"Clinically meaningful changes of MVPA in Pulmonary Fibrosis revealed by FDA predefined exploratory anchoring analysis"

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- Incorporating the Patients Perspective into clinical trial designs and endpoints – Patient Centric Drug Development

- FDA and CFDA acceptance of a DHT measure- Actigraphy as a single primary endpoint for Phase 3

- REBUILD TLR – lessons learnt
  - Efficacy & Safety
  - Actigraphy Exploratory Anchoring Analysis:
    - MVPA to PGIS/PGIC – a preliminary read

“Patient-Centric” Drug Development

Voice of the Patient (VOP) places patients first when assessing the risk / benefit of a treatment

Patient Focused Drug Development (PFDD) in IPF

21st Century Cures Act and PDUFA VI, provided a voice to the patients, their family members and caregivers to inform researchers and regulators to:

Evaluate potential medicines that focus on:

What is most meaningful to the patient

i.e., a **Patient-Centric** benefit-risk assessments

Public meetings were held under the PFDD program to:

Directly report perspectives from those impacted by IPF and other comorbidities associated with IPF such as PH, COPD

“Patient-Centric” Drug Development

Activities of Daily Living (ADL) are presented as the ***Most Meaningful*** to those living with this disease - IPF

“Patient-Centric” Drug Development

FDA had accepted in April 2019 -

- ***Physical Activity (PA) as*** **measured by a digital health technology (DHT) - “Actigraphy”**
  - As the *Primary Regulatory Endpoint* for a Phase 3 study in IPF

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REVIEW ARTICLE

Pulmonary Circulation Open Access | PVRI | WILEY

Pulmonary hypertension in interstitial lung disease: Clinical trial design and endpoints: A consensus statement from the Pulmonary Vascular Research Institute's Innovative Drug Development Initiative—Group 3 Pulmonary Hypertension

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A consensus statement from the Pulmonary Vascular Research Institute's Innovative Drug Development Initiative—Group 3 Pulmonary Hypertension.

- Patients with PH-ILD may have **severe limitations on physical activity** which impacts their quality of lives to varying extents.
  - They may **struggle to perform basic activities of daily living (ADLs),** such as walking, climbing stairs, or showering.

- The ability to monitor changes in the level of physical activity accurately, specifically moderate physical activity, which correlates to household tasks and ADLs
  - has the potential to **inform directly on the patient's overall health**, wellbeing, and quality of life.

A consensus statement from the Pulmonary Vascular Research Institute's Innovative Drug Development Initiative —Group 3 Pulmonary Hypertension.

- With currently available accelerometry technology,
  - these **changes can be assessed as direct quantitative measures** in activity counts or energy expenditure,
  - as well as categorized into activity intensity levels including time spent in sedentary, light, or moderate activities. Moderate activity includes ADLs, such as walking, climbing stairs, or washing dishes.

- Generally, a change in moderate activity of
  - **10%–20% has been considered clinically relevant** in cardiopulmonary diseases.

A consensus statement from the Pulmonary Vascular Research Institute's Innovative Drug Development Initiative—Group 3 Pulmonary Hypertension.

- This nascent emerging technology -
  - Appears to be **an attractive endpoint** that requires further refinement and ongoing validation.

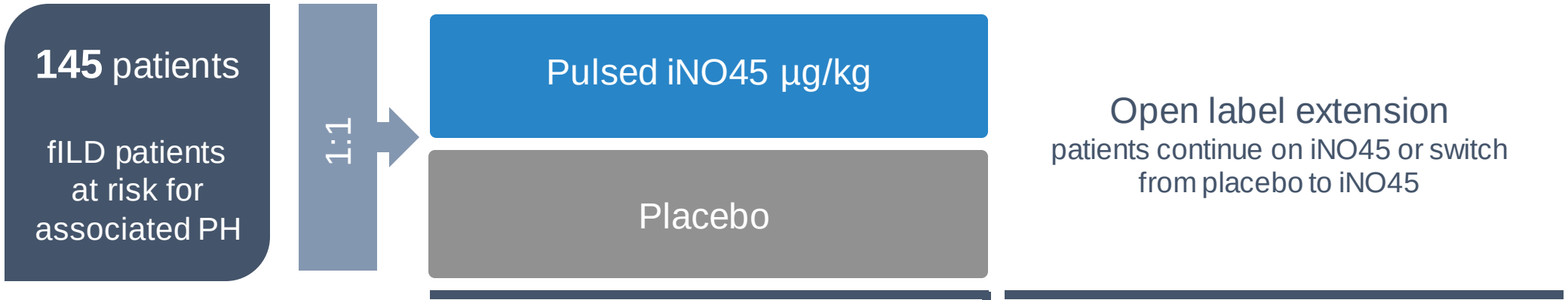
- Whereas the 6-minute walk test informs (at set intermittent intervals) on what patients are capable of doing,
  - Actigraphy informs on **what patients actually do**, through continuous monitoring of their daily activity.
  - This also has the advantage of reflecting patients' reality as it is **outside the confines of the clinic** and research visit.

