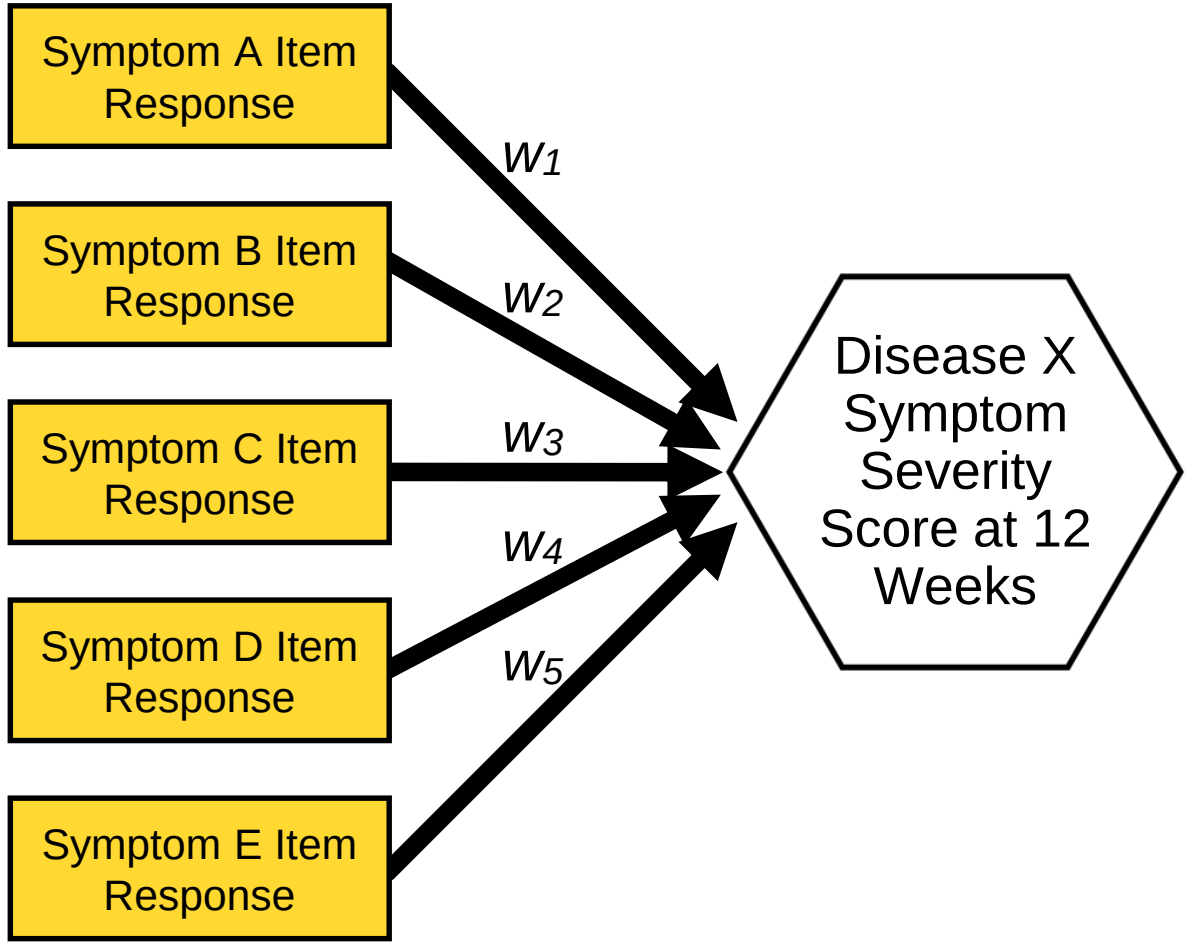


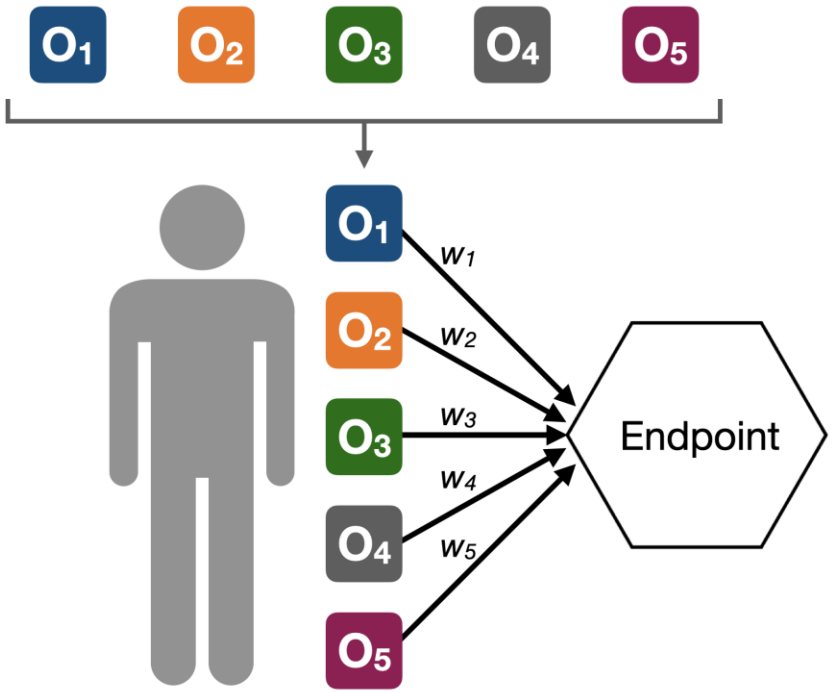
Option 3: Each component could be the response to an item/task from a single COA based on a composite indicator measurement model

PRO Measure (Disease X Symptom Index) Based on Composite Indicator Model



Multi-Component Endpoint Based on Scores from Same PRO Measure at Fixed Time Point





- Has the potential to evaluate the entire range of important disease manifestations
- No multiplicity adjustment needed
- Can be efficient if the treatment effects on the different components are generally concordant
- Challenge: Justifying the weighting/algorithm

