Time To Abandon Clinician-Administered Scales As The Primary Outcome Measure Of Symptomatic And Disease Modifying Trials In Parkinson Disease

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January 23, 2021

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I concede BUT I dissent

Equipoise

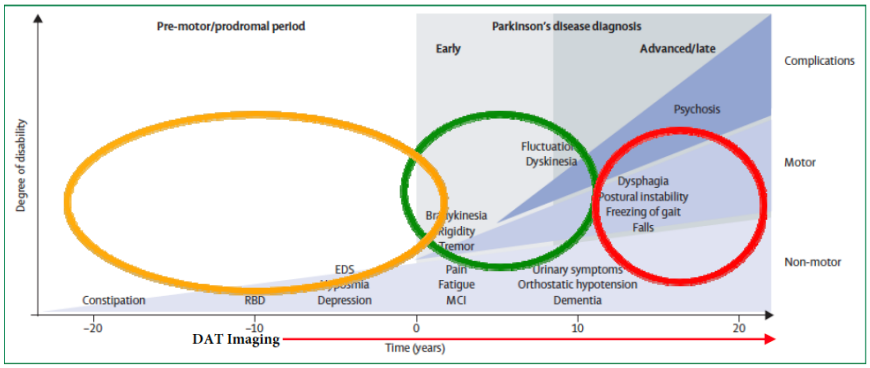
- *"When participating in any dangerous sport, one should maintain an equipoise between fearless boldness and commonsense caution"*

(an example from Webster dictionary)

Talk objectives

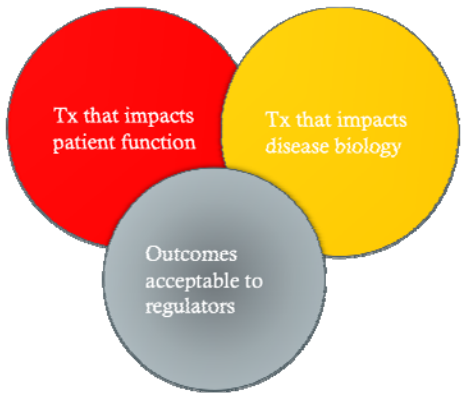
- Review data on the design of the current PD symptomatic Tx studies
- Review limitations of the current design of the disease modification studies
- Discuss pros/cones of existing scales vs novel approaches
- Convince MYSELF in Con position
- Lets get started

PD Clinical Course vs Available Tx



Kalia LV, Lang AE et al, Lancet 2015

Requirements for successful development of new therapeutics



Symptomatic therapies for reduction of motor disability

Let's start with easy staff

Newly approved Tx in PD: last 12 months
Quantitative vs qualitative advances ?

- Target – motor fluctuations
- Rescue Tx
  - Levodopa inhaler
  - Apomorphine SL
- Reduction of OFF time
  - Istradefylline (A2A antagonist) -1 hour OFF/ 6 hours OFF at baseline
  - Opicapone (COMT inhibitor) -1 hour OFF/ 6 hours OFF at baseline

- Outcome measures
  - Reduction of OFF time based on patient completed diaries
    - Patient reported outcome- correct ?
  - Reduction of motor disability based on UPDRS score
    - Long lived and proven – correct ?
    - Accepted by FDA
    - *Do not fix what is not broken*

What do we need for management of motor features ?

- Therapeutics for late manifestations of the disease
  - Freezing of gait
  - Postural instability
  - *Meaningful reduction of OFF time*
  - *Prevention of development of motor complications rather than fixing them*

- Why do we lack such therapeutics
  - Lack of sensitive outcome measures ??
  - Wrong studies design ?
  - Limited understanding of the biology???

When we get there we will see it

What are the most urgent needs in PD symptomatic TX

- Effective management of cognitive symptoms
- Management of fatigue
- Management of autonomic symptoms
- Effective management of mood/ anxiety / sleep

- Why do we lack such therapeutics
  - Lack of sensitive outcome measures ??
  - Wrong studies design ?
  - Limited understanding of the biology???