PA as a Direct Clinically Meaningful Measure for a Regulatory Primary Endpoint

Voice of Patient*	• Activities of daily living - **Most Meaningful** to IPF patients
Direct (DHT) Method of Assessment	• Accelerometer technology allows **Direct Assessment** of a patient's (PA)
Difference PA – Healthy vs Target Population	• **34-65% reduction in (PA)** this disease populations vs. healthy individuals
MCID for PA in Target Population	• **10 to 20% MCID** reported in studies of (PA) in related diseases

*Taken from "The Voice of Patient -Idiopathic Pulmonary Fibrosis Public Meeting: September 26, 2014, Report Date: March, 2015 ", https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm440829.pdf

Pivotal Phase 3 Trial Design



Primary Endpoint

- Change in MVPA assessed by Actigraphy

Additional Endpoints

- Change in Overall Activity assessed by Actigraphy
- Patient Reported Outcomes (SGRQ, UCSD)
- Time to Clinical Worsening

Safety

REBUILD Primary Endpoint (MVPA)

Trial did not meet its primary endpoint of change in MVPA (moderate to vigorous physical activity)

		iNO45	Placebo	Placebo Corrected Change
Change from Baseline	LS Mean (SE)	-9.22 (3.51) min/day	-3.74 (3.76) min/day	-5.49 min/day (p=0.2646*)

Analysis based on all randomized subjects who received at least one dose of study treatment (defined as minimum use of 12 hours); Statistical analysis are calculated from MMRM (mixed model repeat measures) including the treatment group, visit, treatment-by-visit interaction, stratification factors (PH, CTD, PDE5) and baseline as fixed effects.

*p-value calculated based MMRM analysis of log-transformed MVPA as specified in statistical analysis plan

REBUILD Secondary Endpoints

Minimal difference between the two groups

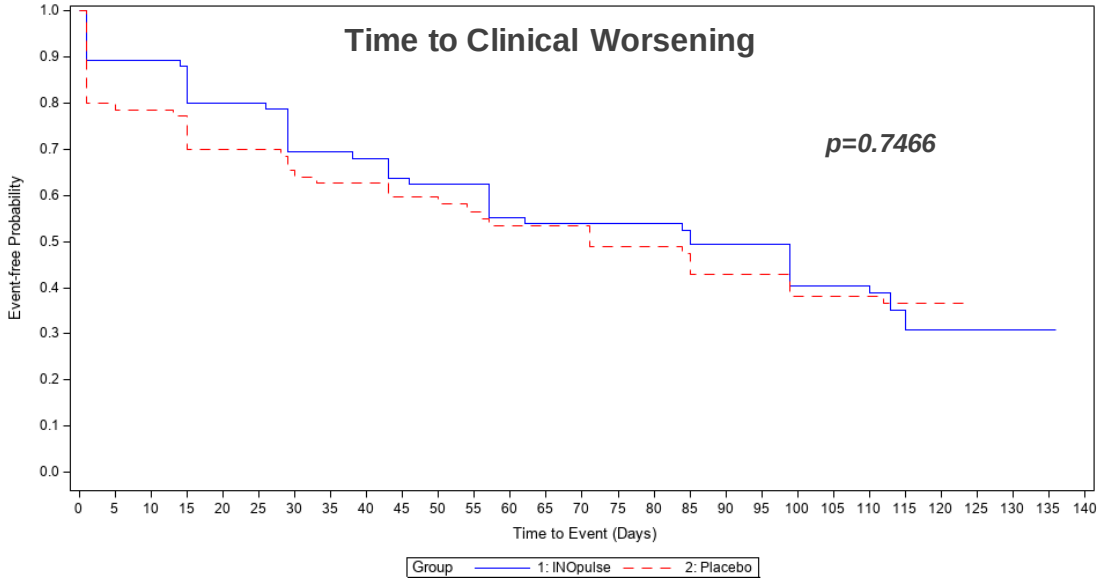
Endpoint	INO45	Placebo	Placebo Corrected Change	p-value
Overall Activity	-74.36 counts/min	-77.88 counts/min	+3.51 count/min	0.8572*
UCSD SOBQ	+4.27 points	-0.25 points	+4.52 points	0.1397
SGRQ – Total	+4.83 points	+3.97 points	+0.86 points	0.6929
SGRQ – Activity	+4.77 points	+1.97 points	+2.79 points	0.2198
SGRQ – Impacts	+5.21 points	+4.12 points	+1.09 points	0.6910
6 minute walk distance	-12.36 meters	-12.54 meters	+0.19 meters	0.9866