Sensitivity Analyses for Weights

Refining clinical trial composite outcomes: An application to the Assessment of the Safety and Efficacy of a New Thrombolytic–3 (ASSENT-3) trial

Paul W. Armstrong, MD,[a] Cynthia M. Westerhout, PhD,[a] Frans Van de Werf, MD,[b] Robert M. Califf, MD,[c] Robert C. Welsh, MD,[a] Robert G. Wilcox, MD,[d] and Jeffrey A. Bakal, PhD[a] *Edmonton, Canada; Leuven, Belgium; Durham, NC; and Nottingham, UK*

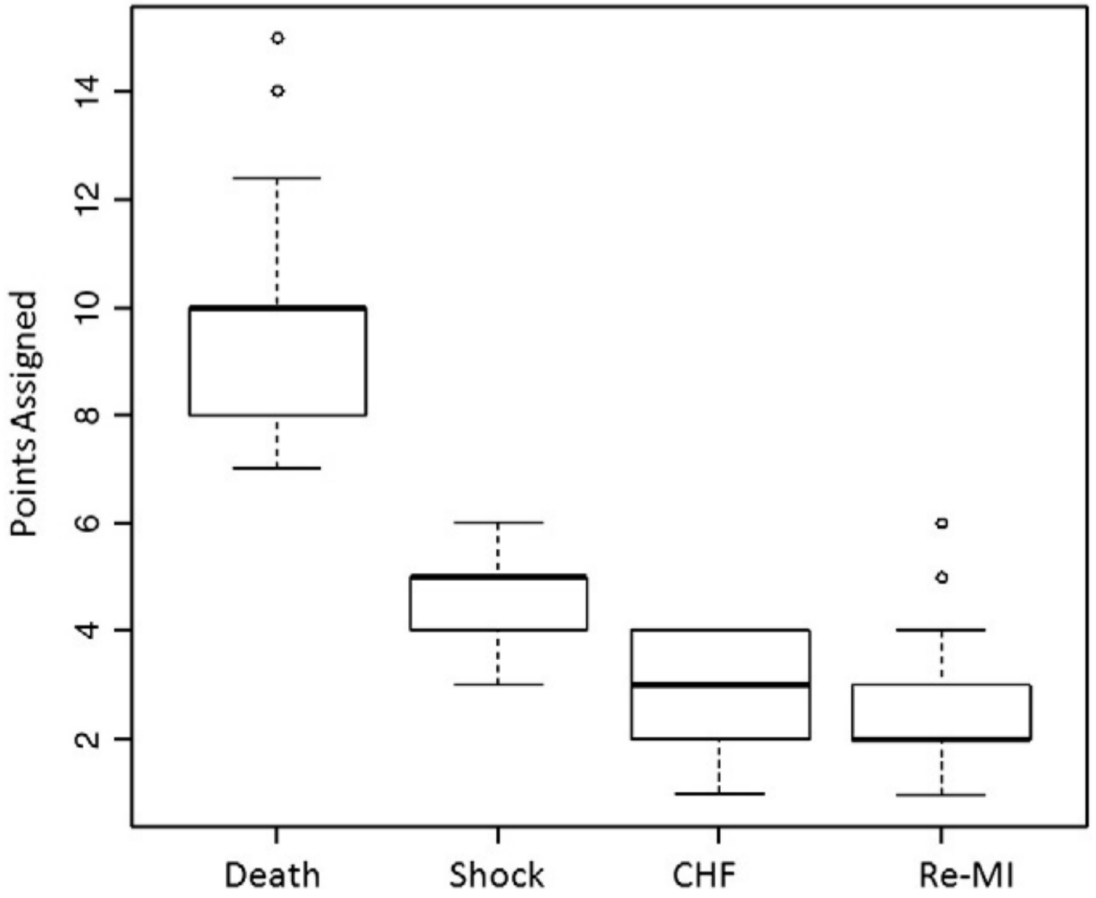
Background Traditional time-to-event analysis assigns equal weight to the first event in the composite end point. This is counterintuitive to many stakeholders.