When we get there we will see it

PD Clinical trials: 2020

DOI 10.3233/JPD-202128
IOS Press

Clinical Trials Review

Parkinson's Disease Drug Therapies in the Clinical Trial Pipeline: 2020

Kevin McFarthing[a], Susan Buff[b], Gary Rafaloff[c], Thea Dominey[d], Richard K. Wyse[d] and Simon R.W. Stott[d,*]
[a]*Parkinson's Research Advocate, Oxford, UK*
[b]*Parkinson's Research Advocate, Sunnyvale, CA, USA*
[c]*Parkinson's Research Advocate, Marlboro, NJ, USA*
[d]*The Cure Parkinson's Trust, London, UK*

NORTHWESTERN UNIVERSITY

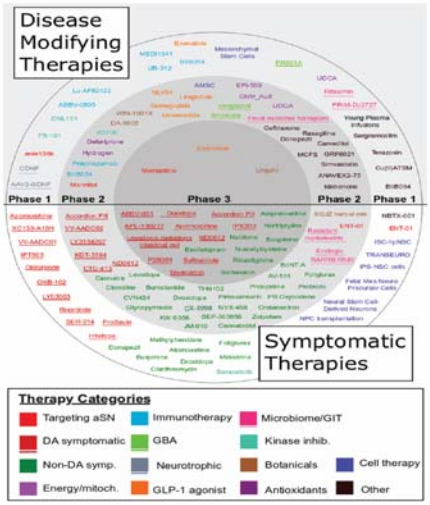
With acknowledgement and gratitude: People with Parkinson's

Kevin McFarthing:
Parkinson's Research Advocate

Susan Buff:
Parkinson's Research Advocate

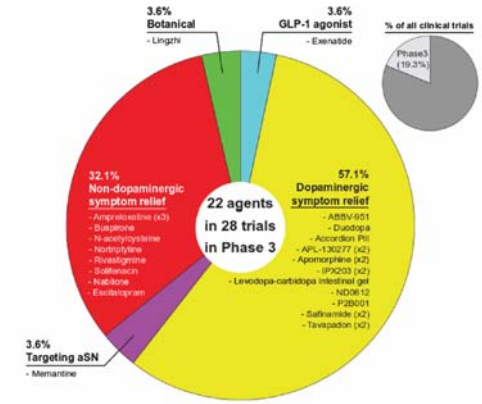
Gary Rafaloff:
Parkinson's Research Advocate

Landscape of PD drug development



K. McFarthing et al. Parkinson's drug development review. J PD 2020

Phase 3 PD drug clinical trials: mostly symptomatic Tx



Disease modification

That is tough …..BUT we are making progress

Disease modification

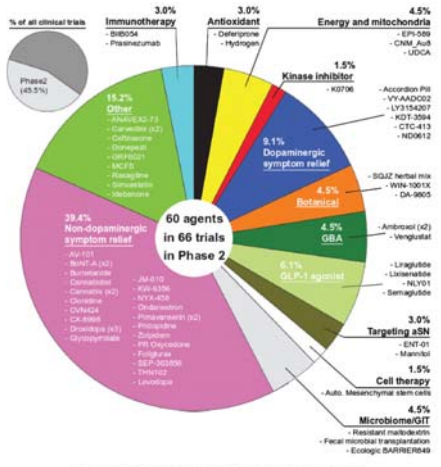


Fig. 5. Therapy Categories for Trials in Phase 2 (as of January 21, 2020, ClinicalTrials.gov).