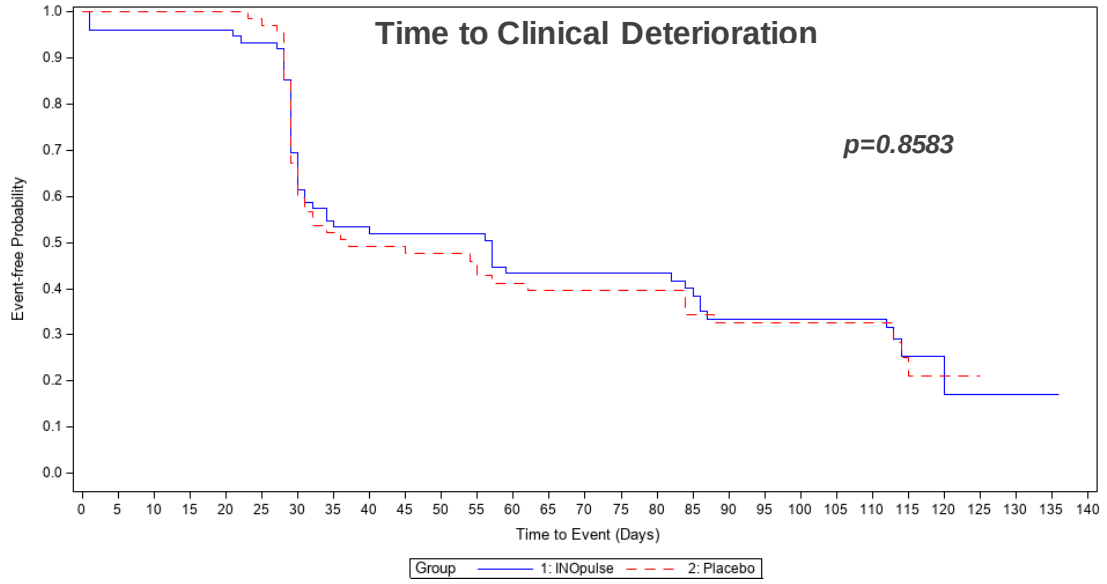
Analysis based on all randomized subjects who received at least one dose of study treatment (defined as minimum use of 12 hours); Statistical analysis are calculated from MMRM (mixed model repeat measures) including the treatment group, visit, treatment-by-visit interaction, stratification factors (PH, CTD, PDE5) and baseline as fixed effects.

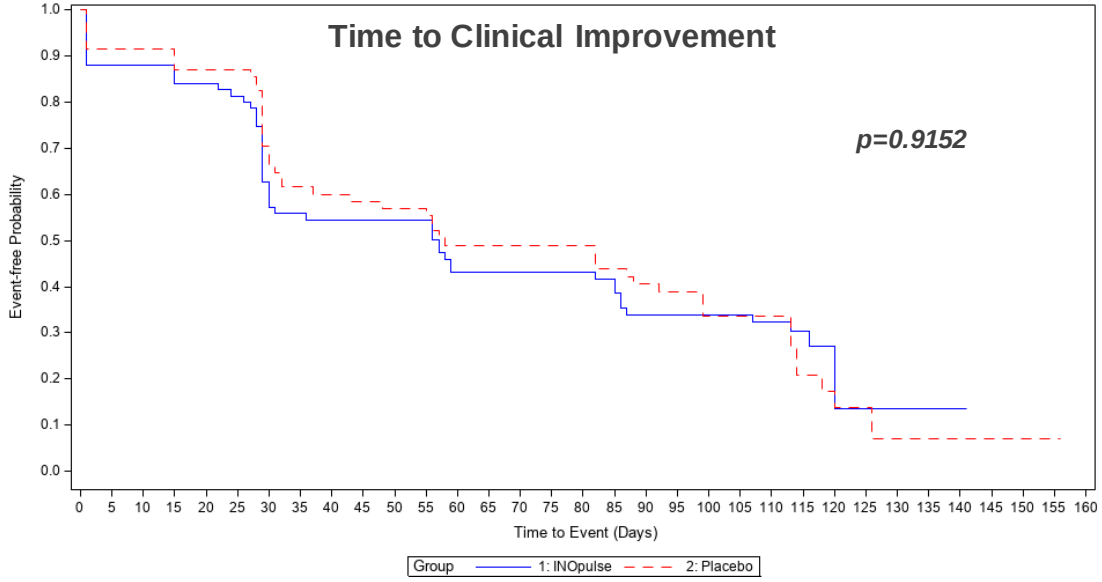
*p-value calculated based MMRM analysis of log-transformed MVPA as specified in statistical analysis plan

UCSD SOBQ (University of California Shortness of Breath Questionnaire); SGRQ (St. George's Respiratory Questionnaire); higher scores indicate deterioration

REBUILD Secondary Endpoints (time to event)







Time to event, defined as first event, otherwise censored to the end date of the double-blind period. Log-Rank p-value is calculated from log rank test comparing INOpulse treatment group to placebo.