Methods We constructed weights for components of a composite efficacy end point and a net clinical outcome by including metrics of safety and efficacy and compared the weighted with the traditional approach. Through an externally validated, clinician-investigator Delphi panel, the relative severity of individual components of a composite end point (30-day death, recurrent myocardial infarction, cardiogenic shock, and congestive heart failure) was determined. The net clinical outcome was assessed through the incorporation of risk thresholds for safety events (intracranial hemorrhage and major systemic bleeding). These weights were then applied to a modified analysis of the ASSENT-3 trial.

Results The weights for the efficacy composite were as follows: death, 1.0; shock, 0.5; congestive heart failure, 0.3; and recurrent myocardial infarction, 0.2. The traditional time-to-first-event approach demonstrated a comparable advantage for both enoxaparin (enox) and abciximab (abx) over unfractionated heparin ($P = .05$), whereas the weighted efficacy analysis suggested an advantage for enox and similar outcomes between unfractionated heparin and abx ($P = .2$). The apparent advantage of enox was attenuated when the net clinical outcome was examined; the apparent efficacy of abx combination therapy was also diminished by an elevated major systemic bleeding rate ($P < .001$).

Conclusion This novel approach adds an alternative dimension to treatment evaluation by more efficiently incorporating the differential value of all events in each patient. Further development and application of this approach to future trial design and analysis are warranted. (Am Heart J 2011;161:848-54.)

- Used a survey procedure to elicit weights for individual endpoint components from 23 experts
- Primary analysis used median weights
- Sensitivity analysis
  - *Monte Carlo simulation of weights, varying weights within range of values supplied by the survey participants*
  - *Empirically derived 95% confidence interval around treatment effect based on 1,000 repetitions*



Components of the efficacy composite end point. Distribution of point medians assigned to each of the components of the efficacy composite end point.

Armstrong et al., 2011

Thank you

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Session 4: Considerations in Developing Rare Disease Endpoints: Multiple Endpoints, with a Focus on Multicomponent Endpoints

Moderator:

- **Laura Lee Johnson,** U.S. Food and Drug Administration

Panelists:

- **Kathleen Fritsch,** U.S. Food and Drug Administration
- **Lili Garrard,** U.S. Food and Drug Administration
- **Naomi Knoble,** U.S. Food and Drug Administration
- **Kevin Weinfurt,** Duke University, U.S. Food and Drug Administration

Session 4: Considerations in Developing Rare Disease Endpoints: Multiple Endpoints, with a Focus on Multicomponent Endpoints

1. What are some of the biggest challenges stakeholders may experience in developing and implementing multiple endpoints, and in particular multicomponent endpoints, for rare disease research? What strategies might be effective for overcoming or minimizing the impact of those challenges?
2. What are some of the general tips, challenges, and interpretation goals when developing or using a multidomain responder index?
3. What are the challenges to incorporating biomarkers and clinical outcome assessments in a single multicomponent endpoint?
4. Sometimes trial data comes from a mixture of sources. Can you comment on how a stakeholder could use a multicomponent endpoint if some, but not all, the data needed for the components is available?
5. What is the interplay between the measure, assessments, the endpoint, analysis, and interpretation?

Day 1 Adjournment

Rare Disease Endpoint Advancement Pilot Program Workshop: Novel Endpoints for Rare Disease Drug Development

June 7, 2023

Thank You!

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