Advancing the Science of Clinical Trial Data Collection

Ninth Annual
Patient-Reported Outcome Consortium Workshop

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Session Overview

- One of PRO Consortium's objectives: to advance the science underpinning reliable and fit-for-purpose assessment of clinical outcomes in treatment trials
  - Gather empirical data to inform ongoing measurement and/or methodological questions
- Today's session will include results of two C-Path projects
  - Measurement equivalence between 4 traditional electronic PRO modes and paper
  - Measurement equivalence between provisioned device and bring your own device (BYOD)
- Presentation on Innovative Medicines Initiative (IMI) PROactive tool: collection of patient-reported and wearable device data in clinical trials

Session Participants

Moderator

- *Sonya Eremenco, MA* – Associate Director, PRO Consortium

Presenters

- *J. Jason Lundy, PhD* – Principal, Outcometrix
- *Louise Newton, MSc* – Senior Director, Clinical Outcome Assessments, Clinical Outcomes Solutions
- *Niklas Karlsson, PhD* – Patient Reported Outcomes Director Respiratory, AstraZeneca

Panelists

- *Bill Byrom, PhD* – Vice President, Product Strategy and Innovation, CRF Health, and Vice Director, ePRO Consortium
- *Wen-Hung Chen, PhD* – Team Leader, COA Staff, Office of New Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration
- *David Reasner, PhD* – Vice President, Data Science and Head, Study Endpoints, Ironwood Pharmaceuticals

Session Outline

- **Part 1: Equivalence Studies**
  - *EQ-5D-5L Measurement Equivalence Study: J. Jason Lundy, PhD*
  - *Comparison of Provisioned Device and BYOD in COPD: Louise Newton, MSc*
  - *Q&A (10 minutes)*

- **Part 2: Case Study of IMI PROactive Tool: Incorporating Data from a Wearable Device**
  - *Presenter: Niklas Karlsson, PhD*
  - *Panel Discussion (15 minutes)*
    - *Bill Byrom, PhD*
    - *Wen-Hung Chen, PhD*
    - *David Reasner, PhD*
  - *Q&A (10 minutes)*

EQ-5D-5L Electronic Measurement Equivalence Project

J. Jason Lundy, PhD

Outcometrix

Background

- In 2015, C-Path received a grant from the EuroQol Research Foundation to conduct a measurement equivalence study of the EQ-5D-5L
- The study qualitatively and quantitatively assessed the comparability of four electronic formats (handheld, tablet, web, IVR) and the paper format of the EQ-5D-5L
  - Convenience sample from the UK general population, equal number of subjects with and without a chronic health condition causing daily pain or discomfort, depression or anxiety, or problems dressing/washing, walking or performing usual activities
- Members of the ePRO Consortium provided in-kind support for the study
  - Instrument implementation on the various electronic modes
  - Supplied the devices to conduct the study
  - Provided database and technical support
- ICON was contracted to collect the data, analyze qualitative data
- Outcometrix was contracted to analyze the quantitative data

Qualitative Study Design

- Stage 1: Qualitative assessment of conceptual understanding and usability (n=30)
  - 15 subjects with, and 15 subjects without, a chronic health condition
  - Participants were assigned to one of three groups:
    - Group 1: Handheld and paper (n=10)
    - Group 2: Web and paper (n=10)
    - Group 3: IVR and paper (n=10)
- Stage 2: Comparison of interviewing methodologies (n=30)
  - 15 subjects with, and 15 subjects without, a chronic health condition
  - Participants were allocated to one of three interview methodology groups, all of which compared the tablet to the original paper-based format
    - Interview Method 1 (n=10)
    - Interview Method 2 (n=10)
    - Interview Method 3 (n=10)

Qualitative Study Design

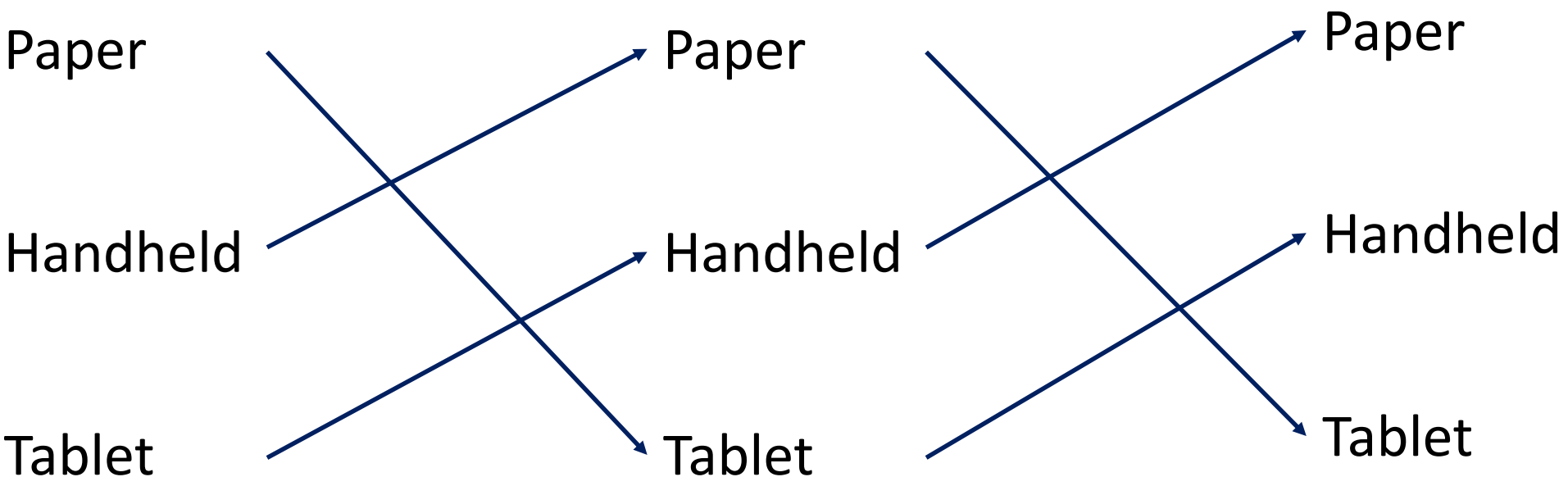
- Three different cognitive interviewing methods were used in Stage 2
  - Method 1: Participants completed both paper and tablet formats, with debriefing conducted on the tablet format. When responses differed, participants were asked how they interpreted the question on paper and the reason(s) for the discrepant response.
  - Method 2: Participants completed both paper and tablet formats. Debriefing was conducted on the paper format, and whether their interpretation of each item was any different on the tablet.
  - Method 3: Participants completed both paper and tablet formats, and were asked questions about perceived differences between the formats of the instrument overall rather than at the individual item level. Participants were also asked whether any of their answers would be different due to the change in presentation of the questionnaire from paper to electronic format.

Quantitative Study Design

- As part of the foundational work for this study, the test-retest reliability of the paper-based, UK English version of the EQ-5D-5L was assessed
  - Single group (n=60), two-period, repeated measures design
- To compare paper and electronic modes of data collection, four independent samples (n=60) were recruited into a three period, crossover study
  - Each subject was assigned to one of six groups, each having different orders of administration of the various modes.
  - Data were collected in a single visit; subjects performed a 30-minute distraction task
  - Three schemes compared two electronic modes to paper, one scheme compared electronic modes to each other
- These data were analyzed for mean differences and ICC using the test-retest data as the thresholds

Quantitative Study Design

Three-period Crossover Example



- Each subject was assigned to one of six groups, each having different orders of administration

Qualitative Study Results

- Overall, the items of the EQ-5D-5L were interpreted consistently by participants across all device groups (Stage 1)
  - All participants were able to interpret each item and response option appropriately
  - The majority of issues reported by participants were related to issues with the original content, rather than any differences in understanding or interpretation between the different modes.
- When asked whether their answers might be different on paper versus ePRO due to the differences in layout, the majority of participants indicated that their answers would not be different.
- On the 0 to 100 scale, a number of participants in the web, handheld, and tablet groups noted answering differently between paper and electronic formats due to the size of the scale and the inability to pinpoint an exact response.

Qualitative Study Results

Stage 2: Comparison of interviewing methodologies

	Method 1	Method 2	Method 3

Interview Results	• For 5 main items, only one instance of an actual discrepant response (mobility item - one point difference).
	  ○ Respondent wasn't aware he/she had given a different response. Indicated it was not related to difference in interpretation.
	• 4 discrepant responses on overall health item (usability issue)
		• Not a single instance of a participant reporting a difference in interpretation between paper and tablet.
		• 1 participant spontaneously reported different answer on overall health item (usability issue)
			• 5 participants reported their answers differed (or may have differed).
			  ○ 1 maybe because answered more quickly on tablet
			  ○ 1 maybe because "thought more" when answering on tablet
			  ○ 3 overall health item (usability issue)

- Size Matters - Participants had difficulty selecting the number on the 0 to 100 scale due to the size of the scale on the tablet (usability issue)

Quantitative Study Results

- Subject characteristics
  - Females ranged from 42% to 65% of the samples
  - Average age ranged from 38 to 49 years
  - Representation across education levels and ethnic groups

Test-retest results

	Mean (SD)	Mean Difference (95% CI)	ICC (95% CI)
Index – Time 1	0.860 (0.155)	0.003 (-0.011, 0.017)	0.946 (0.911, 0.967)
Index – Time 2	0.857 (0.168)		
EQ VAS – Time 1	81.550 (16.384)	-0.800 (-1.927, 0.327)	0.964 (0.940, 0.978)
EQ VAS – Time 2	82.350 (16.275)		

- ½ SD was used to set the equivalence intervals; mean differences -0.040 to 0.040 for the index, and -4.0 to 4.0 for the EQ VAS.
- ICC (3,1) thresholds are lower 95% CI $\geq$ 0.911 for the index and $\geq$ 0.940 for the EQ VAS

Quantitative Study Results

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Paper-handheld-web

	Mean Difference (95% CI)	Mode x Order Interaction	ICC (95% CI)
Index: Paper-Handheld	0.004 (-0.009, 0.017)		0.952 (0.921, 0.971)
Index: Paper-Web	0.006 (-0.006, 0.019)	$p = 0.757$	0.964 (0.941, 0.978)
Index: Handheld-Web	0.003 (-0.008, 0.014)*		0.970 (0.950, 0.982)
EQ VAS: Paper-Handheld	0.050 (-0.694, 0.794)		0.985 (0.975, 0.991)
EQ VAS: Paper-Web	0.117 (-0.248, 0.482)	$p = 0.165$	0.996 (0.993, 0.997)
EQ VAS: Handheld-Web	0.067 (-0.528, 0.661)		0.991 (0.984, 0.994)

*Point estimate reflects rounding to nearest thousandth decimal place

Paper-handheld-tablet

	Mean Difference (95% CI)	Mode x Order Interaction	ICC (95% CI)
Index: Paper-Handheld	0.001 (-0.002, 0.005)		0.996 (0.993, 0.997)
Index: Paper-Tablet	-0.004 (-0.009, 0.002)	$p = 0.926$	0.989 (0.981, 0.993)
Index: Handheld-Tablet	-0.005 (-0.011, 0.001)		0.983 (0.972, 0.990)
EQ VAS: Paper-Handheld	0.807 (0.144, 1.471)		0.987 (0.977, 0.992)
EQ VAS: Paper-Tablet	0.189 (-0.592, 0.970)	$p = 0.910$	0.984 (0.973, 0.990)
EQ VAS: Handheld-Tablet	-0.619 (-1.478, 0.241)		0.980 (0.967, 0.988)

Quantitative Study Results

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Paper-web-IVR

	Mean Difference (95% CI)	Mode x Order Interaction	ICC (95% CI)
Index: Paper-IVR	-0.005 (-0.015, 0.005)		0.989 (0.981, 0.993)
Index: Paper-Web	-0.001 (-0.012, 0.009)	$p = 0.552$	0.990 (0.983, 0.994)
Index: Web-IVR	-0.004 (-0.017, 0.010)		0.982 (0.969, 0.989)
EQ VAS: Paper-IVR	0.067 (-0.392, 0.526)		0.997 (0.994, 0.998)
EQ VAS: Paper-Web	-0.059 (-0.434, 0.316)	$p = 0.147$	0.998 (0.996, 0.999)
EQ VAS: Web-IVR	0.126 (-0.408, 0.661)		0.996 (0.993, 0.997)

Handheld-tablet-web

	Mean Difference (95% CI)	Mode x Order Interaction	ICC (95% CI)
Index: Handheld-Tablet	0.000 (-0.006, 0.006)		0.990 (0.983, 0.994)
Index: Handheld-Web	0.000 (-0.010, 0.009)	$p = 0.660$	0.972 (0.953, 0.983)
Index: Tablet-Web	0.000 (-0.011, 0.010)		0.966 (0.943, 0.979)
EQ VAS: Handheld-Tablet	-0.393 (-0.735, -0.051)		0.995 (0.990, 0.997)
EQ VAS: Handheld-Web	-0.031 (-0.800, 0.737)	$p = 0.389$	0.971 (0.952, 0.983)
EQ VAS: Tablet-Web	0.361 (-0.305, 1.027)		0.978 (0.963, 0.987)