REBUILD Safety Assessment

Overall Safety profile was balanced

	INO45	Placebo
Subjects with TEAE	84.0%	74.3%
Subject with Serious TEAE	20.0%	21.4%
Death	4.0%	4.3%

Safety analysis based on all subjects who received at least one dose post randomization (defined as exposure to INOpulse of any duration) of treatment intervention.

TEAE (treatment emergent adverse event) is defined as an AE with onset after the administration of treatment intervention through the end of the study or any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the investigator through the end of the study.

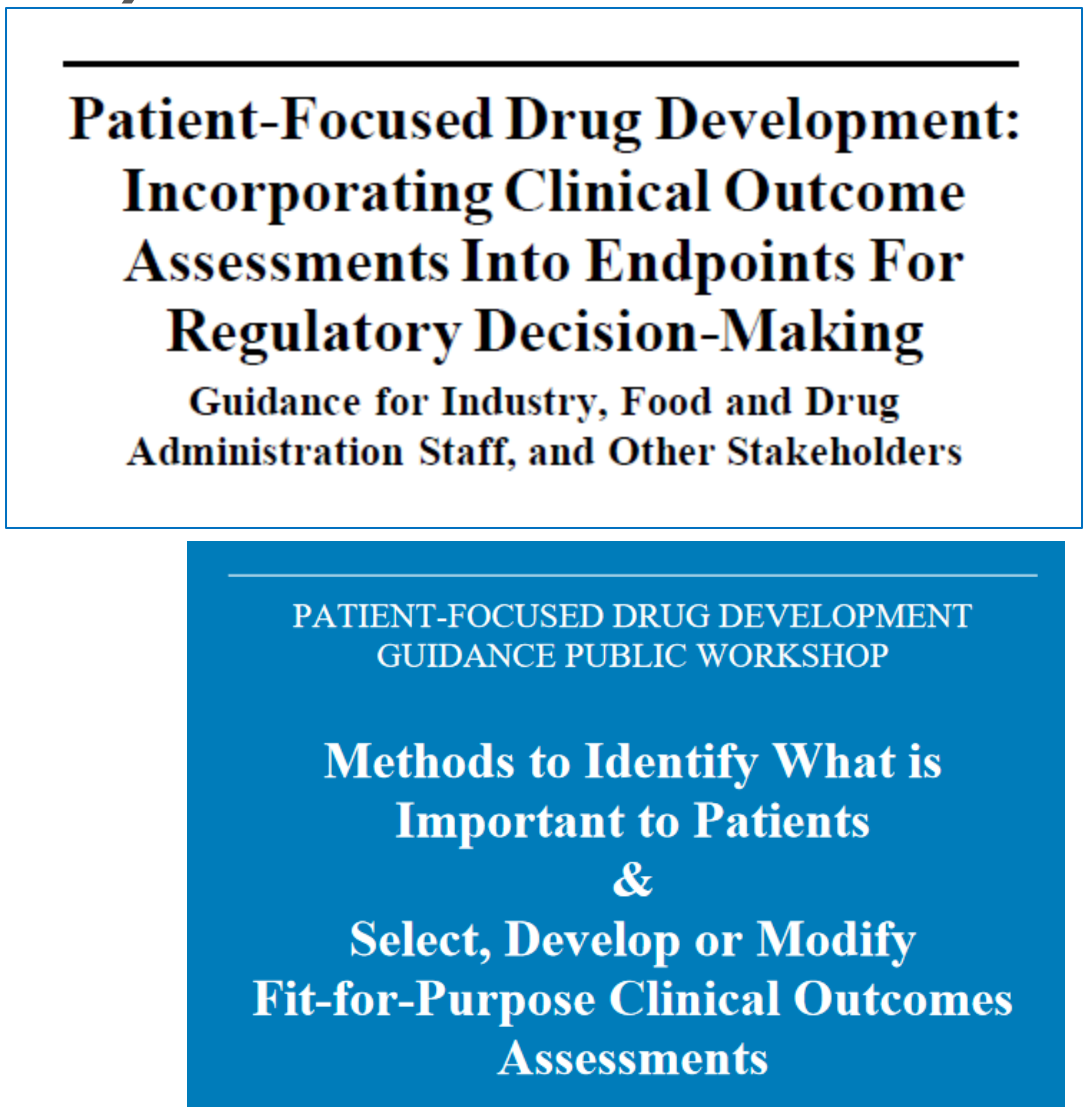
If a subject experienced more than 1 event in a given category, that subject is counted only once in that category.