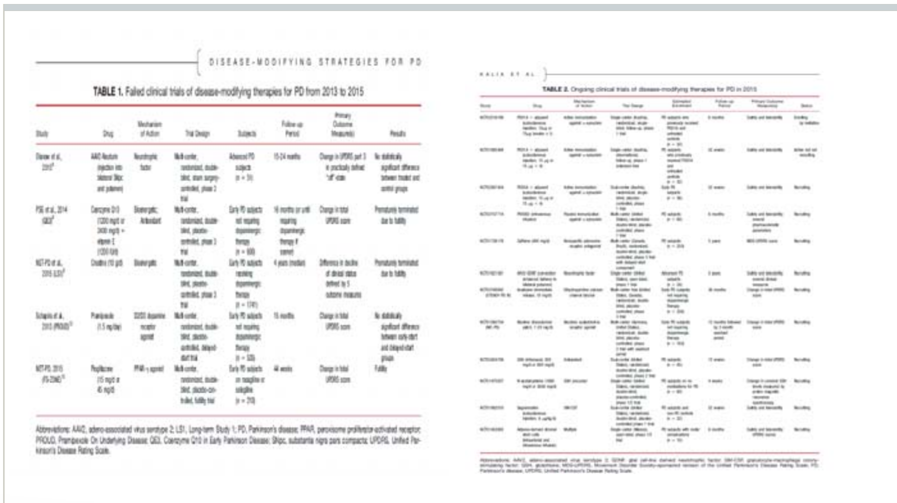
REVIEW

CME

Disease-Modifying Strategies for Parkinson's Disease

Lorraine V. Kalia, MD, PhD,[1,2,3,4] Suneil K. Kalia, MD, PhD,[4,5] and Anthony E. Lang, MD[1,2,3,4]

[1]Division of Neurology, Department of Medicine, Toronto Western Hospital, University of Toronto, Canada
[2]Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Canada
[3]Morton and Gloria Shulman Movement Disorders Clinic and the Edmond J. Safra Program in Parkinson's Disease, Toronto Western Hospital
[4]Toronto Western Research Institute, University Health Network, Toronto, Ontario, Canada
[5]Division of Neurosurgery, Department of Surgery, Toronto Western Hospital, University of Toronto, Canada

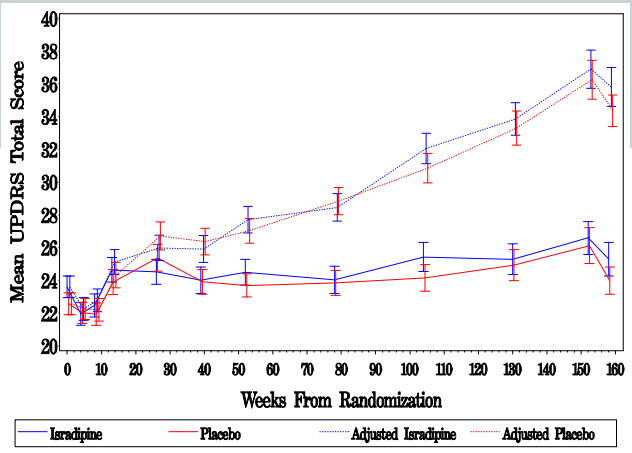


Outcome measures in PD disease modification trials

- Time to initiation of ST
- Change in UPDRS score
- Time to onset of motor complications
- Composite measure (NET-PD)

STEADY-PD III. Primary Outcome

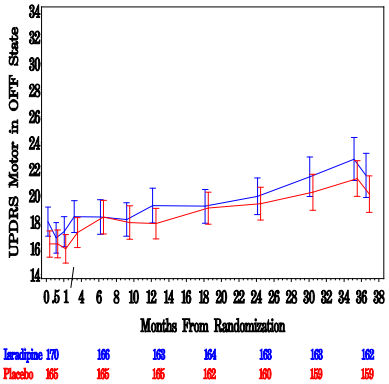
Mean UPDRS Total Score in Meds ON state
Raw and LED Adjusted