Study Conclusions

- In general, the items of the EQ-5D-5L were interpreted consistently by participants across all device groups
  - Usability problems were associated with the EQ VAS
- No single method was identified as best at identifying issues that undermined conceptual equivalence. Method 2 appears to be most closely aligned with the assessment of ‘conceptual equivalence’
- ICCs were high across comparisons
  - Mean differences were negligible; no order effects
- Limitations: Sample generalizability is limited; quantitative study utilized short re-test interval

Comparability of a Provisioned Device Versus Bring Your Own Device for Completing Patient-Reported Outcome Measures in Participants with Chronic Obstructive Pulmonary Disease

Louise Newton MSc, Senior Director, Clinical Outcomes Solutions

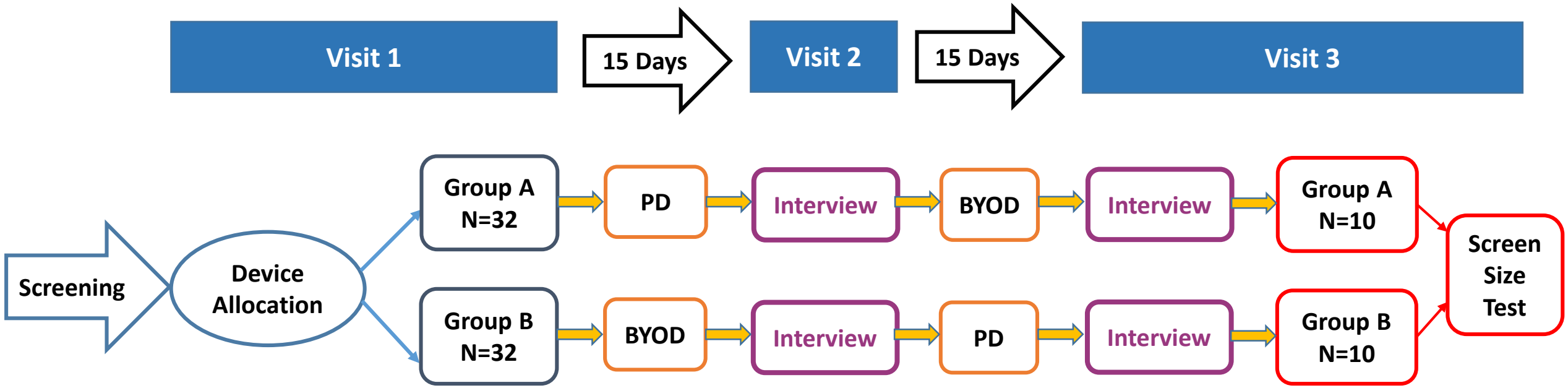
Overview of Study Scope

- FDA PRO Guidance[1] encourages use of ePRO data collection because it allows for attributable and time-stamped data
- Historically, electronic devices have been provided for the participant to use (provisioned device; PD)
- An alternative approach – bring your own device (BYOD) – allows participants to use their own smartphone instead of a PD
- BYOD is thought to be more user-friendly and cheaper for industry than PD, but several technical, logistical, and scientific questions remain unanswered[2]
- On behalf of the PRO Consortium's ePRO Subcommittee and the ePRO Consortium, COS undertook this study to evaluate the qualitative and statistical equivalence associated with completing PRO measures using BYODs versus PDs
- Findings relating to the following study objectives will be presented today:
  - To test the **EQUIVALENCE** of PRO data collected on PD vs BYOD
  - To compare **COMPLIANCE** rates on PRO measures using PD vs BYOD
  - To **QUALITATIVELY** describe participants' experiences of using each device

Study Design (1/2)

- N=64 adults with COPD participated in a 30-day, cross-over study
- The EXAcerbations of Chronic pulmonary disease Tool (EXACT®) was completed every day for 15 days
  - *The EXACT® is a 14-item daily diary used to quantify and measure exacerbations of COPD. Per licence requirements, the entire EXACT® was administered but only the 11-item E-RS™: COPD was used in analyses. It measures the effect of treatment on the severity of respiratory symptoms in stable COPD.*
- The COPD Assessment Test (CAT) and Patient Global Impression of Severity (PGIS) were completed every 7 days (Day 1, 8, 15, 16, 23, 30)
  - *The CAT comprises 8 items that assess domains related to the impacts of COPD: cough, phlegm, tightness of chest, breathlessness, activities at home, confidence to leave the home, sleep, and energy.*
  - *The PGIS is a single item measure that asks participants to report the severity of their COPD symptoms over the previous 7 days.*
- Interviews were conducted at the end of each 15-day period
- After the 2nd interview, 20 participants took part in a screen size equivalence test (results to be reported at a later date)

Study Design (2/2)



PD: Provisioned Device
BYOD: Bring Your Own Device

Eligibility Criteria

Inclusion Criteria

1. Age ≥ 40 years
2. Clinical diagnosis of COPD in accordance with the joint American Thoracic Society/European Society's definition
3. Forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ratio of <0.70 post-bronchodilator
4. FEV_1 of predicted <80%
5. Current or former smoker with history of at least 10 pack years
6. Clinical status and treatment unlikely to change in the next 30 days in the opinion of the investigator or referring clinician
7. Owns compatible smartphone for the BYOD component of the study
8. Able to read, comprehend, and complete questionnaires and interviews in United States (US) English
9. Able to provide written informed consent given prior to undertaking any study-related procedures

Exclusion Criteria

1. COPD exacerbation, including hospitalization or hospitalization for pneumonia, within previous 90 days
2. Professional involvement in, or immediate family member of staff working on this study
3. Participation in any BYOD study within previous 90 days
4. Learning, emotional, mental illness, or cognitive difficulties that might limit ability to meaningfully complete the questionnaires
5. Evidence of alcohol or drug abuse

Reasons for Non-Participation

Data provided by recruitment agency:

	N (%)
No record of FEV_1 (inclusion criterion #3/4)	25 (42)
Did not own a smartphone (inclusion criterion #7)	**9 (15)**
Did not meet English language requirements (inclusion criterion #8)	7 (12)
Time commitment too great	7 (12)
Did not want to use own phone in study	**5 (8)**
Not physically well enough to take part	4 (7)
Not available for all study visits	2 (1)
Total	59

Study Flow

Enrolled into Study; N=64

Technical issues meant n=9 who were due to start on PD started on BYOD instead

Assigned to PD; N=23

Assigned to BYOD; N=41

n=1 had technical issues and did not submit any data for period 1
- 01_010_BA

Diary Period 1; N=63

Completed 1st interview; N=61

n=2 did not show for interview and were excluded from Period 2:
- 02_006_BI
- 04_007_BI

n=1 who had technical issues in period 1 was included in Period 2
- 01_010_BA

Switched to PD; N=38

Switched to BYOD; N=23

n=1 completed 1st interview but two weeks late, thus missed training and was excluded from Period 2:
- 01_003_BA

Diary Period 2; N=61

Completed 2nd interview; N=60

n=1 did not show for interview:
- 02_005_BA

Excluded participants:
- 01_002_PA; 01_007_PA: duplicates on same day, different scores
- 02_006_BI; 04_007_BI: no period 2 data due to missing 1st interview
- 01_003_BA: no period 2 data due to late 1st interview and missed training
- 01_010_BA: no period 1 data due to technical issues
- 04_003_BA; 04_005_BI: child entered data on their behalf

Quantitative Data Available; N=60

Longitudinal; N=56
PD 1st; N=21
BYOD 1st; N=35

Cross-Sectional; N=60
PD 1st; N=21
BYOD 1st; N=39

Excluded participants:
- 01_002_PA; 01_007_PA: duplicates on same day, different scores
- 04_003_BA; 04_005_BI: child entered data on their behalf

Qualitative Data Available; N=60

Longitudinal; N=57
PD 1st; N=23
BYOD 1st; N=34

Cross-Sectional; N=60
PD 1st; N=23
BYOD 1st; N=37

Excluded participants:
- 02_006_BI; 04_007_BI: did not show for either interview
- 04_003_BA; 04_005_BI: child entered data on their behalf

Excluded participants:
- 02_006_BI; 04_007_BI: did not show for either interview
- 02_005_BA: did not show for 2nd interview
- 01_003_BA: did not complete 2nd interview
- 01_010_BA: did not complete 1st interview
- 04_003_BA; 04_005_BI: child entered data on their behalf

Sample Characteristics (1/3)

		Quantitative Sample (N=60)	Qualitative Sample (N=60)
Age	N Mean (SD) Median Min - Max	60 58.82 (10.33) 62.0 40-77	60 58.7 (10.29) 60.5 40-77
Gender	Female	38 (63.3)	40 (66.7)
	Male	22 (36.7)	20 (33.3)
Race	Black/African American	30 (50.0)	29 (48.3)
	White	25 (41. 7)	26 (43.3)
	Missing	5 (8.3)	5 (8.3)
Ethnicity	Hispanic/Latino	5 (8.3)	5 (8.3)
	Not Hispanic/Latino	54 (90.0)	54 (90.0)
	I do not wish to state my ethnicity	1 (1.7)	1 (1.7)

Sample Characteristics (2/3)

		Quantitative Sample (N=60)	Qualitative Sample (N=60)
Education	Did not complete high school	5 (8.3)	4 (6.7)
	High school diploma	17 (28.3)	18 (30.0)
	Some college or certificate prog	19 (31.7)	19 (31.7)
	College or University degree	17 (28.3)	17 (28.3)
	Graduate degree	2 (3.3)	2 (3.3)
Work Status	Employed full-time	26 (43.3)	26 (43.3)
	Employed part-time	5 (8.3)	5 (8.3)
	Homemaker	2 (3.3)	2 (3.3)
	Disabled/on disability	11 (18.3)	11 (18.3)
	Retired	12 (20.0)	12 (20.0)
	Unemployed	3 (5.0)	3 (5.0)
	Missing	1 (1.7)	1 (1.7)
Years Since Diagnosis	N Mean (SD) Median Min - Max	60 7.5 (6.31) 6.6 0 - 33	60 7.3 (6.36) 5.6 0 - 33

Sample Characteristics (3/3)

		Quantitative Sample (N=60)	Qualitative Sample (N=60)
Participant-Reported Overall Health	Poor	2 (3.3)	2 (3.3)
	Fair	16 (26.7)	17 (28.3)
	Good	32 (53.3)	31 (51.7)
	Very good	10 (16.7)	10 (16.7)
COPD Severity	Very mild	1 (1.7)	1 (1.7)
	Mild	11 (18.3)	11 (18.3)
	Moderate	34 (56.7)	34 (56.7)
	Severe	13 (21.7)	13 (21.7)
	Very severe	1 (1.7)	1 (1.7)
Comfort Level with Mobile Phones	Not at all comfortable	1 (1.7)	1 (1.7)
	A little bit comfortable	3 (5.0)	2 (3.3)
	Somewhat comfortable	8 (13.3)	8 (13.3)
	Quite a bit comfortable	10 (16.7)	11 (18.3)
	Very much comfortable	38 (63.3)	38 (63.3)
Type of BYOD owned	iOS	22 (36.7)	21 (35.0)
	Android	38 (63.3)	39 (65.0)

Were there Differences in Compliance Rates on the E-RS™: COPD Between BYOD vs. PD?