Patient-focused drug development (PFDD)

Actigraphy: Clinical Outcome Assessment (COA)

- *Differences in COA scores should be related to differences in one or more anchors.*
  - *Stronger the relationship, the more confidence.*

- PGIC and PGIS recommended by FDA as Anchors



https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

FDA Recommended Anchoring Analysis for Actigraphy

- To our knowledge, this development program was the **first registration trials with actigraphy-based primary agreed by FDA**
- The ability of the new endpoint to **detect the change in comparison with widely used PROs** was part of Phase 3 program
- **FDA guidelines recommend anchor-based approach** to define Minimal Important Change (MIC) for the clinical outcome of interest, which is actigraphy-based MVPA in our case
- As recommended by FDA widely used Patient Reported Outcomes (PRO) were the selected anchor measures for this exploratory assessment:
  - Patient Global Impression of **Change (PGIC)** and
  - Patient Global Impression of **Severity (PGIS)**

Patient Global Impression of Change (PGIC)

Thinking about your usual daily physical activities:

Check the one number that best describes the change in your impairment in performing moderate intensity physical activities:

- that may include walking climbing stairs, household chores and exercise

1. Much better
2. A little better
3. No change
4. A little worse
5. Much worse

Patient Global Impression of Severity (PGIS)

Thinking about your usual daily physical activities:

Check the one number that best describes the **severity** of **your impairment in performing moderate intensity physical activities**

- that may include walking climbing stairs household chores and exercise:

1. None
2. Mild
3. Moderate
4. Severe
5. Very Severe

When conducting and presenting the anchoring analyses, PGIC and PGIS will be grouped into the categories.

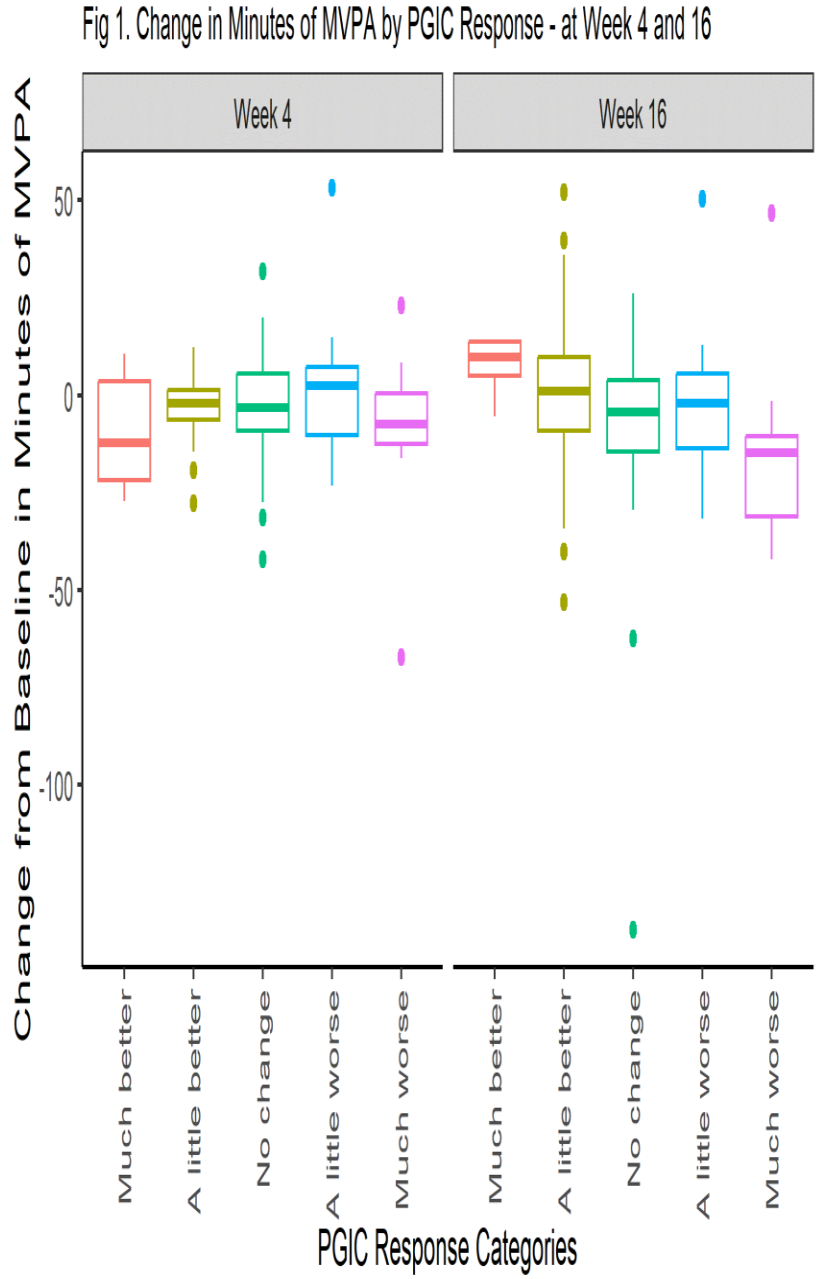
As the processed PGIS data can range from:

-4 to +4,

a change of 2 or more points is consolidated into 1 group.

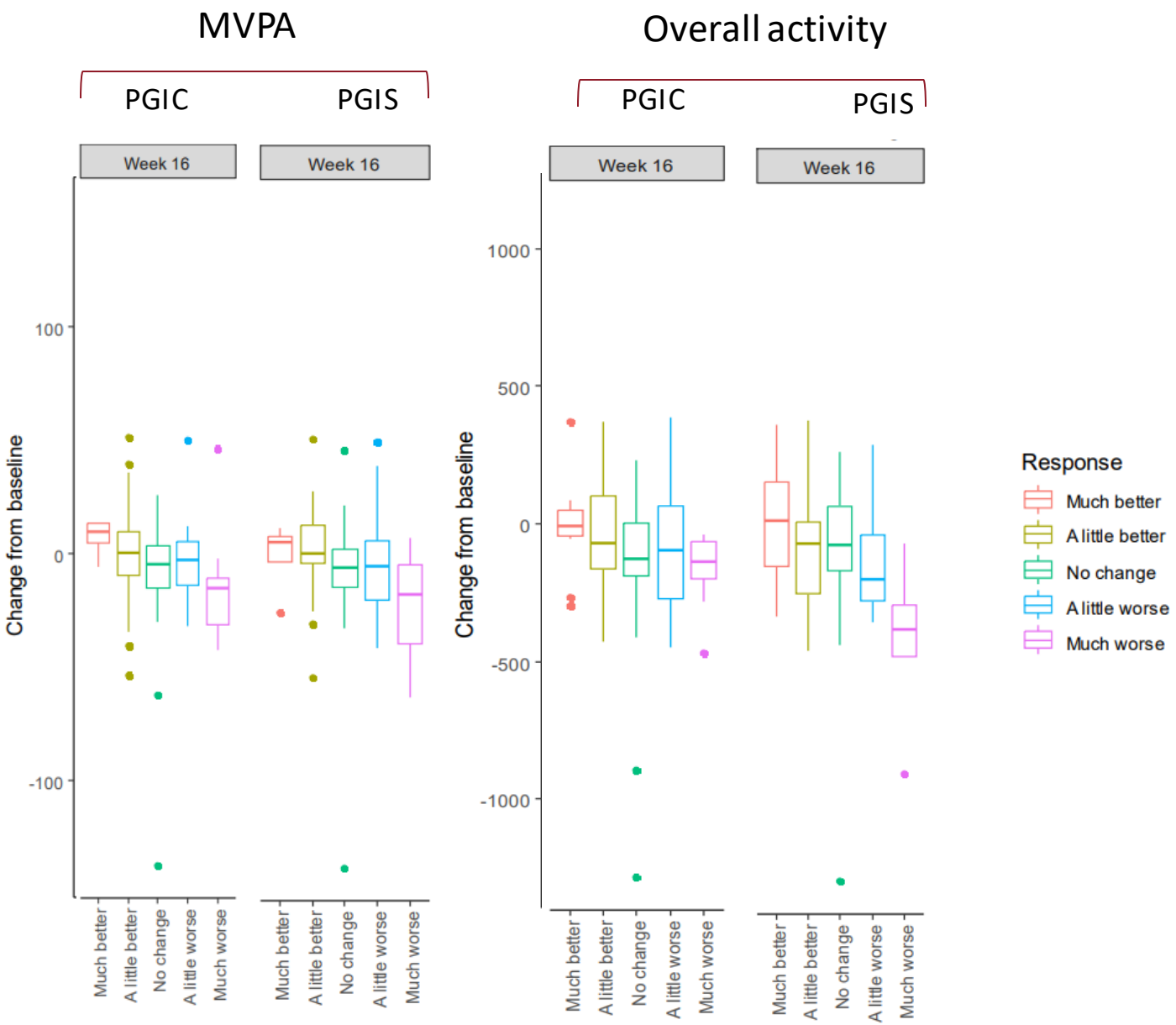
PGIS Score (change from baseline)	PGIC Score
≥2 Category improvement (+2, +3, +4)	Much better (1)
1 Category improvement (+1)	A little better (2)
No change (0)	No change (3)
1 Category decline (-1)	A little worse (4)
≥2 Category decline (-2, -3, -4)	Much worse (5)

