UNDERSTANDING AND ADDRESSING POTENTIAL BIAS IN PATIENT-REPORTED OUTCOMES FROM CLINICAL TRIALS

ISPOR Barcelona Workshop

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14:00-15:00

Workshop Presenters

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Important Note

- *This part of the presentation is being made by Stephanie Mansion and Steffi Knoll. The opinions they express in this presentation and on the following slides are solely their own and not those of the organization at which they work (Novartis Pharmaceuticals Corporation "NPC"). NPC does not in any way guarantee the accuracy or reliability of the information provided herein.*

Poll Question

Instructions: Go into ISPOR app and select 'Take a Poll' or to myispor.cnf.io and select session W10

- Did you ever experience a situation where bias impacted interpretation of PRO results?
  - Yes
  - No

Live Content Slide

When playing as a slideshow, this slide will display live content

Poll: Did you ever experience a situation where bias impacted interpretation of PRO results?

Poll Question

Instructions: Go into ISPOR app and select ‘Take a Poll’ or to myispor.cnf.io and select session W10

- Do you feel that bias plays a significant role in interpreting PRO results?
  - Yes
  - Maybe, depending on source of bias
  - No

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Poll: Do you feel that bias plays a significant role in interpreting PRO results?

Regulatory Perspective on bias

- *There are, however, methodological obstacles that historically have **reduced the impact of PRO data** on regulatory decisions e.g. **bias, missing data, quality of data, timing of assessments, only single-dimensional PRO measure reporting, and lack of post-progression data**.*

– EMA 2016 Guideline on use of PRO measures in oncology

Addressing and Understanding Bias in PRO Trial Design

Steffi Knoll, Novartis

Data Collection – missing data introducing bias

- Understand when data is not missing at random
- Minimize source of missing data with data collection
  - Example Oncology:
    - PRO data collection stops at discontinuation of treatment / progression
    - Results in missing data from patients with adverse events or disease progression
    - Increased reporting of compliance AND completion rates[1]
  - GOG-218[2] (bevacizumab in frontline ovarian cancer): PRO beyond progression
    - ***Study subjects completed QOL questionnaires at scheduled assessment time points regardless of disease progression or if protocol directed therapy was stopped secondary to toxicity***
  - More frequent: one or two assessments beyond progression
- Build missingness into analysis plan
  - Imputation
    - Informed by external data collection?

1) Schadendorf et al. 2016 Europ. J. of Cancer 67: 46e54. 2) Monk et al 2013 Gynecologic Oncology 128: 573–578.

Data Collection

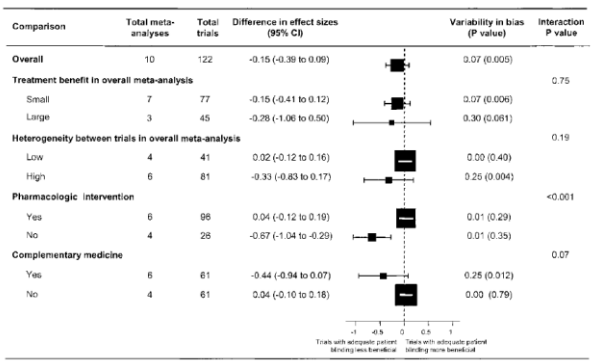
Reasons for Missing PRO

- ✓**Patient too unwell due to progression**
- ✓**Patient too unwell due to AE**
- ✓**Patient too unwell due to other reason**
- ✓Insufficient time for PRO completion
- ✓PRO not offered to patient

Open Label vs Double Blind RCTs

- Exaggerated treatment effect with lack of blinding[1,2,3,4,5]

Differences in effect sizes (ES) between 64 trials with and 58 trials without adequate patient blinding[3)]



