Conflict of Interest Statement: Michael Schlichting

I have the following financial relationships to disclose

- Employee of Merck KGaA, Darmstadt, Germany
- Holding shares of Merck KGaA, Darmstadt, Germany

How Will New Guidance Impact the Statistical Analyses and Interpretation for Patient-Reported Outcomes (PRO) in the Context of HA and HTA Submissions

A sponsor perspective

Michael Schlichting, Biostatistician at Merck KGaA, Darmstadt, Germany

Outline: Biostatistical reflection

High variability in the analyses and presentations of PRO data for regulatory & HTA submissions

Sources and types of variability

How new guidance impact PRO analysis

ICH E9 (R1) addendum – estimands

SISAQOL recommendations

IQWiG Methods Paper Version 6 (draft) – re: MID

Conclusion / Outlook

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PRO Analysis: Sources and types of variability

Some perceptions

- Protocols less precise on PRO study objectives and PRO endpoints.
- PRO analysis results rarely impact USPI or SmPC, but part of the value framework in HTA in general.

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Are PRO Analysis inefficently performed?

- Complexity of PROs
- Research questions
  - Differences between groups
  - Within groups
  - Within patient changes
- Exploration in various populations
- Sensitivity analysis
  - Missing data
  - Intercurrent events

Example

~ 30 endpoints

*

~ 3 outcome measures

*

~ 20 subgroups, populations etc

=

~ 1800 analyses

Adopt Estimand Framework

Appropriate statistical analysis methods require concrete research question considering the estimand framework[1]

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17 February 2020
EMA/CHMP/ICH/436221/2017
Committee for Medicinal Products for Human Use

ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials

PRO Research Objective

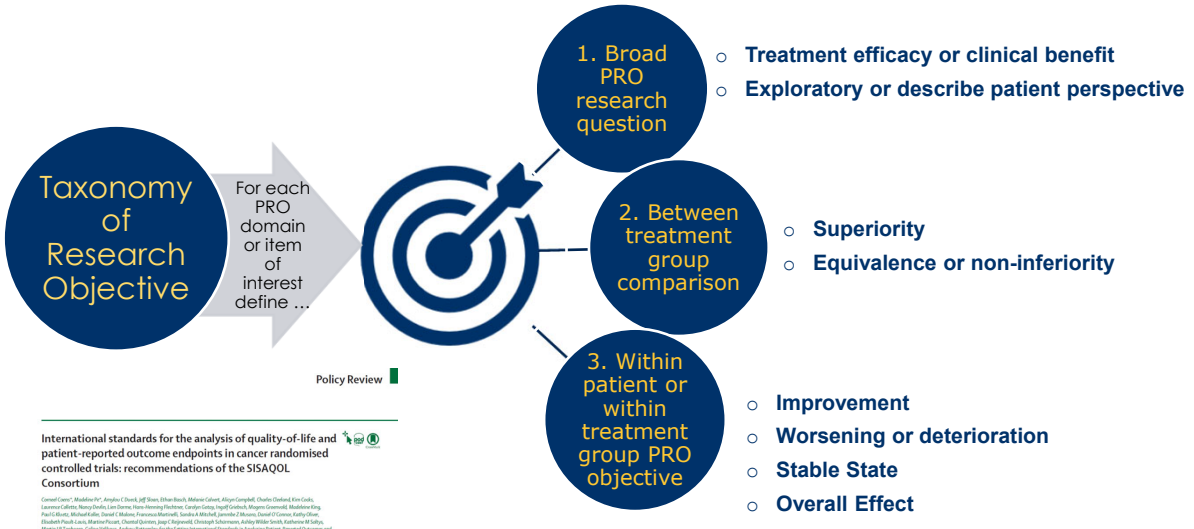
Estimand
- Target Study Population
- Endpoint of Interest
- Treatment
- Population level summary
- Intercurrent Events

Statistical Analysis Plan

How scientific questions vary by stakeholder

Stakeholders	PRO Research Question	Estimand Strategy
Regulators	How does the treatment impact QoL while the patient takes it as prescribed?	Hypothetical Treatment policy While-on-treatment
HTA	How will a patient respond in terms of symptoms, functioning, health state given the initial randomized decision to treat?	Treatment policy
Patients	What will happen to me if I start this treatment, stop this treatment or if I don´t start treatment at all?	Treatment policy While-on-treatment
Sponsors	How does the treatment work if randomized treatment is taken as directed by the study protocol?	Hypothetical