MVPA (Actigraphy) vs PGIC Response (All 145 subjects)

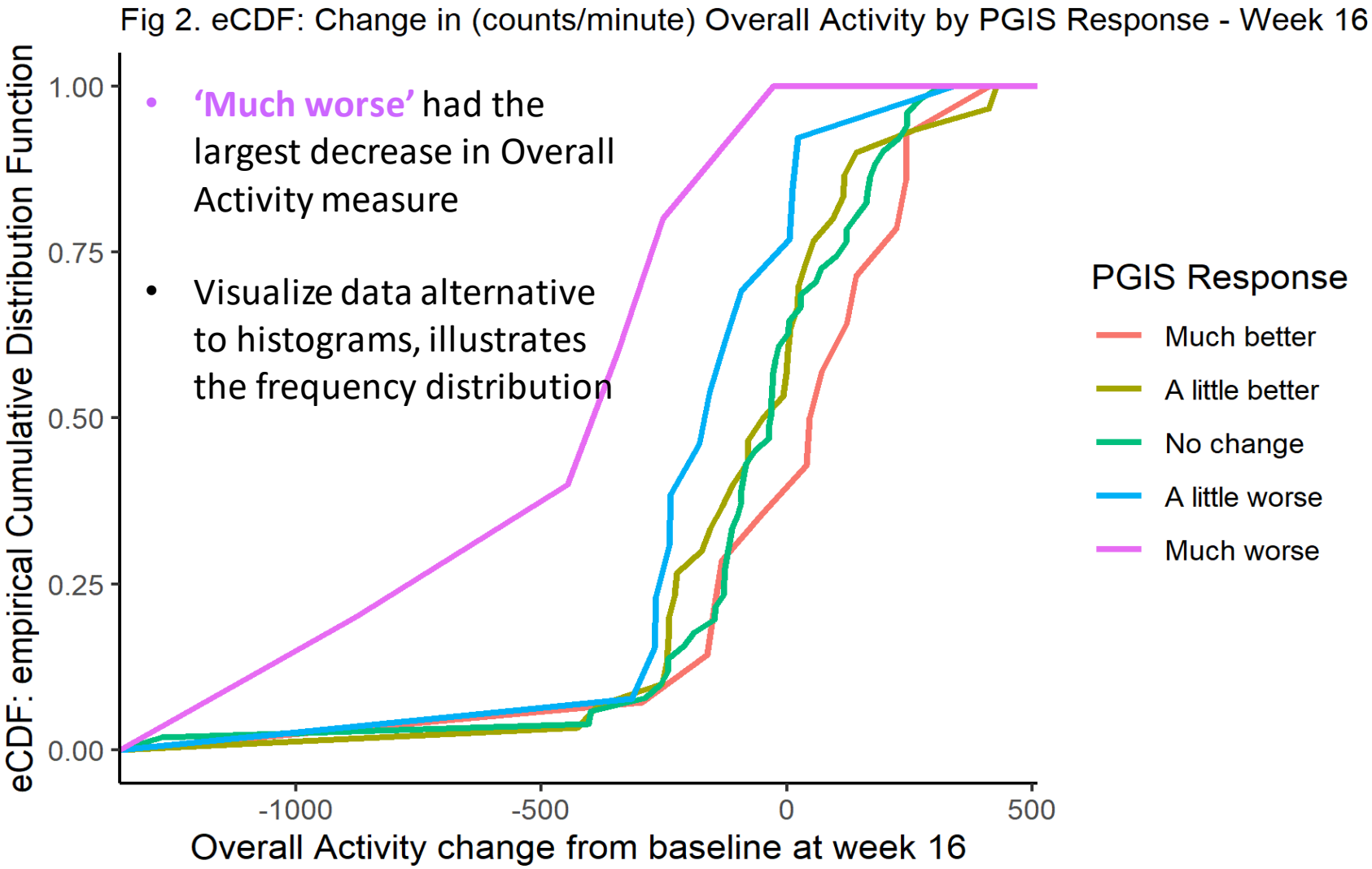


- Exploratory analysis at Week 16, subjects reporting
  - **'Much better'** had the smallest decrease in the MVPA measure
  - **'Much worse'** had the largest decrease from baseline in minutes of daily MVPA