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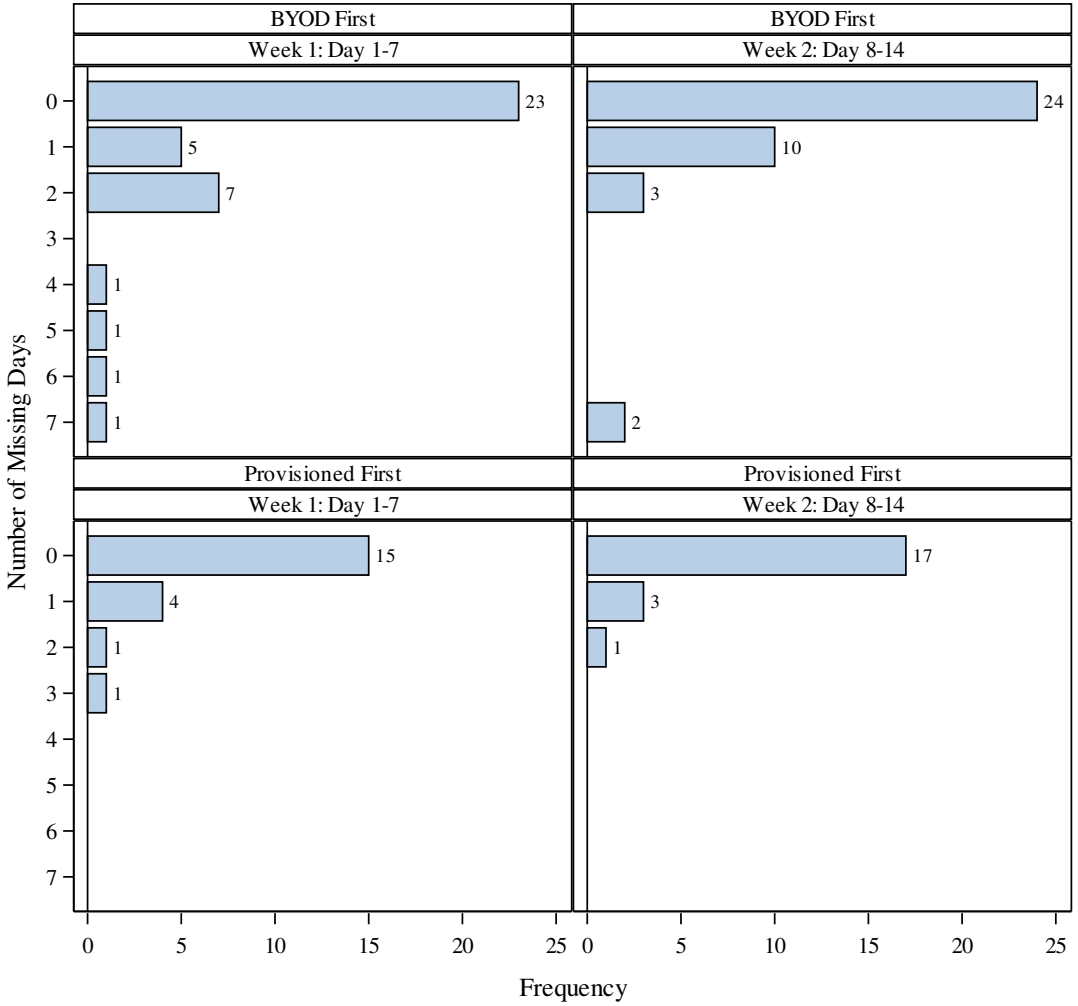
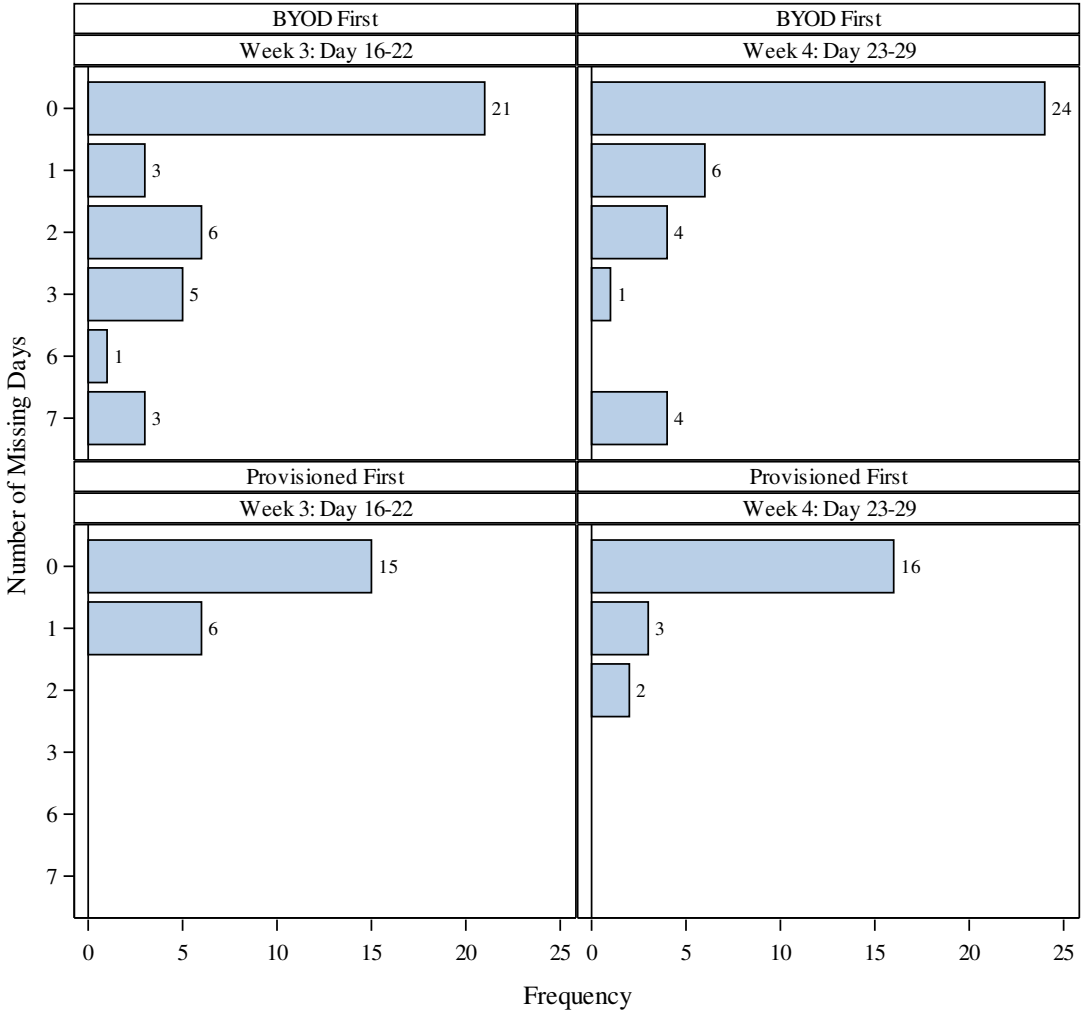
Number of Missing Diary Days in Period 1 (Weeks 1 and 2)



Number of Missing Diary Days in Period 2 (Weeks 3 and 4)



Were there Differences in Compliance Rates on the E-RS™: COPD Between BYOD vs. PD?

- When completing the diary on BYOD, 89.7% to 100% of participants completed at least 5 diary days in each week
- On PD, 76.9% to 100% of participants completed at least 5 diary days in each week
- Of note, in general, PD 1st participants were more compliant (95.2% to 100%) compared to BYOD 1st participants (76.9% to 94.8%)

	Week 1	Week 2	Week 3	Week 4
BYOD	89.7%	94.8%	100%	100%
PD	95.2%	100%	76.9%	87.2%

PD 1st participants

BYOD 1st participants

Were there Differences in Compliance Rates on the E-RS™: COPD Between BYOD vs. PD?

- When completing the diary on BYOD, 89.7% to 100% of participants completed at least 5 diary days in each week
- On PD, 76.9% to 100% of participants completed at least 5 diary days in each week
- Of note, in general, PD 1st participants were more compliant (95.2% to 100%) compared to BYOD 1st participants (76.9% to 94.8%)
  - For example, n=1 BYOD 1st participant in Week 1 and n=2 in Week 2 did not complete any of the 7 diary days.
  - The difference in compliance was particularly prominent in the switch-over period
    - n=3 BYOD 1st participants in Week 3 and n=4 in Week 4 did not complete any of the 7 diary days when using the PD.

	Week 1	Week 2	Week 3	Week 4
BYOD	89.7%	94.8%	100%	100%
PD	95.2%	100%	76.9%	87.2%

PD 1st participants

BYOD 1st participants

Were E-RSTM: COPD Scores Equivalent Between BYOD vs. PD?

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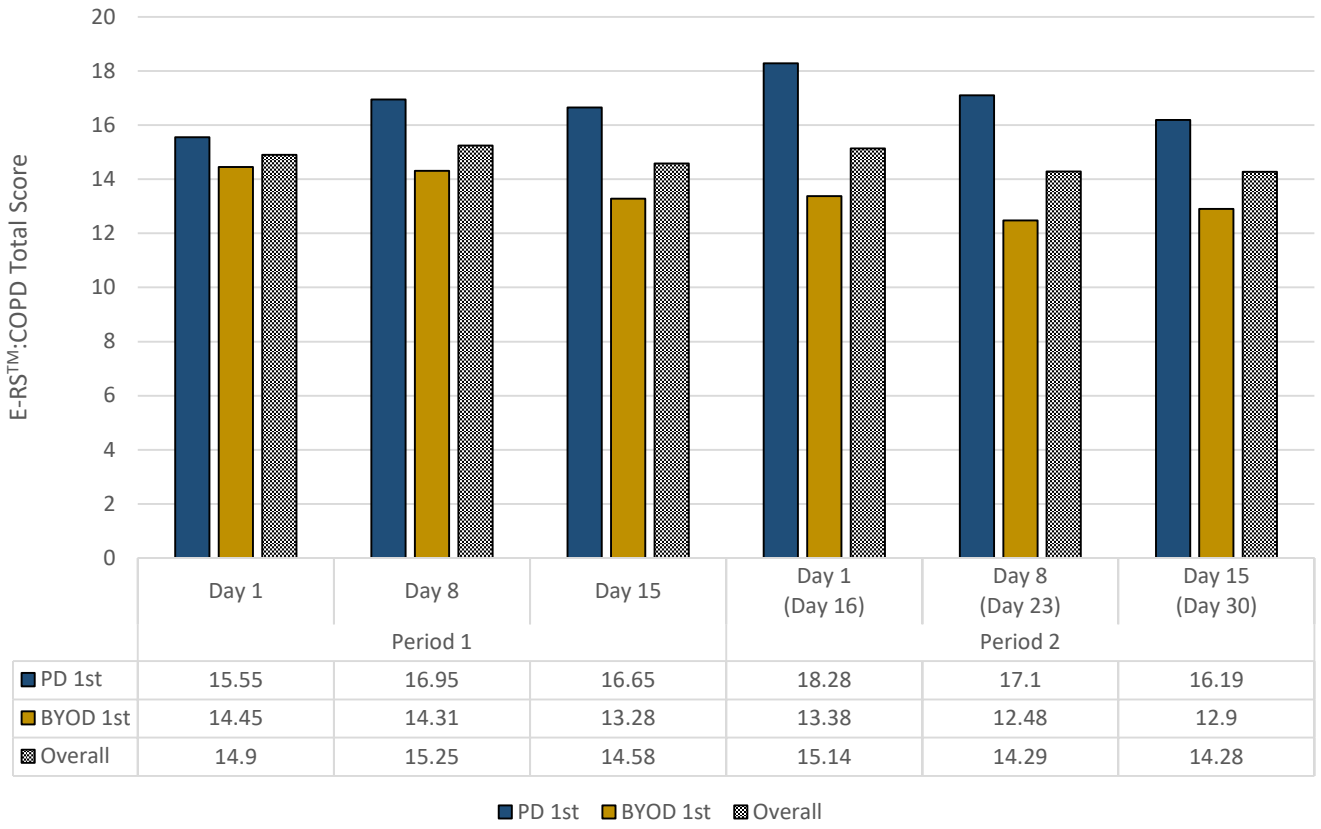
PD 1st participants had slightly higher E-RS™: COPD total mean scores than BYOD 1st participants across the study.



	Day 1	Day 8	Day 15	Day 1 (Day 16)	Day 8 (Day 23)	Day 15 (Day 30)
PD 1st	15.55	16.95	16.65	18.28	17.1	16.19
BYOD 1st	14.45	14.31	13.28	13.38	12.48	12.9
Overall	14.9	15.25	14.58	15.14	14.29	14.28

Within-participant variability was assessed using ICC (2,1)