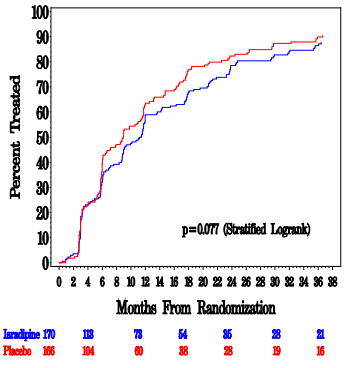
PSG STEADY PD investigators. Annals Internal Medicine 2020

Key Secondary Outcome

Mean OFF State UPDRS Motor Score



Time to Initiation of Antiparkinson Medications



PSG STEADY PD investigators. Annals Internal Medicine 2020

Quality of life measures

Important – absolutely. Sensitive to change -??

Number and percent of change scores exceeding or falling within the conditional minimal detectable change (cMDC) threshold over 3 years (STEADY-PD3)

Neuro-QoL Domain	Score worsened, N, (%)*	No change**	Score improved,N, (%)†
Anxiety	40 (12.90%)	246 (79.35%)	24 (7.74%)
Depression	33 (10.65%)	263 (84.84%)	14 (4.52%)
Stigma	19 (6.13%)	287 (92.58%)	4 (1.29%)
Lower extremity function	28 (9.06%)	278 (89.97%)	3 (0.97%)
Upper extremity function	17 (5.48%)	286 (92.26%)	7 (2.26%)
Positive affect	54 (17.53%)	207 (67.21%)	47 (15.26%)
Applied Cognition – general concerns	59 (19.03%)	237 (76.45%)	14 (4.52%)
Executive function	33 (10.65%)	271 (87.42%)	6 (1.94%)

C. Marras et al. Manuscript in submission

Quality of life measures

Suitable as outcome measures ?

Sample sizes estimates (per group) for a clinical trial using components of the Neuro-QoL and corresponding legacy measures

Measure	Sample per group for 25% reduction in worsening	Sample per group for 50% reduction in worsening	Sample per group for 100% reduction in worsening
Neuro-QoL Anxiety	>1,000	>1,000	>1,000
Neuro-QoL Depression	>1,000	>1,000	>1,000
Neuro-QoL Lower Extremity	>1,000	517	130
PDQ 39 Mobility	>1,000	556	140
Neuro-QoL Upper Extremity	>1,000	960	240
PDQ 39 ADL	>1,000	473	119
Neuro-QoL Stigma	>1,000	>1,000	>1,000
PDQ 39 Stigma	>1,000	>1,000	>1,000
Neuro-QoL Executive Function	>1,000	427	107
MDS-UPDRS 1.1	>1,000	848	212

These sample sizes, which assume a two-sided test with alpha = 0.05 and beta = 0.2, are estimated using data from the STEADY III study.

C. Marras et al. Manuscript in submission

Outcome measures in PD disease modification trials

- Time to initiation of ST
- Change in UPDRS score
- Time to onset of motor complications
- Composite measure (NET-PD)

- What is missing in this picture
  - Holistic patient focused outcomes
  - Outcomes that are linked to disease biology
  - Outcomes that are linked to biological substrate in specific DX subset (GBA, etc)