SISAQOL recommendations(2) …



Policy Review

International standards for the analysis of quality-of-life and patient-reported outcome endpoints in cancer randomised controlled trials: recommendations of the SISAQOL Consortium

Summary: Variations of PRO Analysis in Oncology Studies

Estimand Framework and SISAQOL recommendations are essential to clarify

- Stakeholder objectives
- Well defined selection of endpoints
- Appropriate choice of outcome measures
- Mapping key outcome measures with appropriate statistical methods
- Approaches to deal with intercurrent events and missing data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International standards for the analysis of quality-of-life and patient-reported outcome endpoints in cancer randomised controlled trials: recommendations of the SISAQOL Consortium

Corneel Coens*, Madeline Pe*, Amylou C Dueck, Jeff Sloan, Ethan Basch, Melanie Calvert, Alicyn Campbell, Charles Cleeland, Kim Cocks, Laurence Collette, Nancy Devlin, Linn Dorme, Hans-Henning Flechtner, Carolyn Gotay, Ingolf Griebsch, Mogens Groenvold, Madeleine King, Paul G Kluetz, Michael Koller, Daniel C Malone, Francesca Martinelli, Sandra A Mitchell, Jammbe Z Musoro, Daniel O'Connor, Kathy Oliver, Elisabeth Piault-Louis, Martine Piccart, Chantal Quinten, Jaap C Reijneveld, Christoph Schürmann, Ashley Wilder Smith, Katherine M Soltys, Martin J B Taphoorn, Galina Velikova, Andrew Bottomley, for the Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data Consortium

High variability in regulatory decision making

Review of prescribing information with variations in terms of handling of

- Endpoints
- Outcome measures
- Multiplicity issue
- Open-label trials

	Drug A	Drug B
EMA SMPC	- Significant improvement in global QOL - change from baseline score - Symptom benefits by significantly prolonging TTD (symptom x,y,z) - Hochberg-adjusted log-rank 2-sided p-value	Not granted
FDA USPI	- Exploratory: delay in time to worsening of symptom x, but not y or z - Overestimation, because patients were not blinded to treatment assignment	Not granted

High variability in HTA decision making

Selected example of HTA submission with variations in

- Endpoints
- Outcome measures
- Multiplicity issue
- Completeness / missingness of data
- Open-label trials
- **MCID / MID** validation ?

	Drug A	Drug B
HTA Germany (IQWiG; G-BA)	Statistically significant effect for symptom a,b,c, … (morbidity) and functional scores (QoL)	• Statistically significant difference for certain endpoints; • IQWIG: PRO outcomes should be recorded over the total period of time similar to survival analysis. • Responder analysis not used as **MID validation study is unsuitable** • G-BA accepted responder analyses as used in earlier evaluations.
HTA France (HAS)	Analysis are unable to support any reliable conclusions (open label study)	Results are not conclusive: - No multiplicity adjustment - **MCID not discussed a-priori** - Missing data

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How new guidelines will impact PRO analysis and interpretation: The MID case

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FDA

IQWiG

HAS
HAUTE AUTORITÉ DE SANTÉ

EORTC
The future of cancer therapy

Established MID (minimal important difference) for EORTC QLQ-C30

- EMA, FDA suggest anchor based MIDs. In general MID of 10 score-points[3] currently accepted.
- Challenged by HTA agencies: IQWiG Methods Paper Version 6 (draft)[4] suggests a new threshold of 15% of scale width.
- EORTC research[5] will provide MIDs by cancer indication with variations by scale, direction of change, and anchor.

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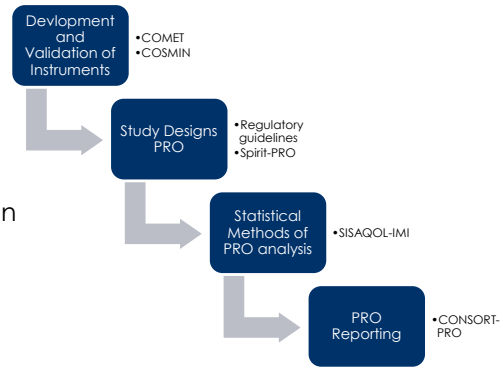
Conclusions / Summary / Outlook

- Estimand framework and SISAQOL recommendations provide a common ground for analysis and interpretation of PRO data.
- Local guidances may simplify analysis, but complexify interpretation of PROs.
- Divergent approaches of minimally and/or clinically relevant differences by stakeholders will add variability in PRO analyses and interpretation.
- SISAQOL-IMI consortium, FDA-ASCO PFDD workshops,… will further impact PRO analysis and interpretation.



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