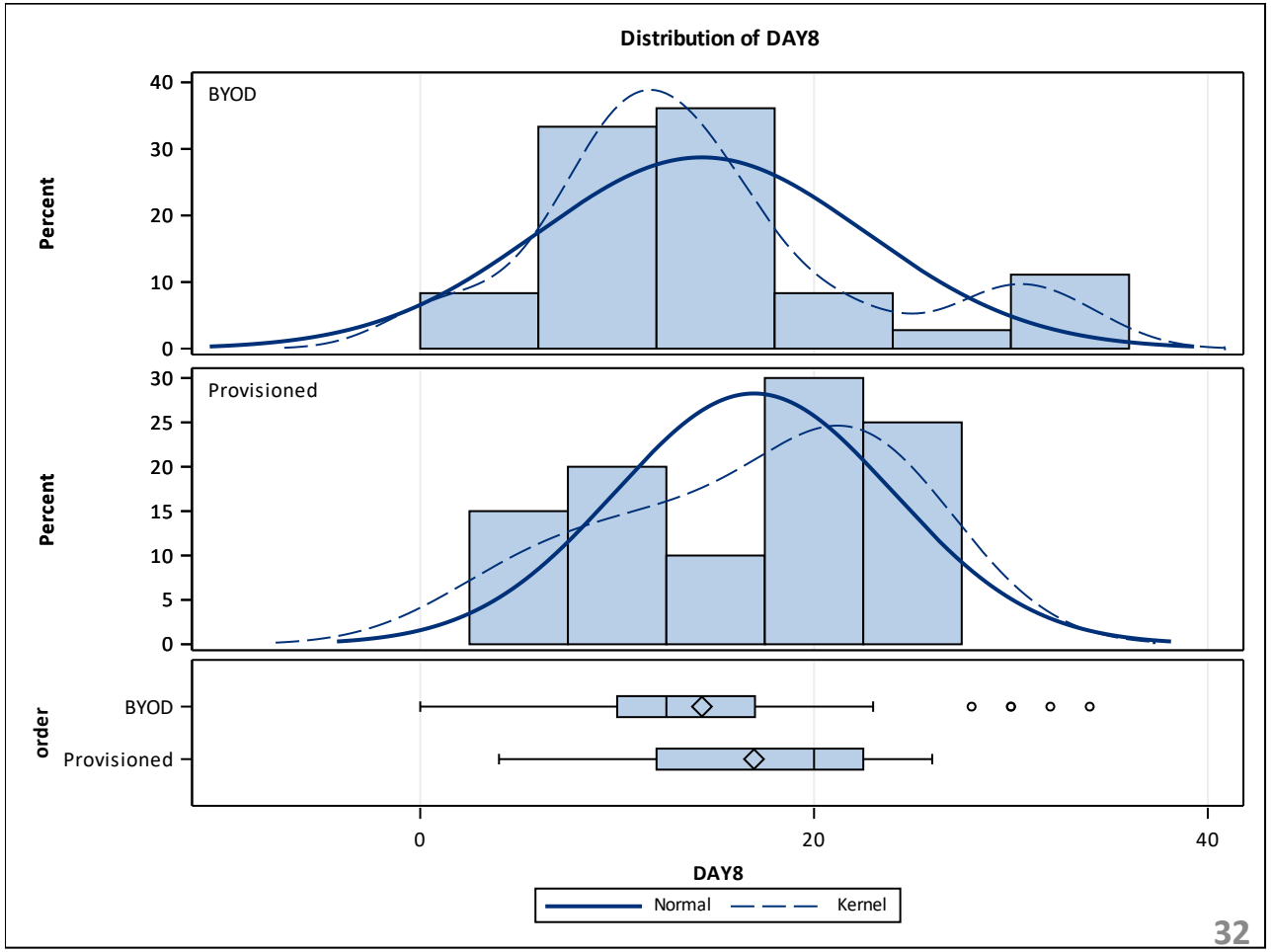
- For the E-RS: COPD™ weekly average score, the agreement in scores across devices comparing Weeks 2 and 3 was $ICC_{(2,1)}$=0.827
- For the E-RS: COPD™ daily score comparing Day 15 and Day 16 (the point at which participants switch devices), $ICC_{(2,1)}$=0. 622
- The CAT daily scores at Day 15 and 16 showed higher reliability, with $ICC_{(2,1)}$=0.836

- Prespecified criteria for evaluating the magnitude of the relationship was Cohen's thresholds: small (0.2), moderate (0.5), and large (0.8) with an acceptable threshold of > 0.7.

Were E-RS™: COPD Scores Equivalent Between BYOD vs. PD?

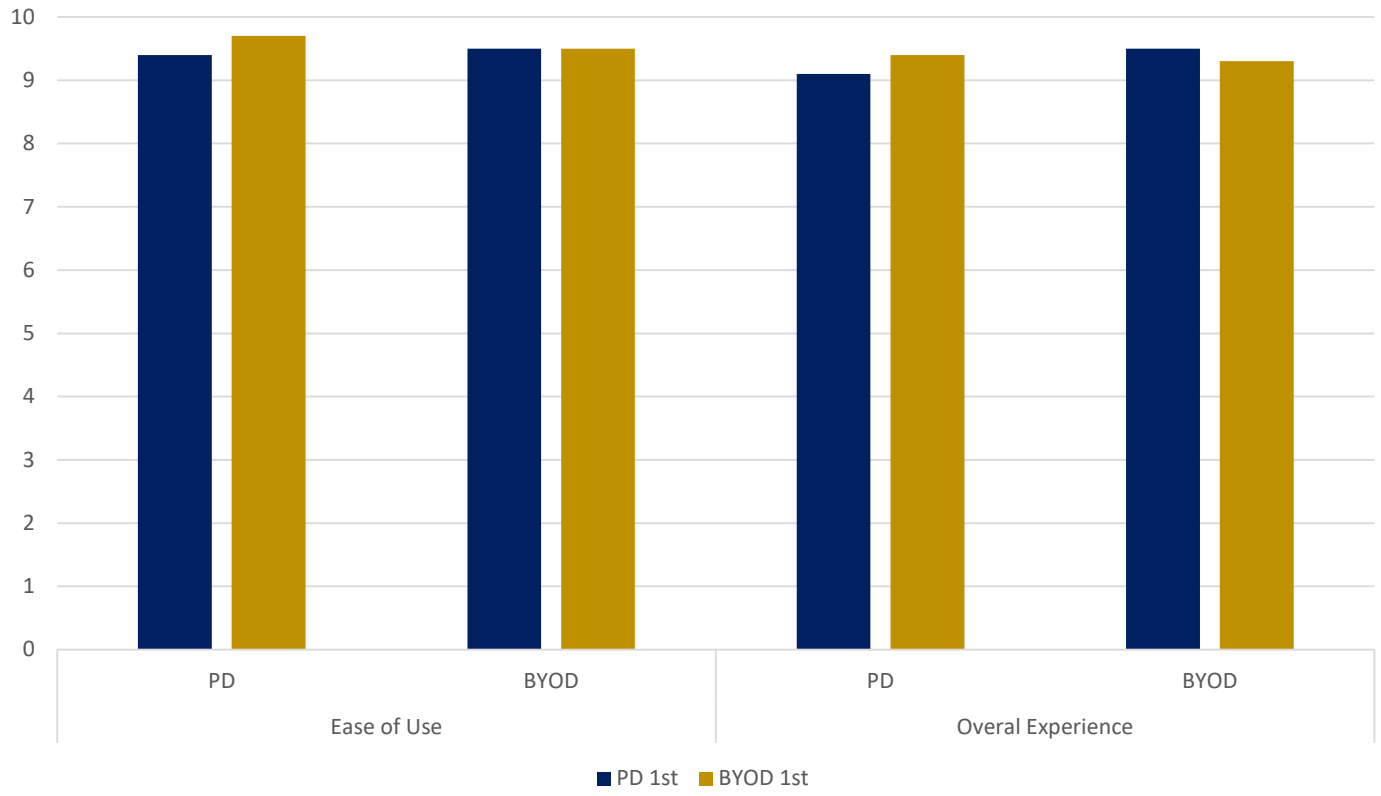
- Two one-sided tests (TOST) at Days 1, 8, 15, 16, 23, and 30 showed that the daily scores were equivalent between PD and BYOD for both the E-RS™: COPD and the CAT at 20% equivalence levels at most time points and the 40% equivalence levels for all time points
- The 10% level did not show equivalence

Illustration at Day 8: E-RS™: COPD Total Scores



Were There Differences in Participants' Ease of Use and Overall Experience When Using BYOD vs. PD?

- Participant-reported ease of using the device* and overall experience^ was equivalent at both time points.



*Select the number below that best describes the **ease of using** the device to answer the questions over the past 15 days. 1=Very Difficult – 10=Very Easy
^Select the number below that best describes your **overall experience** of using the device to answer the questions over the past 15 days. 1=Very Poor – 10=Very Good

Which Device Did Participants Prefer and Why?

There was no clear preference for either device.
Sub-group and quantitative analyses suggested a preference for Period 2 device.

45.6% (n=26*) preferred PD

- N=17 liked that the PD was specific to the diary/study
- N=7 liked that they could not be interrupted by emails/calls during completion (easier to focus)
- N=7 liked that the PD was not "cluttered" with other Apps
- N=4 felt is was easier to remember to complete the PRO measures on the PD than the BYOD
- N=3 perceived their data to be more secure

04-010-BA: *"I think I like this one better, because my phone have all those apps, this phone did not. So, you know, you opening, you turn it on and it's there. So, that phone. The phone that you issued."*

50.9% (n=29*) preferred BYOD

- N=17 liked not having an "extra device" to carry
- N=13 liked the convenience of always having their BYOD with them
- N=13 were more familiar with their own device
- N=4 felt the notifications were louder than on the PD
- N=3 felt their BYOD performed faster than the PD
- N=3 preferred BYOD because of PD technical issues
- N=3 felt is was easier to remember to complete the PRO measures on the BYOD than the PD

02-011-BI: *"…I don't have to keep up with somebody's else's stuff and my phone stay's right beside me all the time.*

*2 (3.5%) did not have a preference

On Which Device Did Participants Miss More Days and Why?

Over half reported missing at least one day, with n=8 saying they missed days in both phases. The number of reported missing days was lower in the interview than shown in the quantitative analysis. Sub-group analysis indicated that BYOD 1st participants generally missed more days than PD 1st participants across the 4 weeks.

33% (n=20) missed at least 1 day on PD

Missed 1 day	n=16
Missed 2 days	n=3
Missed 4-5 days*	n=1

Reasons for missing days:
- n=7 social engagements
- n=6 poor health/in hospital
- n=5 forgot
- n=4 too tired/asleep
- n=2 **tech difficulties**
- n=2 **PD out of battery**

03_015_PA: *"The battery wasn't charged, full charged, so I know I skipped one maybe at the, the beginning. It didn't take or hold the charge or something like that."*

40% (n=24) missed at least 1 day on BYOD

Missed 1 day	n=17
Missed 2 days	n=5
Missed 3 days	n=1

Reasons for missing days:
- n=7 too tired/asleep
- n=6 social engagements
- n=5 **tech issues**
- n=5 poor health/in hospital
- n=5 forgot
- n=2 **mobile out of battery**

03_010_PA: "The only problem I had was when you get to the very end and you're ready to go out and you hit "done" or whatever, and it doesn't, it doesn't go forward. And I think one day, I missed the uh, it did that and I don't think it ever got submitted for one day."

*N=1 was not sure if missed 4 or 5 days hence recorded as "4-5"

What Did Participants Say about the Reminder (Push) Notifications?

- The majority of participants received the notifications and found them useful on both devices (PD: n=36; BYOD: n=37)
- However, several said they did not receive notifications (PD: n=18; BYOD: n=9; both devices: n=6)
  - However, 17 participants (PD n=11; BYOD n=6) commented that they typically completed the PRO measures before the first notification would have been sent
- When using either device, many participants set an additional reminder (PD: n=15; BYOD: n=14), most often using the alarm function on their BYOD, or asking a family member to remind them
- The most requested change to the notifications was that they be louder (PD: n=9; BYOD: n=9)

Were Participants Interrupted While Using BYOD and What Were the Impacts?

- 17 reported that while completing the eDiary, they received
  - a phone call (n=11)
  - a text message (n=2)
  - a phone call and a text message (n=3)
  - notification from another app (n=1)
- 9 received only 1 to 2 interruptions during the 15-day period
- The majority (n=10) always ignored the interruption
- Of the 7 who answered a phone call, only one had to restart the eDiary
- 7 preferred the PD because it avoided the potential for interruptions

Summary and Conclusions

- This mixed methods study has demonstrated that scores on the PRO measures were equivalent between devices
- In line with the quantitative findings, the interviews demonstrated that the experience of using each device was largely consistent
- Compliance was 89.7% to 100% on BYOD and 76.9% to 100% on PD
- The reasons for missing days were similar across devices
  - n=70 (out of 826) missed days on BYOD (8.5% across both periods)
  - n=116 (out of 840) missed days on PD (13.8% across both periods)
- There was no clear qualitative preference for either BYOD or PD, and in a relatively older population, the findings are supportive of BYOD as a potential complement to PD for use in clinical trials in COPD; additional research is needed

References

- 1 – US Department of Health and Human Services. Guidance for industry. Patient-reported outcome measures: use in medical product development to support labeling claims. 2009. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf. [Accessed April 19, 2018].
- 2 - Coons SJ, Eremenco S, Lundy JJ, O'Donohoe P, O'Gorman H, Malizia W. Capturing Patient-Reported Outcome (PRO) Data Electronically: The Past, Present, and Promise of ePRO Measurement in Clinical Trials. Patient. 2015 Aug;8(4):301-9.