Path to personalized medicine Genetically Targeted Tx in PD

SARDI ET AL

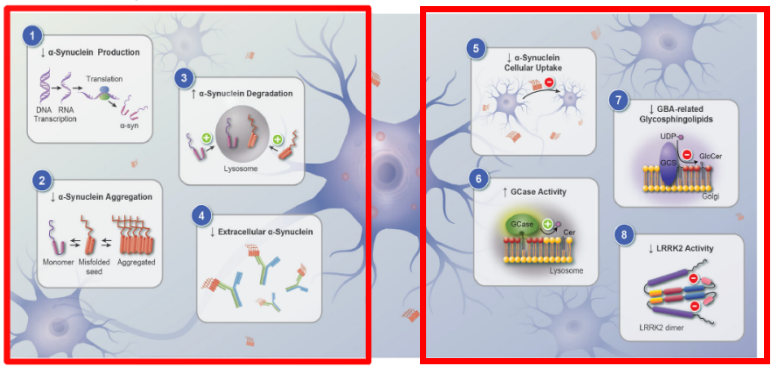


FIG. 1. Potential mechanisms for genetic-based investigational therapies for Parkinson's disease targeting α-synuclein (*SNCA*), glucocerebrosidase (*GBA*), and leucine-rich repeat kinase (*LRRK2*). Targeting *SNCA*: (1) reducing α-synuclein production, (2) decreasing α-synuclein aggregation, (3) enhancing autophagy, (4) reducing availability of extracellular aggregates, (5) inhibiting cellular uptake of α-synuclein. Targeting the *GBA* pathway: (6) increasing glucocerebrosidase (GCase) activity, (7) modulating *GBA*-related glycosphingolipids. Targeting *LRRK2*: (8) LRRK2 kinase inhibitors.

Sardi et al, Movement disorders 2018

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Genetically targeted therapeutics

Table 1
Disease modifying genetic-based targeted therapies in active PD clinical trials[a].

Gene	Targeting mechanism	Mechanism of action	Drug	Therapeutic modality	Status	Target population (n)	Placebo	Primary Outcome	Enrolling Countries	ClinicalTrials.gov ID[b]	Sponsor
SNCA	Decrease α-synuclein aggregation	Inhibition of α-synuclein misfolding	NPT200-11	Small molecule	Phase I	HV (55)	Yes	Safety, Tolerability and PK/PD	USA	NCT02606682	Neuropore Therapies and UCB Pharma
		Reduction of α-synuclein aggregation	NPT088	Biologic	Phase I	AD (66) [b]	Yes	Safety	USA	NCT03008161	Proclara
	Increase α-synuclein degradation	Inhibition of c-Abl	Nilotinib	Small molecule	Phase II	Advanced PD (75)	Yes	Safety	USA	NCT02954978	Georgetown University
					Phase II	Early and moderate PD (135)	Yes	Incidence of TEAE	USA	NCT03205488	Northwestern University, MJFF, Cure Parkinson's Trust and Van Andel Institute
	Decrease extracellular α-synuclein	Passive immunization	RO7046015	Biologic	Phase II	Early PD (300)	Yes	Change in total MDS-UPDRS (I, II & III)	Austria, France, Germany, Spain, USA	NCT03100149	Prothena and Roche
			BIIB054	Biologic	Phase II	Early PD (311)	Yes	Safety, PK/PD	USA	NCT03318523	Biogen
			MEDI1341	Biologic	Phase I	HV (48)	Yes	Safety, Tolerability, PK/PD	United States	NCT03272165	AstraZeneca and Takeda
		Active immunization	PD01A, PD03A	Biologic	Phase I	Early PD (36)	Yes	Safety and Tolerability	Austria (completed)	NCT02267434 2014-000568-16	AFFITOPE
GBA	Increase in GCase	GCase activation	Ambroxol	Small molecule	Phase II	GBA-PD (10) PD (10)	No	Safety, Tolerability and PK/PD	UK	NCT02941822	UCL and Cure Parkinson's Trust
					Phase II	PDD (75)	Yes	Changes in ADAS-cog and CGIC	Canada	NCT02914366	Lawson Health Research Institute and Weston Foundation
			LTI291	Small molecule	Phase I	PD and GBA-PD	Yes	Safety, Tolerability and PK/PD	Netherlands	NTR6960[c]	LTI, Allergan
	Reduction of *GBA*-related GSLs	Glucocylceramide synthase inhibitor	Venglustat	Small molecule	Phase II	GBA-PD (243)	Yes	Change in MDS-UPDRS parts II & III	Austria, Canada, France, Germany, Israel, Italy, Japan, Norway, Portugal, Singapore, Spain, Sweden, Taiwan, UK, USA	NCT02906020	Sanofi
LRRK2	LRRK2 kinase inhibition	Kinase inhibitor	DNL201	Small molecule	Phase I	HV	Yes	Safety, Tolerability and PK/PD	USA	N/A[d]	Denali