Change in Minutes of MVPA and overall activity by PGIC and PGIS

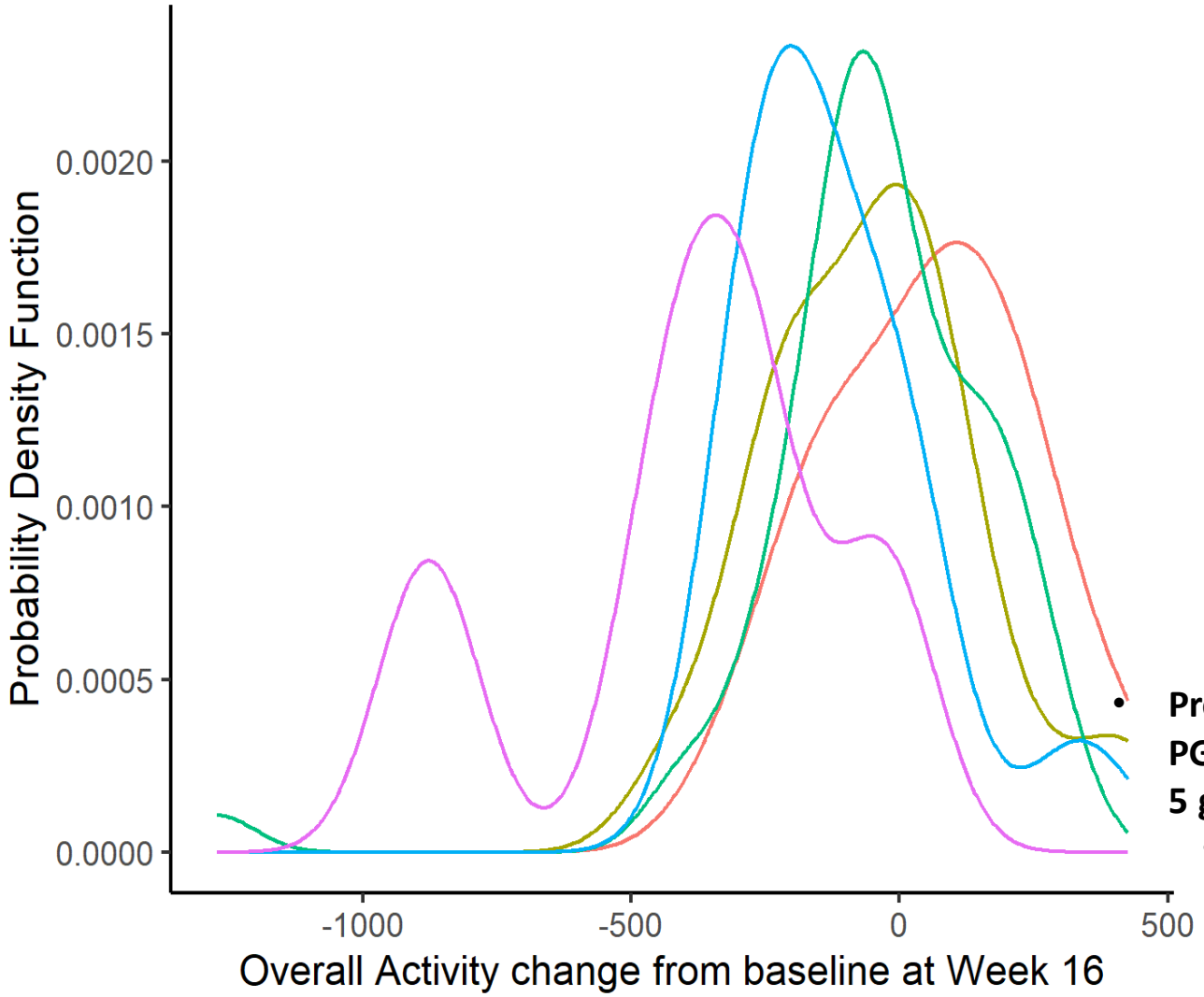


Overall Activity (Actigraphy) vs PGIS Response Categories (All 145 subjects)



Overall Activity (Actigraphy) vs PGIS Response Categories All 145 Subjects

Fig 3. Change in Overall Activity (counts/minute) by PGIS Categories – Week 16



Probability Density show some indication of expected ordering of PGIS response categories, and distribution of values in each of the 5 groups.

- By the extent of change from baseline in Overall Activities

Conclusions:

- Wearable DHT-derived measures can and should be used as patient-centric endpoints in registration trials, as a direct measure of function
- It was the first time that a novel actigraphy-derived measure was accepted by both the FDA & CFDA as a primary regulatory endpoint in the US and China
- We successfully operationalized the deployment of wearable DHTs under the highest clinical and regulatory oversight

The predefined exploratory anchoring analyses:

- Supports the clinical validity of the simple yet novel Actigraphy DHT Measure as anchored by PROs