Measurement Studies Q & A

Moderator

- *Sonya Eremenco, MA* – Associate Director, PRO Consortium

Presenters

- *J. Jason Lundy, PhD* – Principal, Outcometrix
- *Louise Newton, MSc* – Senior Director, Clinical Outcome Assessments, Clinical Outcomes Solutions
- *Niklas Karlsson, PhD* – Patient Reported Outcomes Director Respiratory, AstraZeneca

Panelists

- *Bill Byrom, PhD* – Vice President, Product Strategy and Innovation, CRF Health, and Vice Director, ePRO Consortium
- *Wen-Hung Chen, PhD* – Team Leader, COA Staff, CDER, FDA
- *David Reasner, PhD* – Vice President, Data Science and Head, Study Endpoints, Ironwood Pharmaceuticals

IMI PROactive: developing a patient-centered measure of physical activity (PA) in chronic obstructive pulmonary disease (COPD)

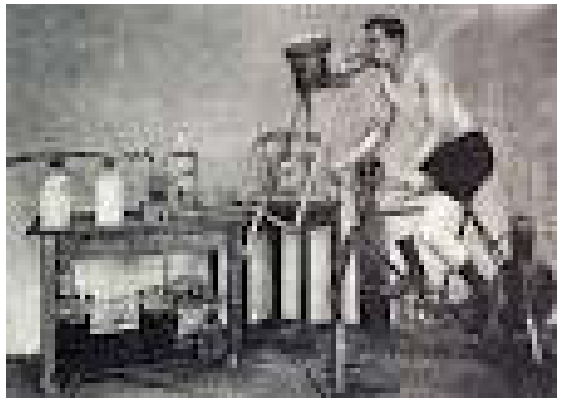
Niklas Karlsson, PRO Director, AstraZeneca

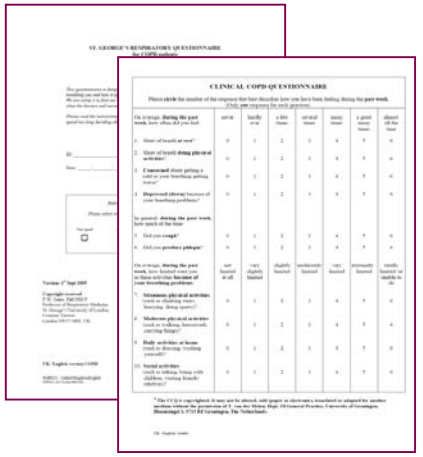
Outline

1. Background - Physical activity (PA) in COPD and the need for PROactive
2. The PROactive Consortium and its objectives
3. Overview of the IMI PROactive development project
4. Developing the instrument – input from patients, literature, experts; and identification/selection of activity monitors (WP2)
5. Item reduction and initial validation study (WP4)
6. Further validation studies (WP6)
7. The final PROactive instruments – items, domains and scoring
8. PROactive endpoints for clinical trials
9. ACTIVATE – an example of implementing PROactive in a clinical trial
10. EMA qualification
11. Summary and next steps

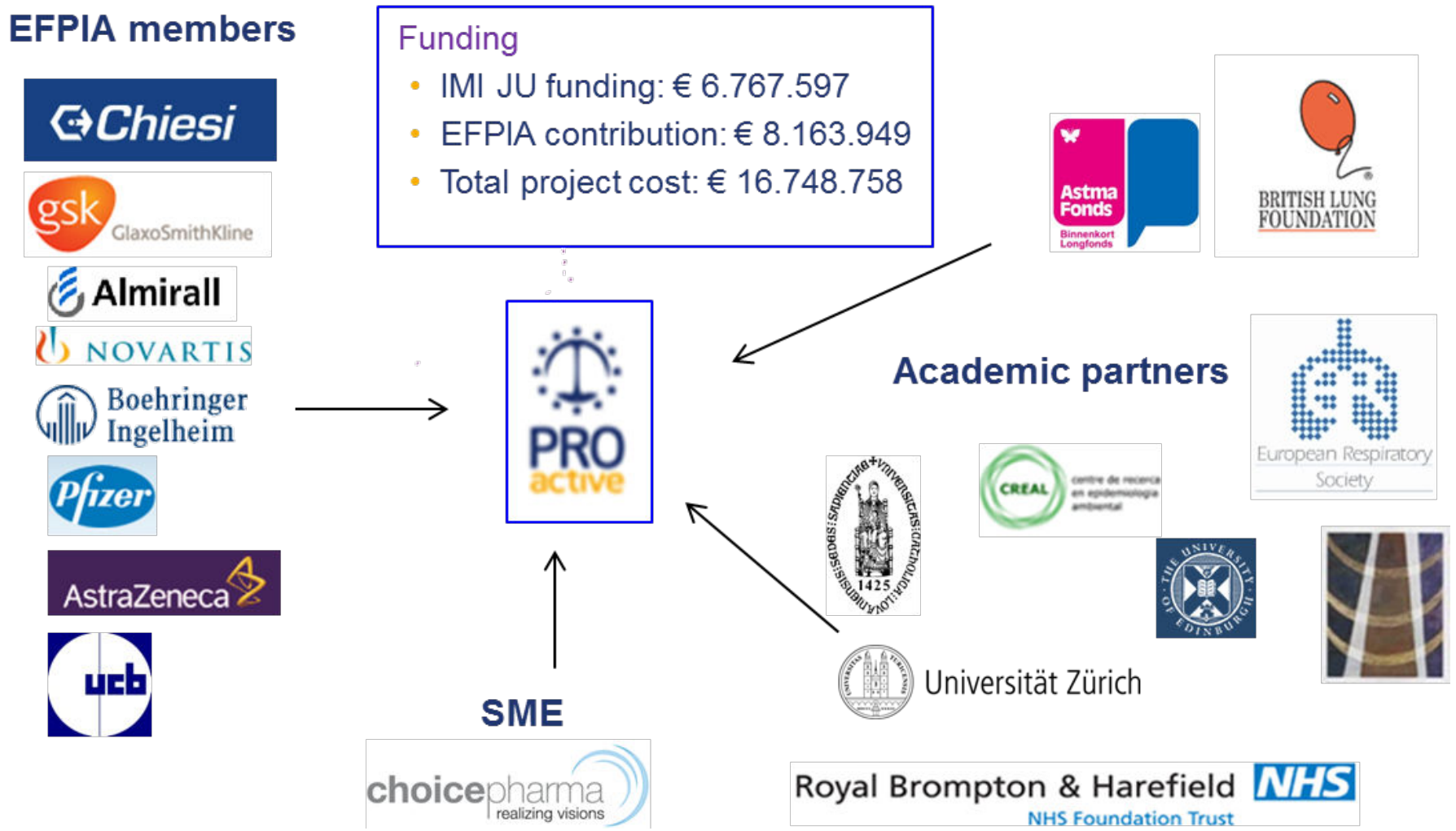
Background - Physical activity in COPD and the need for PROactive

- Patients (and physicians) report that physical activity limitations is a major concern in COPD
- Physical activity is associated with disease progression, and an important predictor of mortality in COPD
- There are available measures related to physical activity, but no targeted measure of all relevant aspects of physical activity experience in COPD





The PROactive Consortium and its objectives



The PROactive Consortium and its objectives

- The Consortium objective was to develop and validate PRO instruments that capture relevant dimensions of PA in COPD patients, are sensitive to change with interventions including pharmacotherapy, and can support labelling claims

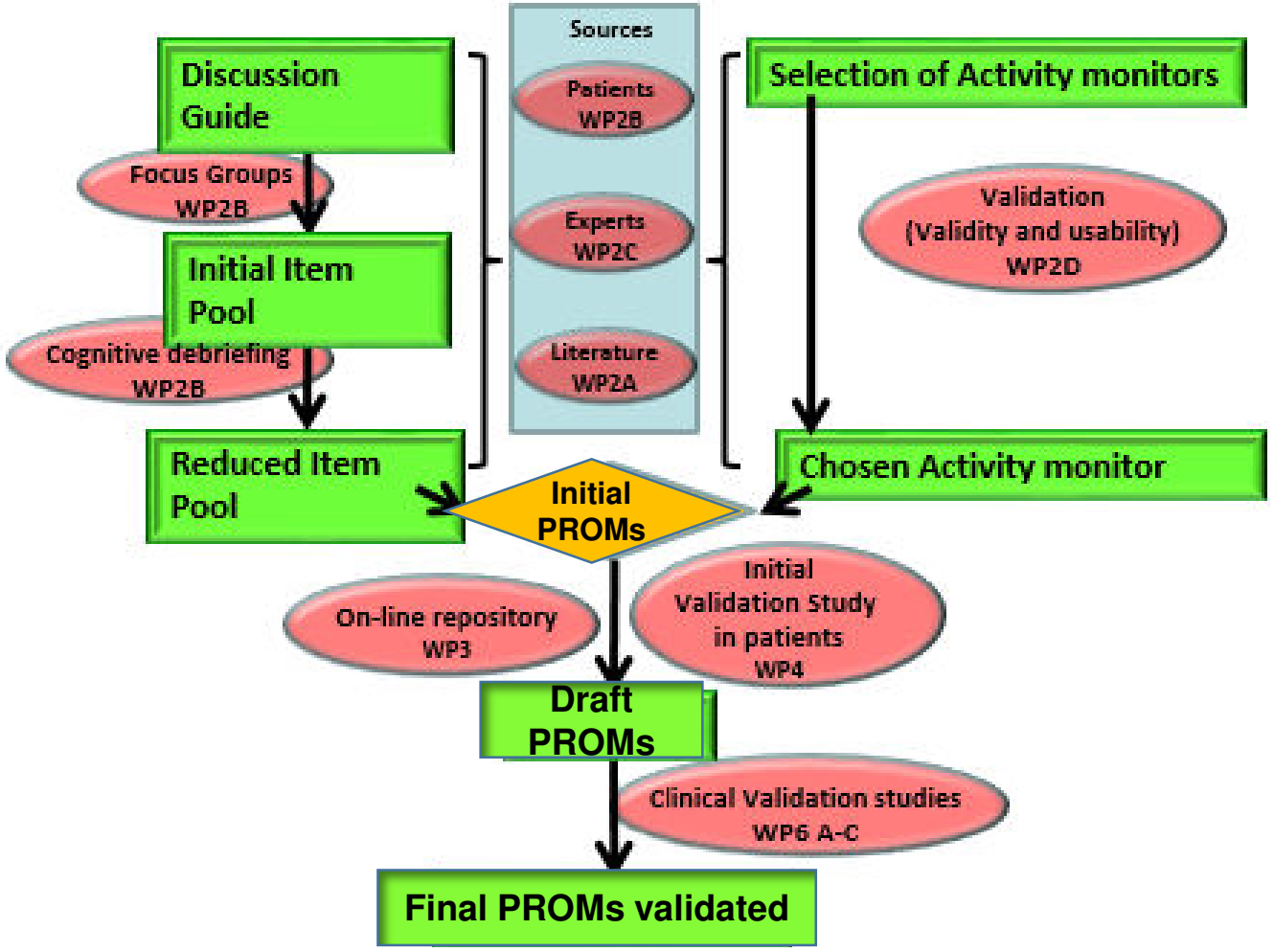
Responsive to clinically relevant treatment effects

Meaningful to clinicians

Based on patients' experience

Acceptable to Regulatory Authorities

Overview of the IMI PROactive development project



2009 – 2010
Development of draft PRO instrument

EMA Qualification advice in 2011

2011– 2012
Item reduction and Initial validation

EMA follow up Qualification advice in 2013

2013– 2015
Validation

EMA draft Qualification opinion in June 2017

EMA final Qualification opinion in March 2018

Developing the instrument – input from literature

Williams et al. Health and Quality of Life Outcomes 2012, 10:28
http://www.hqlo.com/content/10/1/28

HEALTH AND QUALITY OF LIFE OUTCOMES

RESEARCH Open Access

Patient-reported physical activity questionnaires: A systematic review of content and format

Kate Williams[1], Anja Frei[2,3*], Anders Vetsch[2,3], Fabienne Dobbels[4], Milo A Puhan[2,5] and Katja Rüdell[1]

Frei et al. Health and Quality of Life Outcomes 2011, 9:116
http://www.hqlo.com/content/9/1/116

HEALTH AND QUALITY OF LIFE OUTCOMES

RESEARCH Open Access

A comprehensive systematic review of the development process of 104 patient-reported outcomes (PROs) for physical activity in chronically ill and elderly people

Anja Frei[1,2*], Kate Williams[3], Anders Vetsch[1,2], Fabienne Dobbels[4], Laura Jacobs[5], Katja Rüdell[3] and Milo A Puhan[1,6], for the PROactive consortium

Gimeno-Santos et al. Health and Quality of Life Outcomes 2011, 9:86
http://www.hqlo.com/content/9/1/86

HEALTH AND QUALITY OF LIFE OUTCOMES

REVIEW Open Access

Validity of instruments to measure physical activity may be questionable due to a lack of conceptual frameworks: a systematic review

Elena Gimeno-Santos[1,2,3], Anja Frei[4,5], Fabienne Dobbels[6], Katja Rüdell[7], Milo A Puhan[4,8] and Judith Garcia-Aymerich[1,2,3,9*], for the PROactive consortium

OPEN ACCESS

ORIGINAL ARTICLE

Determinants and outcomes of physical activity in patients with COPD: a systematic review

Elena Gimeno-Santos,[1,2,3,4] Anja Frei,[5,6] Claudia Steurer-Stey,[6] Jordi de Batlle,[1,2,7] Roberto A Rabinovich,[8] Yogini Raste,[9] Nicholas S Hopkinson,[9] Michael I Polkey,[9] Hans van Remoortel,[10] Thierry Troosters,[10] Karoly Kulich,[11] Niklas Karlsson,[12] Milo A Puhan,[5,13] Judith Garcia-Aymerich,[1,2,3] on behalf of PROactive consortium