GCase: glucocerebrosidase; GSLs: glycosphingolipids
HV: healthy volunteer; AD: Alzheimer's disease; PDD: PD dementia; GBA-PD; PK/PD: Pharmacokinetics, and Pharmacodynamics; TEAE: Treatment-Emergent Adverse Events; MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale; ADAS-cog: Alzheimer's Disease Assessment Scale-cognitive subscale; CGIC: ADCS-Clinician's Global Impression of Change.
[a] From ClinicalTrials.gov unless noted otherwise. Accessed September 2018.
[b] Phase I in AD patients might support advancement into Phase 2/3 for PD.
[c] From http://www.trialregister.nl.
[d] LRRK2 program from: https://www.denalitherapeutics.com/press.

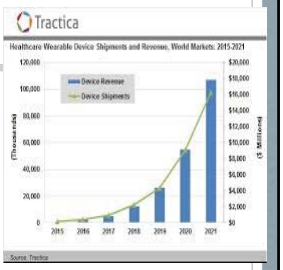
Sardi , Simuni , PRD 2018;

What do we need

- Reliable and sensitive measures to assess PD disability in real time
- Measures that are superior to the current rating scales
- Measures that capture patient reported outcomes
- Tools that are scalable
- Data outputs that are readily interpretable
- Measures that are accepted by the investigators and regulatory authorities
- Are we there yet ?

Digital outcomes. What do we have ?

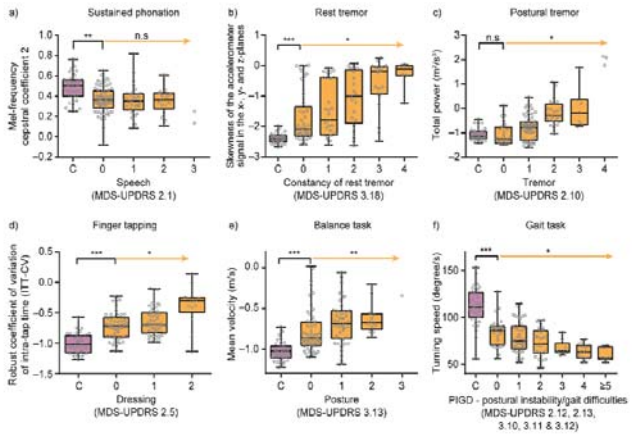
- A LOT and a LITTLE



RESEARCH ARTICLE

Evaluation of Smartphone-Based Testing to Generate Exploratory Outcome Measures in a Phase 1 Parkinson's Disease Clinical Trial

Florian Lipsmeier, PhD,[1] Kirsten I. Taylor, PhD,[1] Timothy Kilchenmann, MSc,[1] Detlef Wolf, MSc,[1] Alf Scotland, MSc,[1]



MIRELMAN ET AL

RESEARCH ARTICLE

Arm Swing as a Potential New Prodromal Marker of Parkinson's Disease

Anat Mirelman, PhD,[1,2,3,4] Hagar Bernad-Elazari, BSc,[1,4] Avner Thaler, MD, PhD,[2,3] Eytan Giladi-Yacobi, MD,[2]

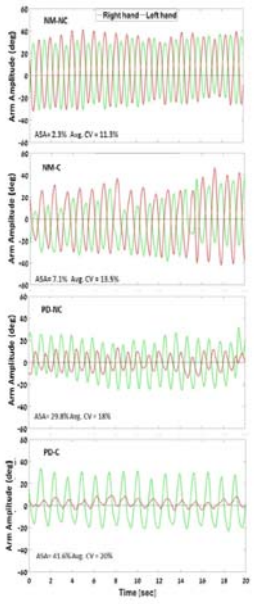


FIG. 1. Example of arm swing acceleration traces during dual-task walking. Representative participants are matched within group (Parkinson's