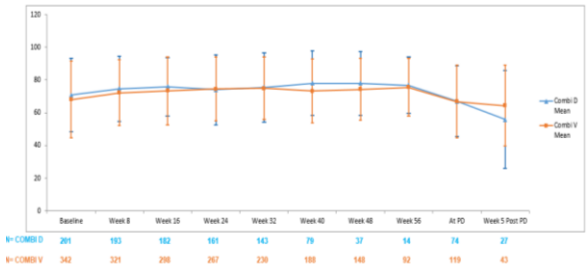
Comparison	Total meta-analyses	Total trials	Difference in effect sizes (95% CI)	Variability in bias (P value)	Interaction P value
Overall	10	122	-0.15 (-0.39 to 0.09)	0.07 (0.005)	
Treatment benefit in overall meta-analysis					0.75
Small	7	77	-0.15 (-0.41 to 0.12)	0.07 (0.006)	
Large	3	45	-0.28 (-1.06 to 0.50)	0.30 (0.061)	
Heterogeneity between trials in overall meta-analysis					0.19
Low	4	41	0.02 (-0.12 to 0.16)	0.00 (0.40)	
High	6	81	-0.33 (-0.83 to 0.17)	0.25 (0.004)	
Pharmacologic intervention					<0.001
Yes	6	98	0.04 (-0.12 to 0.19)	0.01 (0.29)	
No	4	28	-0.67 (-1.04 to -0.29)	0.01 (0.35)	
Complementary medicine					0.07
Yes	6	61	-0.44 (-0.94 to 0.07)	0.25 (0.012)	
No	4	61	0.04 (-0.10 to 0.18)	0.00 (0.79)	

1) Berkman et al 2014 www.effectivehealthcare.ahrq.gov/reports/final.cfm. 2) Page et al 2016 PLoS ONE 11(7): e0159267. doi:10.1371/journal.pone.0159267 3) Nüesch et al Arthritis & Rheumatism 2009 61(12): 1633–1641 4) Hróbjartsson International Journal of Epidemiology, 2014, 1272–1283 5) Beyer-Westendorf and Büller J Thromb Haemost 2011; 9: 2153–8. 6) Jessica Roydhouse et al 2018 Journal of Clinical Oncology 36, no. 15_suppl 6572-6572 7) Chakravarti et al 2018 J Clin Oncol 36, 2018 (suppl; abstr e18702) 8) Knoll et al ISPOR 2018

Understand source of PRO open label bias

- In case of competing open label and blinded trials – patient burden could lead to patient allocation bias (e.g. anticoagulant trials[5])
- Imbalances in PRO completion rates between arms higher in open label studies[6]
- Comparisons of trials same drug, same population, same PRO: open label vs blinded
  - Chakravarti 2018: preliminary analyses failed to support differences in emotional domain PRO by blinding status[7]
  - Dabrafenib plus trametinib in metastatic melanoma: PRO remarkably consistent qualitatively and numerically across 2 independent trials[8]

QLQ-C30 GHS: Open Label (COMBI-V) vs Double Blind (COMBI-D) in metastatic melanoma (dabrafenib + trametinib)[8]



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Maximizing Technology

- Key is to integrate PRO data collection seamlessly into patients' lives
- At Home ePRO/Bring Your Own Device
  - Untie PRO reporting from trial visit schedule – measure when change occurs
  - Many patients don't want to carry a separate trial device plus smart phone
  - Challenge to meet regulatory requirement using BYOD

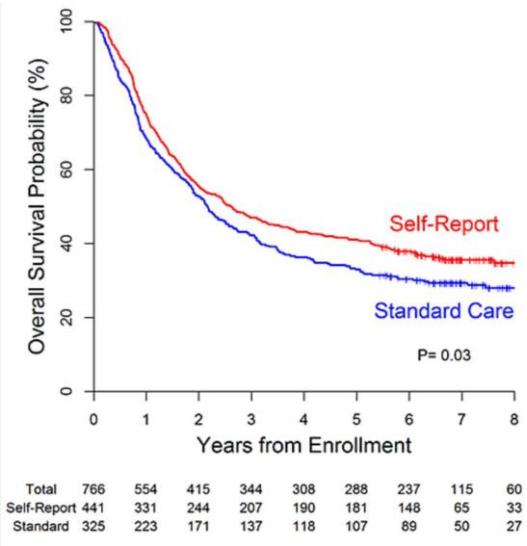
Smartphone Penetration by Age Group (US)

	Age Group				
	18-24	25-34	35-44	45-54	55-75
2017	93%	91%	90%	82%	67%
2016	88%	86%	84%	75%	62%
2015	89%	85%	77%	65%	53%

Source: Deloitte

Site Communication

- Communicate clear PRO narrative
  - Include in investigator meeting, site training, written site material
- Create alerts to sites when key symptoms are elevated on PRO
- PRO w alert to site vs no PRO increased cancer survival by 5m (OS 31.2m vs 26.0m)[1]



1) Basch 2017 ASCO

'We all see only that which we are trained to see'

- Robert Anton Wilson