Van Remoortel et al. International Journal of Behavioral Nutrition and Physical Activity 2012, 9:84
http://www.ijbnpa.org/content/9/1/84

INTERNATIONAL JOURNAL OF BEHAVIORAL NUTRITION AND PHYSICAL ACTIVITY

REVIEW Open Access

Validity of activity monitors in health and chronic disease: a systematic review

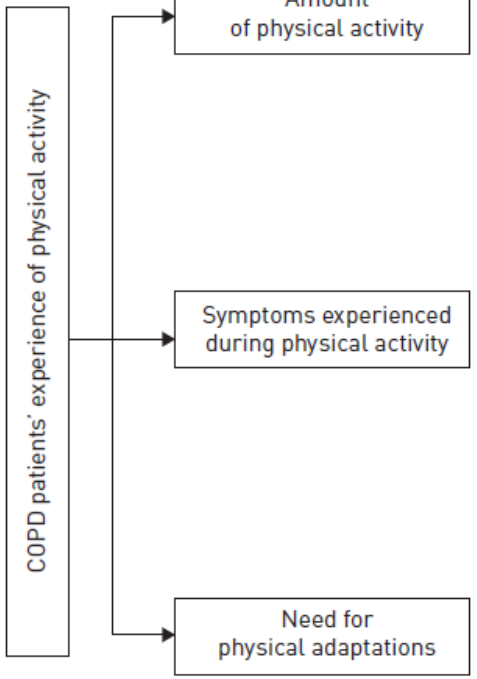
Hans Van Remoortel[1†], Santiago Giavedoni[2†], Yogini Raste[3], Chris Burtin[1], Zafeiris Louvaris[4], Elena Gimeno Santos[5], Daniel Langer[1], Alastair Glendenning[6], Nicholas S Hopkinson[3], Ioannis Vogiatzis[4], Barry T Peterson[7], Frederick Wilson[7], Bridget Mann[6], Roberto Rabinovich[2], Milo A Puhan[8,9] and Thierry Troosters[1,11*], on behalf of PROactive consortium

Developing the instrument – input from the patients

1) *One-to-one interviews*: To learn about the language that patients currently living with COPD use to describe dimensions referring to physical activity

2) *Focus groups*: To generate items related to the dimensions of physical activity in patients with COPD

3) *Cognitive debriefings*: To assess potential redundancy, and patients' understanding of the instructions, items, and scoring options



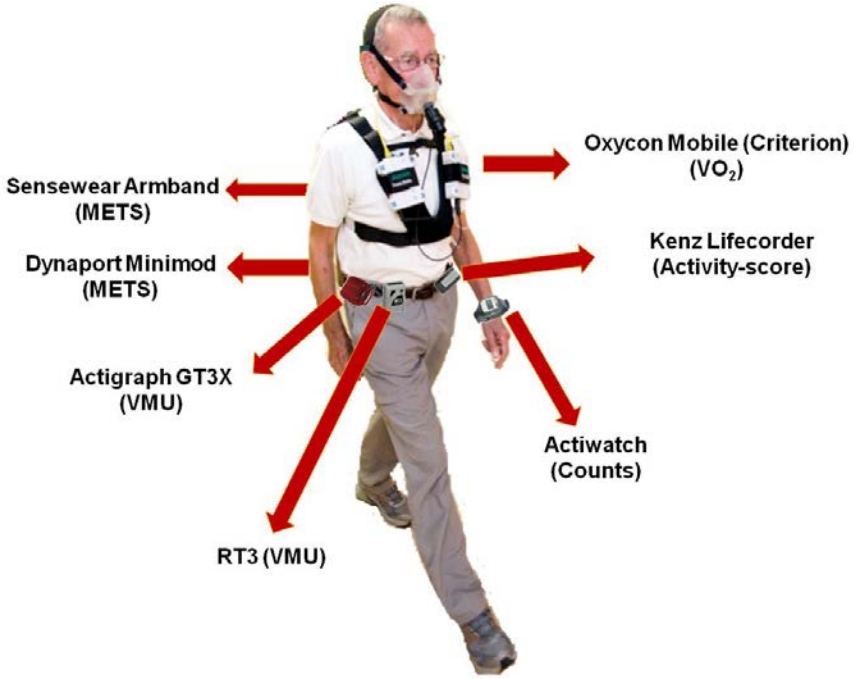
How much walking did you do outside today?
How many tasks did you do inside the house today?
How many tasks did you do outside the house today?
How much physical leisure activity did you do today?
How much difficulty did you have getting dressed today?
How much difficulty did you have with carrying things you needed to today?
How much difficulty did you have climbing stairs today? (If climbed stairs today)
How much difficulty did you have showering/bathing today? (Depending on whether patient usually baths or showers and whether they did this)
How much difficulty did you have bending over today?
How much difficulty did you have washing today?
How much difficulty did you have walking up a small slope today?
How much difficulty did you have when hurrying today?
In the past 7 days, how much difficulty did you have getting out and about?

How breathless were you in general during your activities today?
How often did you lack physical strength to do things today?
How often did you experience lack of strength in your legs during your physical activity today?
How tired were you in general during your activities today?
How breathless were you when walking on level ground inside and outside today?
How breathless were you when climbing stairs today? (If climbed stairs today)
In the past 7 days, how often did you cough during your physical activities?

How often did you avoid doing activities because of your lung problems today?
How often did you have to take breaks during your physical activities today?
How often did you have to pace yourself during your physical activities today?
How often did your lung problems prevent you from doing activities that you needed to do today?
How often did you have to slow down while walking today?
How much time did you need to recover from your physical activities today?
Did you need to spread your activities throughout the day today because of your lung problems?
Did your lung problems stop you from doing the physical activities that you wanted to do today?
How many puffs of [insert name of rescue medication here] in addition to your regularly used medication did you need to take for your physical activities today? (If on medication only)
Did you need to consider your lung problems when you planned your activities today?
How much help from others did you need with any of your activities today?
In the past 7 days, how often did you exercise to maintain or improve your physical condition?
In the past 7 days, how often did you use aids to facilitate your physical activities?
In the past 7 days, how often did you overexert yourself during your practical activities?

Dobbels F *et al. Eur Respir J* 2014;44:1223-33

Evaluating and selecting activity monitors



- Laboratory study
- Field study
- Usability study

WP2A
- Literature review
- 40 monitors

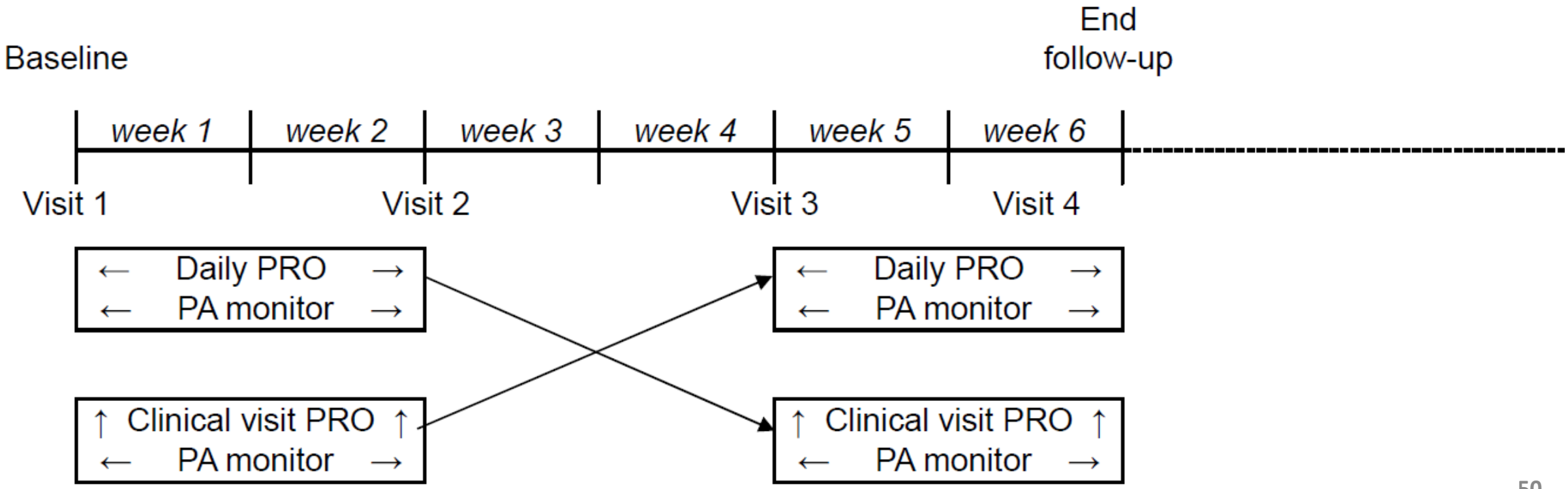
WP2D
- 6 monitors tested
- 3 Acceptable Field/Lab/Usability

Sel.
- Potentially acceptable to regulators
- Collaborative spirit of the Vendor
- 2 Monitors retained

Van Remoortel 2012, PLoS one; Ravinovich 2013, ERJ

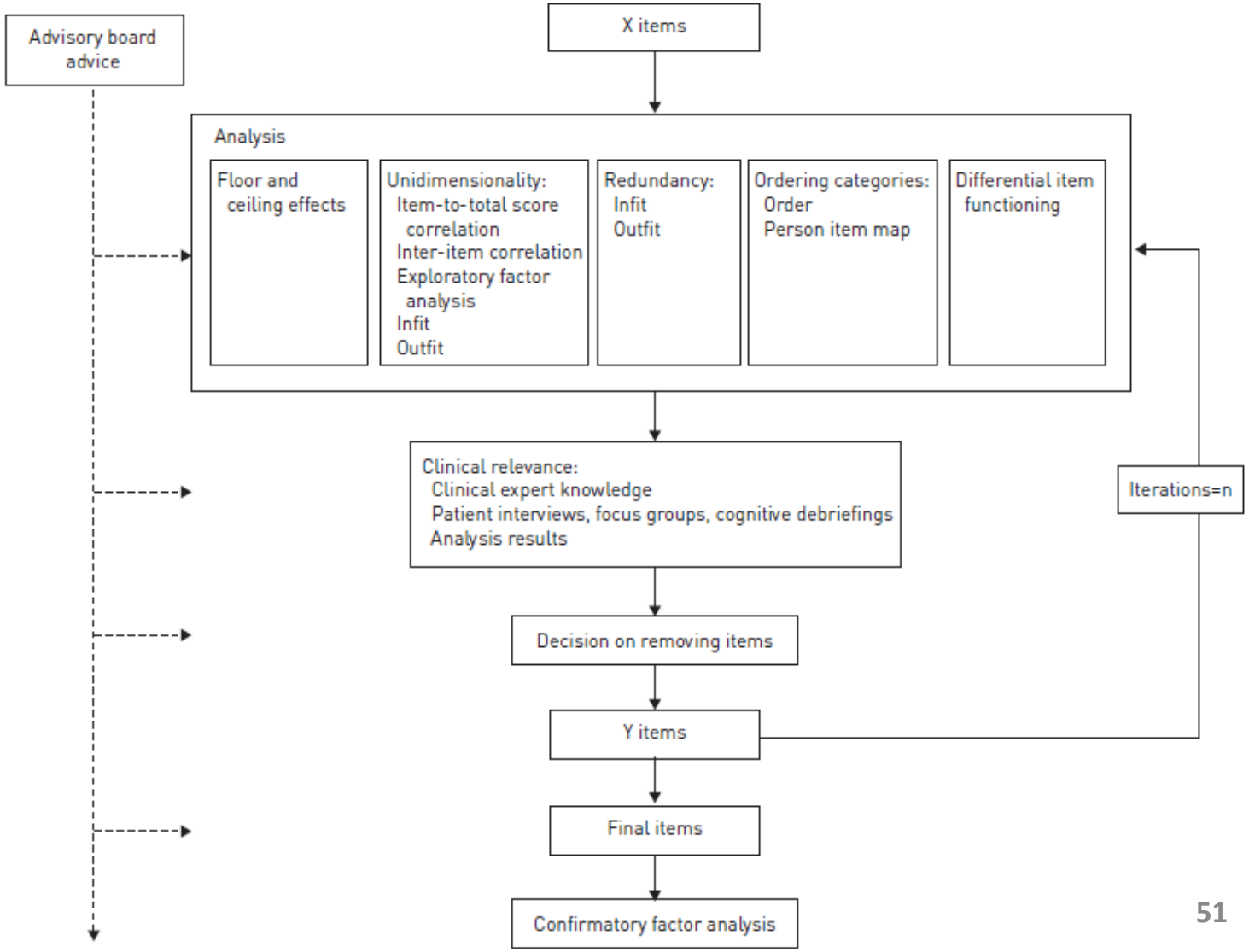
Item reduction and initial validation study

- Non-interventional, 6-week, 2-way cross-over, multi-centre study
- n=236 COPD patients; mean age 67 years; 68% male; 98% white; FEV_1 (% pred) 57; patients distributed across all GOLD I – IV and mMRC dyspnea categories
- 5 sites in Europe (hospital, primary care, rehabilitation centres)



Item reduction and initial validation study

- Item pools were reduced:
  - Daily version - 17 iterations → 9 items
  - Clinical visit version - 20 iterations → 14 items
- PA is a bidimensional concept
  - Factor 1: 'Amount of PA'
  - Factor 2: 'Difficulty with PA'
- Requires a PRO instrument + Activity monitor



Daily PROactive Physical Activity in COPD (D-PPAC) tool

Physical activity

Amount of physical activity

How much **walking** did you do **outside** today?
How many **chores** did you do **outside** the house today?
+
Daily **steps**
Daily **vector magnitude units**

Difficulty during physical activity

How much **difficulty** did you have **getting dressed** today?
How often did you **avoid** doing **activities** because of your lung problems today?
How **breathless** were you **in general** during your activities today?
How **tired** were you **in general** during your activities today?
How often did you have to **take breaks** during your physical activities today?