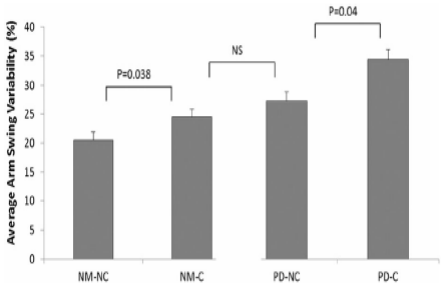


FIG. 2. Differences in arm-swing variability (coefficient of variation

CIS- PD STUDY: DEVELOPMENT OF A CLINICIAN FRIENDLY PLATFORM TO VISUALIZE DIGITAL READ OUTS

intel served as the study technology partner

Study participants used the Fox Wearable Companion app on their smartphones (iOS) and a Apple Smartwatch (provided) to collect data on their movements and other PROs.

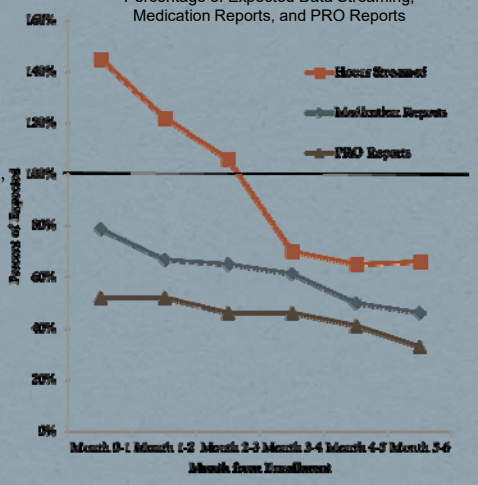
Patient data will feed into a Clinician Dashboard that will be reviewed at each in-person study visit. Clinicians will assess how this data matches or differs from other clinical assessments and assess the utility of the data for clinical care.

Clinicians will participate in monthly calls with Intel to suggest improvements to the Clinician dashboard, iteratively developing the tool throughout the study.

FEASIBILITY OF USE AND COMPLIANCE

- **Average compliance was 66%**
- Total hours of accelerometer data streamed was 83,432 (91% of expected– 12 hours/day, 5 days/week).
- Streaming was lower than expected in October and November 2017 (74% and 52%, respectively) due to issues with the study app functionality and technical support.
- Medication intake reporting was 60% of expected.
- Symptom reporting was 44% of expected.
- **Compliance level was similar across demographics and PD characteristics.**

Percentage of Expected Data Streaming, Medication Reports, and PRO Reports



Key issues to be addressed

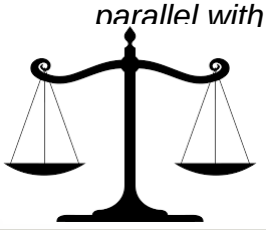
- Data validation
- Data sharing
- Regulatory pathway– will the regulators accept digital readouts as key outcome in clinical trials ?
  - Yes
  - BUT more work needs to be done (WATCH-PD)

Biological outcomes

- Essential for early phase development
  - Biological substrate
  - Target engagement
  - Surrogate biomarkers
- Examples in other Dx states
  - AD amyloid and tau imaging
  - Serum biomarkers
- Will not replace clinically meaningful outcomes in Phase III studies

Conclusions. Equipoise

- *We do need better outcome measures*
- *These will come from better understanding of the disease biology*
- *Therapeutic development has to advance in parallel with the refinement of the outcomes*



Novel outcomes in PD clinical trials
How to get to the finish line

Funding:

National Institute of Neurological Disorders and Stroke

The Michael J. Fox Foundation for Parkinson's Research

CTCC Clinical Trials Coordination Center

PSG Parkinson Study Group

Northwestern University

- Studies sites
- Studies participants