Clinical visit PROactive Physical Activity in COPD (C-PPAC) tool

Physical activity

Amount of physical activity

In the past 7 days, how much **walking** did you do **outside**?
In the past 7 days, how many **chores** did you do **outside** the house?
+
Weekly **steps**
Weekly **vector magnitude units**

Difficulty during physical activity

In the past 7 days, how much **difficulty** did you have **getting dressed**?
In the past 7 days, how much **difficulty** did you have **getting out** and about?
In the past 7 days, how often did you **avoid** doing **activities** because of your lung problems?
In the past 7 days, how **breathless** were you **in general** during your activities?
In the past 7 days, how often did you **lack physical strength** to do things because of your lung problems?
In the past 7 days, how **tired** were you **in general** during your activities?
In the past 7 days, how often did you have to **take breaks** during your physical activities?
In the past 7 days, how **breathless** were you when **walking on level ground** indoors and outdoors?
In the past 7 days, how much **time** did you need **to recover** from your physical activities?
In the past 7 days, did you need to **consider** your **lung problems** when you planned your activities because of your lung problems?

Further validation studies (WP6)

- N=995 COPD patients
- 6 clinical trials (2 drugs, 1 drug+rehab, 2 behav, 1 rehab)
- 16 countries
- Wide range of settings, patients' characteristics (severity…)

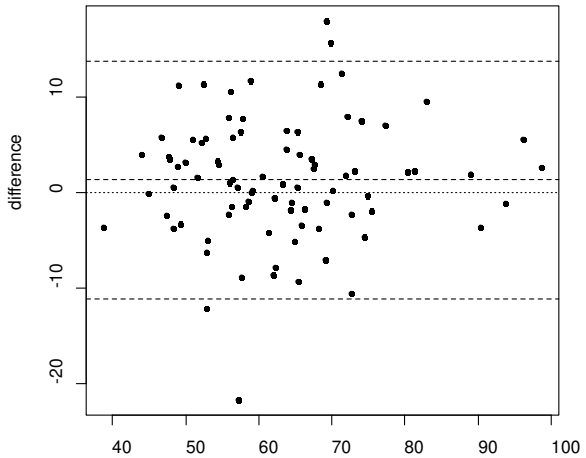
	PHYSACTO (BI)	URBAN TRAINING (CREAL)	T9 TRIGON (Chiesi)	ExOS (UK NHS Trust)	Pulmonary Rehabilitation (ATHENS)	MrPAPP (Academic-TT)
CT number	NCT02085161	NCT01897298	NCT02189577	-	-	NCT02158065
N	220	412	161	33 (Pilot)	100	343
Phase	Ph3	-	Ph2	-	-	-
PROactive	Key 2nd endpoint	Exploratory endpoint	Exploratory endpoint	Co- primary endpoint	Primary endpoint	Key 2nd endpoint
D-PPAC	X		X	X		X
C-PPAC		X			X	X
Activity Monitor(s)	Dynaport	Dynaport	Dynaport	SenseWear & ActiGraph	Actigraph	Dynaport & Actigraph
Study duration	19 weeks	12 months	12 weeks	7-9 weeks	8 weeks	3 months

Further validation studies (WP6)

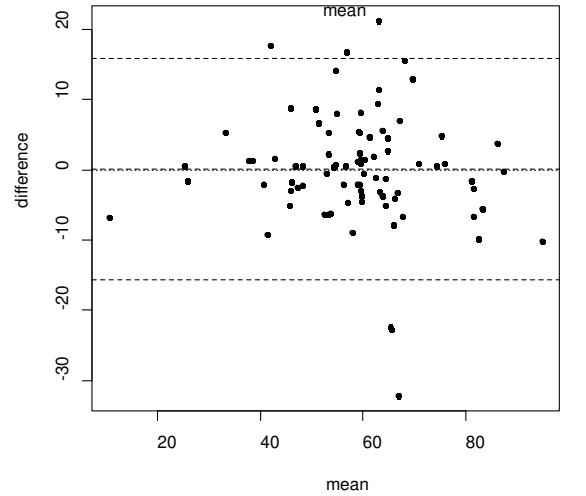
		EFPIA			Academic		External
		Physacto	T9	EXOS	MrPaPP	Athens	UT
PROactive instrument	Daily	X	X	X	X		
	Clinical visit				X	X	X
	Dynaport	X	X		X	X	X
	Actigraph			X	X		
Reliability							
Internal Consistency		X	X	X	X	X	X
Test-Retest Reliability			X				
Construct validity							
Convergent validity		X	X	X	X	X	X
Discriminant validity		X	X	X	X	X	X
Known groups validity		X	X	X	X	X	X
Ability to detect change (responsiveness)		X		X	X	X	
Confirmation of Conceptual Framework		X	X	X	X	X	X

Reliability and Validity (D-PPAC)

Bland Altman plot (mean week 1 *vs* mean week 2)



Amount ICC=0.92



Difficulty ICC=0.89

Correlation of D-PPAC with dyspnea, health status, exercise capacity and physical activity variables (convergent validity).

	Difficulty	Amount
Dyspnea (mMRC)	-0.50	-0.33
SGRQ-sympt (0-100)	-0.53	0.05
SGRQ-activity (0-100)	-0.61	-0.23
SGRQ-impact (0-100)	-0.54	-0.04
SGRQ-total (0-100)	-0.65	-0.09
6MWD (m)	0.44	0.46
ESWT time (s)	0.23	0.23
ISWT distance (m)	0.34	0.38
Time in any-intensity PA (min)	0.09	0.63
Time in moderate-to-vigorous PA (min)	0.15	0.68
Walking time (min)	0.13	0.70

The final PROactive instruments – items, domains and scoring

How much walking did you do outside today?				
☐	None at all			0
☐	A little bit (up to 10 minutes in total)			1
☐	Some (up to 30 minutes in total)			2
☐	A lot (up to 1 hour in total)			3
☐	A great deal (more than 1 hour in total)			4
How many chores did you do outside the house today? Some examples are gardening, taking the rubbish out, or doing small errands.				
☐	None at all			0
☐	A few			1
☐	Some			2
☐	A lot			3
☐	A large amount			4
How much difficulty did you have getting dressed today?				
☐	None at all		4	
☐	A little bit		3	
☐	Some		2	
☐	A lot		1	
☐	A great deal		0	
How often did you avoid doing activities because of your lung problems today?				
☐	Not at all		4	
☐	Rarely		3	
☐	Sometimes		2	
☐	Frequently		1	
☐	All the time		0	
How breathless were you in general during your activities today?				
☐	Not at all		4	
☐	A little bit		3	
☐	Moderately		2	
☐	Very		1	
☐	Extremely		0	
How tired were you in general during your activities today?				
☐	Not at all		4	
☐	A little bit		3	
☐	Moderately		2	
☐	Very		1	
☐	Extremely		0	
How often did you have to take breaks during your physical activities today?				
☐	Not at all		4	
☐	Rarely		3	
☐	Sometimes		2	
☐	Frequently		1	
☐	All the time		0	
PROactive daily steps score		*Total steps per day*		
		Actigraph / *Dynaport*		
☐	0	≤1000 / ≤1900		0
☐	1	1001-3000 / 1901-3700		1
☐	2	3001-5000 / 3701-5500		2
☐	3	5001-7000 / 5501-7300		3
☐	4	>7000 / >7300		4
PROactive daily VMU score		*Daily mean VMU/min*		
		Actigraph / *Dynaport*		
☐	0	≤100 / ≤50		0
☐	1	101-200 / 51-110		1
☐	2	201-300 / 111-190		2
☐	3	301-400 / 191-270		3
☐	4	401-600 / 271-440		4
☐	5	>600 / >440		5
		Total scores (sum above):	difficulty	amount

Raw Score Difficulty (0-20)

Raw Score Amount (0-17)

Difficulty (D-PPAC)		Amount (D-PPAC)	
raw	Rasch 0-100	raw	Rasch 0-100
0	0	0	0
1	10	1	10
2	20	2	19
3	26	3	25
4	32	4	31
5	36	5	35
6	40	6	39
7	43	7	43
8	46	8	47
9	49	9	50
10	52	10	54
11	56	11	57
12	59	12	61
13	62	13	65
14	65	14	71
15	68	15	80
16	72	16	90
17	77	17	100
18	84		
19	92		
20	100		

Difficulty during PA (0-100)

Amount of PA (0-100)

Total Score PA (0-100) = Average of Amount and Difficulty Domain Scores

The final PROactive instruments – items, domains and scoring

How much walking did you do outside today?			
☐ None at all			0
☐ A little bit (up to 10 minutes in total)			1
☐ Some (up to 30 minutes in total)			2
☐ A lot (up to 1 hour in total)			3
☐ A great deal (more than 1 hour in total)			4
How many chores did you do outside the house today? Some examples are gardening, taking the rubbish out, or doing small errands.			
☐ None at all			0
☐ A few			1
☐ Some			2
☐ A lot			3
☐ A large amount			4
How much difficulty did you have getting dressed today?			
☐ None at all		4	
☐ A little bit		3	
☐ Some		2	
☐ A lot		1	
☐ A great deal		0	
How often did you avoid doing activities because of your lung problems today?			
☐ Not at all		4	
☐ Rarely		3	
☐ Sometimes		2	
☐ Frequently		1	
☐ All the time		0	
How breathless were you in general during your activities today?			
☐ Not at all		4	
☐ A little bit		3	
☐ Moderately		2	
☐ Very		1	
☐ Extremely		0	
How tired were you in general during your activities today?			
☐ Not at all		4	
☐ A little bit		3	
☐ Moderately		2	
☐ Very		1	
☐ Extremely		0	
How often did you have to take breaks during your physical activities today?			
☐ Not at all		4	
☐ Rarely		3	
☐ Sometimes		2	
☐ Frequently		1	
☐ All the time		0	

PROactive daily steps score	*Total steps per day*			
	Actigraph	*Dynaport*		
☐ 0	≤1000	≤1900		0
☐ 1	1001-3000	1901-3700		1
☐ 2	3001-5000	3701-5500		2
☐ 3	5001-7000	5501-7300		3
☐ 4	>7000	>7300		4
PROactive daily VMU score	*Daily mean VMU/min*			
	Actigraph	*Dynaport*		
☐ 0	≤100	≤50		0
☐ 1	101-200	51-110		1
☐ 2	201-300	111-190		2
☐ 3	301-400	191-270		3
☐ 4	401-600	271-440		4
☐ 5	>600	>440		5
		Total scores (sum above):	difficulty	amount

Raw Score Difficulty (0-20)

Raw Score Amount (0-17)

PROactive daily steps score	*Total steps per day*			
	Actigraph	*Dynaport*		
☐ 0	≤1000	≤1900		0
☐ 1	1001-3000	1901-3700		1
☐ 2	3001-5000	3701-5500		2
☐ 3	5001-7000	5501-7300		3
☐ 4	>7000	>7300		4
PROactive daily VMU score	*Daily mean VMU/min*			
	Actigraph	*Dynaport*		
☐ 0	≤100	≤50		0
☐ 1	101-200	51-110		1
☐ 2	201-300	111-190		2
☐ 3	301-400	191-270		3
☐ 4	401-600	271-440		4
☐ 5	>600	>440		5

Difficulty (D-PPAC)		Amount (D-PPAC)	
raw	Rasch 0-100	raw	Rasch 0-100
0	0	0	0
1	10	1	10
2	20	2	19
3	26	3	25
4	32	4	31
5	36	5	35
6	40	6	39
7	43	7	43
8	46	8	47
9	49	9	50
10	52	10	54
11	56	11	57
12	59	12	61
13	62	13	65
14	65	14	71
15	68	15	80
16	72	16	90
17	77	17	100
18	84		
19	92		
20	100		

Difficulty during PA (0-100)

Amount of PA (0-100)

Total Score PA (0-100) = Average of Amount and Difficulty Domain Scores

PROactive endpoints for clinical trials

- Patient's experience of physical activity as measured by the PPAC instruments may serve as primary, co-primary, secondary, or exploratory endpoints, as appropriate to the trial design.
- Choice is driven by the clinical hypothesis being tested and, therefore, the study design
- C-PPAC more likely to be used:
  - where patient experience of PA is a supportive outcome and/or where patient burden of completing a PRO measure is high
  - in a pragmatic study to gather real-world data where intervention is more limited
- D-PPAC more likely to be used:
  - where measurement of patient experience of PA is the primary outcome of the study
  - in a regulatory study to support a labelling claim

ACTIVATE – study design

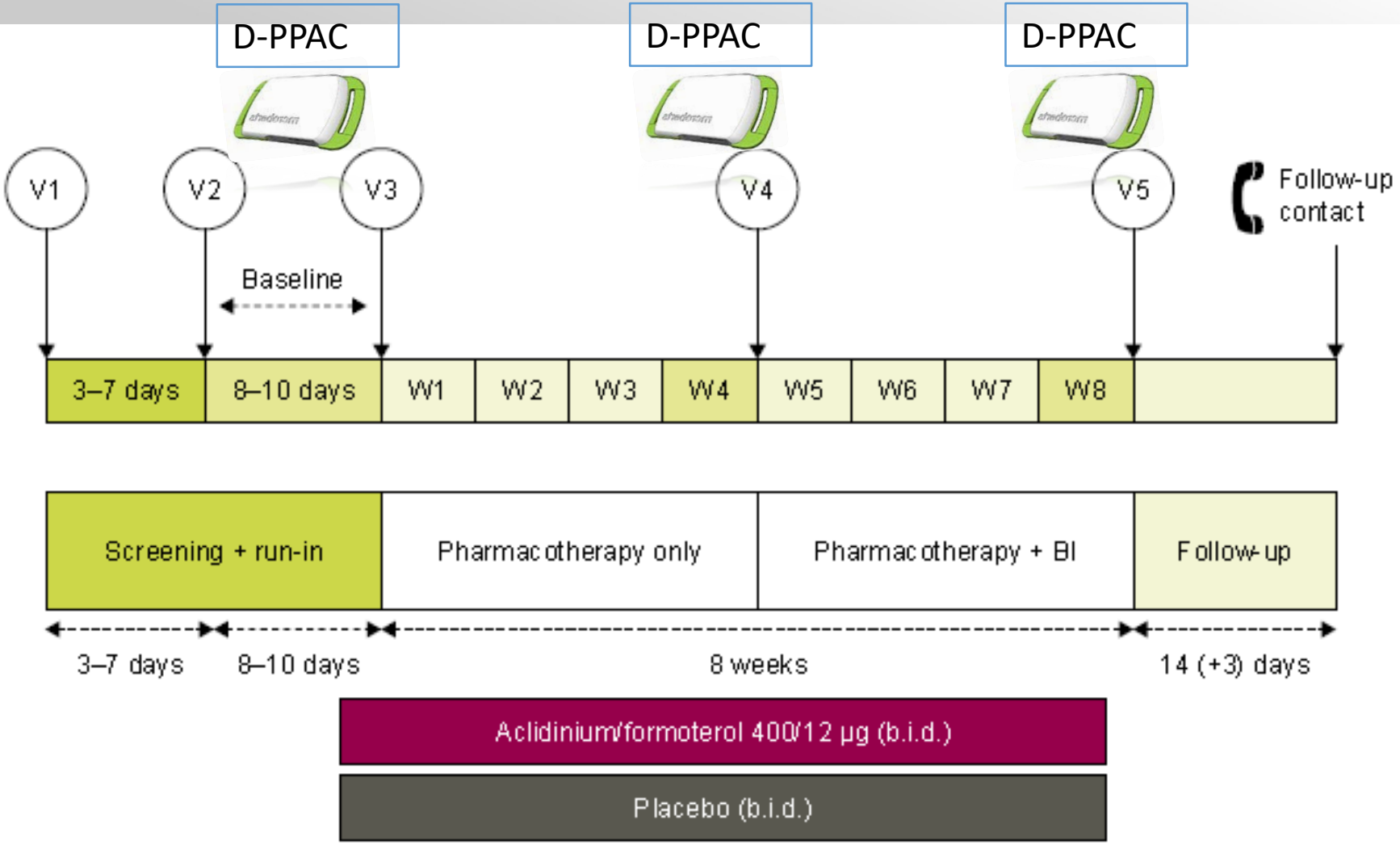


Figure 1 Study design.
Abbreviations: BI, behavioral intervention; b.i.d., twice daily; V, visit; W, week.

Watz et al, Int J of COPD, 2017

ACTIVATE – Results D-PPAC for total score, amount and difficulty domains

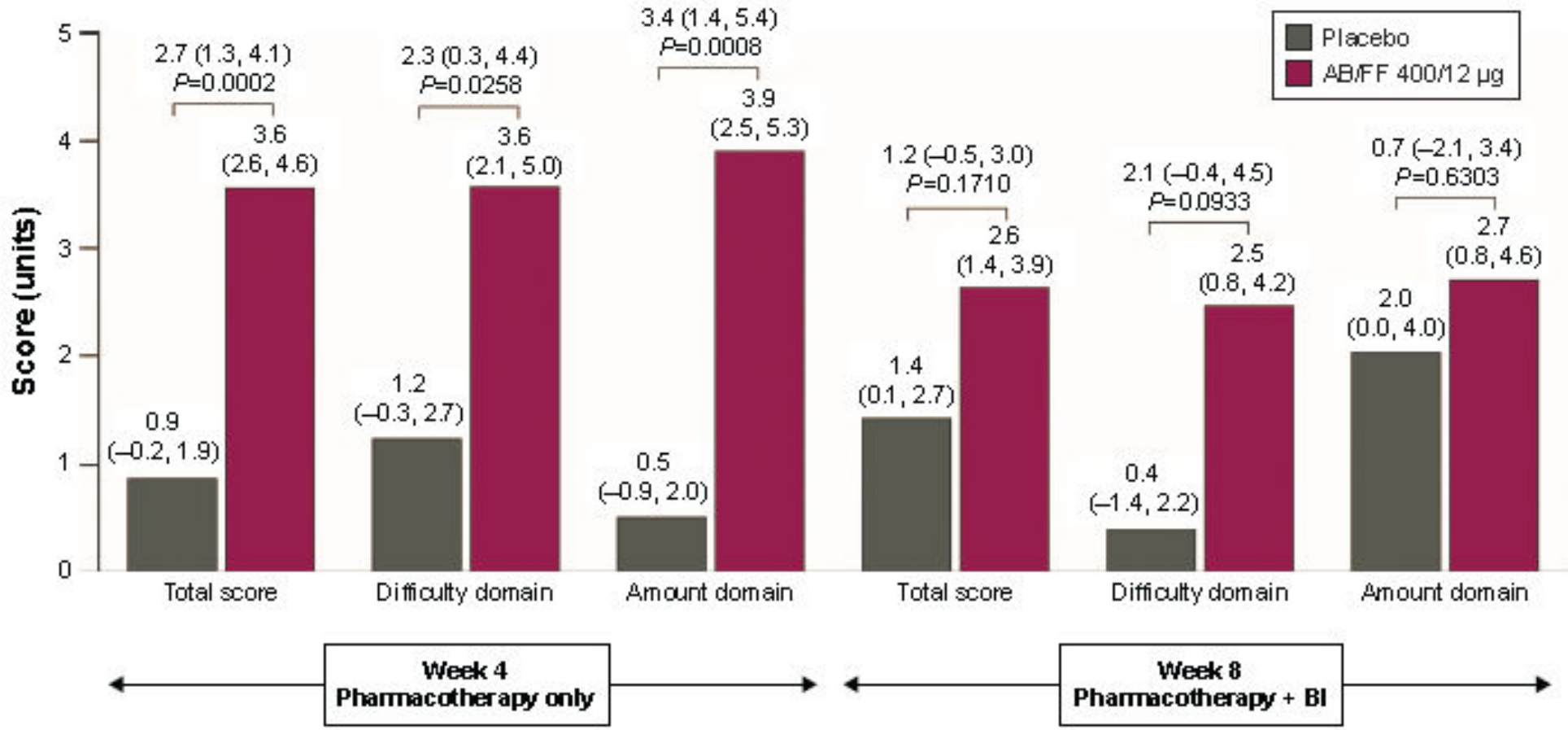


Figure 6 Change from baseline in D-PPAC total score and amount and difficulty domains at Weeks 4 and 8 (ITT population).
Note: Data are LSMs (95% CI).
Abbreviations: AB, aclidinium bromide; BI, behavioral intervention; CI, confidence interval; D-PPAC, Daily PROactive Physical in COPD; FF, formoterol fumarate; ITT, intent-to-treat; LSM, least squares mean.

Watz et al, Int J of COPD, 2017

IMI PROactive in COPD – Qualification Opinion - EMA

- The Consortium developed two PRO tools, the D-PPAC and the C-PPAC, to capture PA in patients with COPD
- Both tools are hybrid tools, combining information from questionnaire items with PA monitor read-outs
  - Actigraph G3TX or the Dynaport MoveMonitor worn at the waist
- State-of-the-art qualitative methodology was applied in the development phase to build a conceptual framework that combines two domains: 'amount of PA' and 'difficulty with PA' into one concept
- Conceptual framework is considered appropriate to describe PA in COPD patients
- The focus is on measuring PA in COPD patients across all levels of severity. Since patients with comorbidities potentially interfering with PA have been excluded, restrictions or careful interpretation may be needed
- The CHMP opinion mention that D-PPAC qualifies for a context of use where a clear (primary) focus is on measuring PA; while for C-PPAC the suggested context of use is for trial settings where patients' experience of PA is a supportive outcome. However, qualification is for method, not for endpoint models and potential positioning of PA
- Final Qualification Opinion communicated on 9 March, 2018. Still to be publicly released
  - Very supportive comments from the European Lung Foundation

Using D-PPAC or C-PPAC to support labelling claim

- Potential positioning of PA in hierarchy of important endpoints is kept separate from the qualification aim, which was to declare the two new PRO tools suitable to capture PA in COPD. The qualification does not address whether the PRO tools are suitable to inform (co)primary/secondary (etc.) endpoints in the various suggested context of use
- **EMA Qualification**: *Incorporating findings based on the PRO tools in 5.1 of the SPC of a compound targeting COPD seems possible but specific content or wording cannot be pre-empted at this point in time and will largely depend on the effects shown in a specific development programme and the perceived relevance of such information to the patient/prescriber, accounting for overall results*
- *http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/12/WC500240706.pdf*

Duaklir Genuair (aclidinium/formoterol) – SPC (Sept. 2017)
Section 5.1 Pharmacodynamic effects

After 4 weeks of treatment, Duaklir Genuair improved the number of steps per day compared to placebo (731 steps/day; 95% CI=279, 1181; p=0.0016) and reduced the percentage of inactive patients (<6000 steps per day) [40.8% compared to 54.5%; p<0.0001]. Improvements in the PROactive total score were observed in patients treated with Duaklir Genuair compared with placebo (p=0.0002).

A behavioural intervention program was added to both treatment groups for an additional 4 weeks. The number of steps/day in the Duaklir Genuair treatment group was maintained resulting in a treatment effect compared to placebo of 510 steps/day (p=0.1588) and a reduction versus placebo in the percentage of inactive patients (<6000 steps per day) (41.5% compared to 50.4%; p=0.1134).

Summary and Next Steps

- Physical activity is an important outcome in COPD
- The IMI PROactive project put extensive efforts in developing a comprehensive measure of PA experience in COPD
- The result were two hybrid instruments, the D-PPAC and the C-PPAC, combing information from PRO questionnaires and data from activity monitors
- The PPAC instruments capture the experience of PA in two domains – amount of PA and difficulty with PA – as well as a total score
- Final EMA Qualification was communicated in March 2018
- Next steps involves a post-IMI continuation of the consortium through a memorandum of understanding, to conduct further evaluations and potential qualification interactions with the FDA

Panel Discussion and Q & A

Moderator

- *Sonya Eremenco, MA* – Associate Director, PRO Consortium

Presenters

- *J. Jason Lundy, PhD* – Principal, Outcometrix
- *Louise Newton, MSc* – Senior Director, Clinical Outcome Assessments, Clinical Outcomes Solutions
- *Niklas Karlsson, PhD* – Patient Reported Outcomes Director Respiratory, AstraZeneca

Panelists

- *Bill Byrom, PhD* – Vice President, Product Strategy and Innovation, CRF Health, and Vice Director, ePRO Consortium
- *Wen-Hung Chen, PhD* – Team Leader, COA Staff, Office of New Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration
- *David Reasner, PhD* – Vice President, Data Science and Head, Study Endpoints, Ironwood Pharmaceuticals