PFDD SIG session

PSI Conference 2025 London

Monday 9th June 11am

Patient-Focused Drug Development (PFDD) SIG objectives

1. **Education for industry statistician & knowledge sharing**: ensure good practices and standards for PRO and COA-based endpoints and their interpretation are well understood and adopted in drug development across all therapeutic areas.
    1. Specifically, to strengthen specialization in PROs among statisticians to enable improved definition of PRO hypotheses and endpoints in clinical trials
2. **Interact with regulators, payers and patients** and the broader clinical community to obtain a better understanding of their requirements relating to PFDD
3. **Advance statistical methodology** for specific PFDD topics: e.g.
    1. Use of PROs in early phase studies (dose finding/optimization)
    2. Estimands and analysis for PROs assessing tolerability and safety
    3. Oncology estimands – how to handle death
4. **Collaboratively partner with other SIGs** in this area, within and outside PSI/EFSPI with common interests such as HTA/RWE SIGs

PFDD SIG Active Workstreams & Activities 2024/2025

Knowledge Sharing	PROs & Tolerability	Use of SEM methods in PRO endpoints in RCTs	Diary Data (ILD)
Missing data	PROs in dose optimization studies	Estimands for PROs	Death as an ICE
PRO completion & study monitoring	Patient reported Pain endpoint	Meaningful score regions (MSR) – case studies	Meaningful change/score interpretation

Patient-Focused Drug Development (PFDD) SIG members

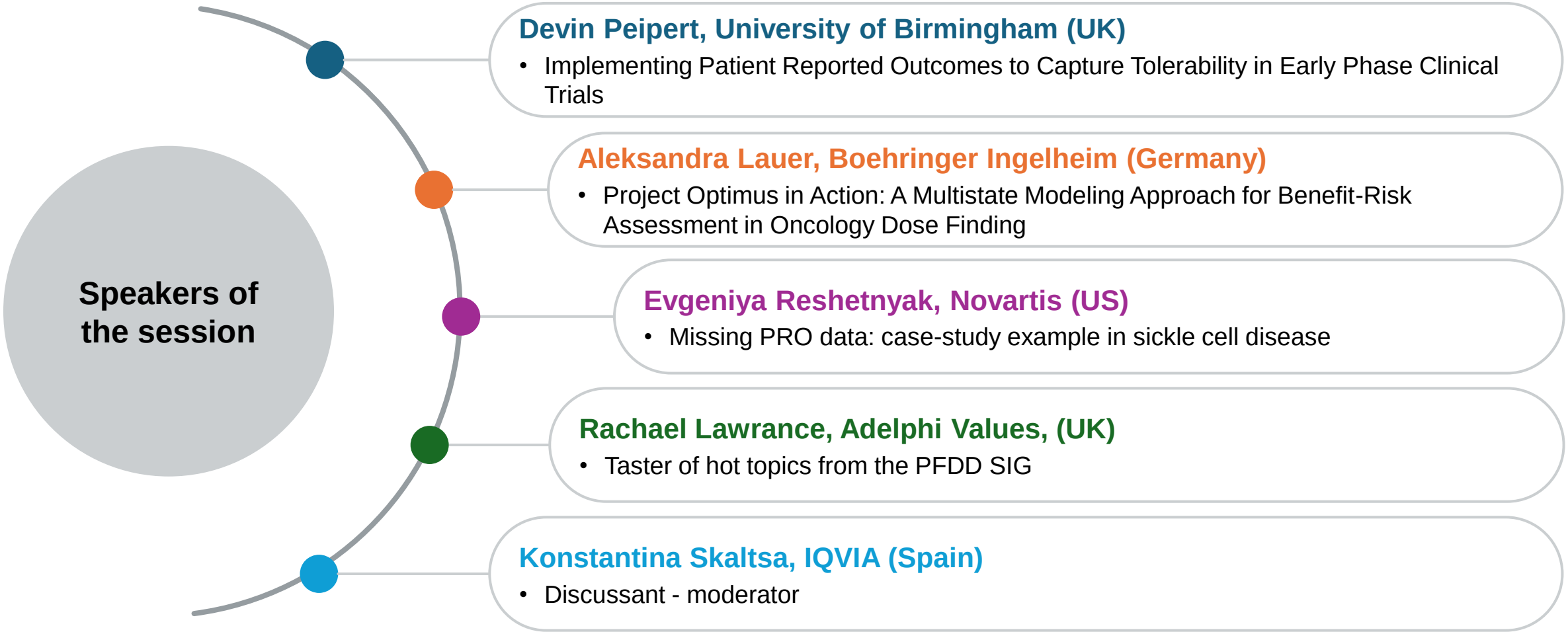
Name	Company
Rachael Lawrance (co-chair)	Adelphi values
Konstantina Skaltsa (co-chair)	IQVIA
Devin Peipert	University of Birmingham
Emilie Gerard	Sanofi
Perman Gochyyev	Sanofi
Cara Arizmendi	AZ
Antoine Regnault	Modus Outcomes
Piper Fromy	SeeingTheta
Alexandra Lauer	BI
Eygenyia Reshetnyak	Novartis
Whitney York	GSK
Anais Andrillon	Saryga
Marvis Sydow	IQVIA

If you are interested in joining any workstream or propose a new topic, please reach out to either

Rachael
Rachael.Lawrance@adelphivalues.com

or Konstantina
Konstantina.Skaltsa@iqvia.com

PFDD SIG: How to use PROs in early phase studies & other hot topics



Our speakers today

Devin Peipert

University of Birmingham (UK)

Devin Peipert is Professor of Health Outcomes Measurement at the University of Birmingham in the UK, working within the Centre for Patient Reported Outcomes Research (CPROR) and Birmingham Health Partners Centre for Regulatory Science. He is an investigator and psychometrician focusing on the methodological advancement and application of patient reported outcomes (PROs) in clinical trials and regulatory decision-making. A significant focus of his research examines new tools and methods to quantify and manage drug intolerability across multiple therapeutic areas, including oncology and solid organ transplantation. His research in this area has been funded by the US FDA and National Cancer Institute's Tolerability Consortium.

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Evgeniya Reshetnyak

Associate Director, Biostatistics, Novartis (US)

Evgeniya is an Associate Director of Biostatistics at Novartis, Global Drug Development. She provides statistical support to Phase II-IV clinical trials in the Global Health Development Unit, with the focus on neglected diseases and underserved patient populations. Prior to Novartis, she was working as a statistician in academia, at Weill Cornell Medicine, and taught graduate level data science courses at Columbia University, NY, USA. Evgeniya holds PhD degree in Psychometrics from Fordham University, NY, USA. Evgeniya's research interests include analyses of PRO data in clinical trials, and application of machine learning algorithms and AI in clinical research.

evgeniya.reshetnyak@novartis.com

Alexandra Lauer

Methodology statistician, BI (Germany)

Alexandra Lauer is a Therapeutic Area & Methodology Statistician at Boehringer Ingelheim. In her work she focuses on Clinical Outcome Assessments (COAs) and their robust implementation throughout the drug development lifecycle to support regulatory decision making, as well as HTA value strategies. Her research interests span the fields of PROs for tolerability in support of oncology dose finding and optimization, PRO estimands, COAs for efficacy in the fields of oncology, inflammation and mental health, and the use of psychometric analyses to enhance the understanding of measurement characteristics for COAs. Alexandra is a mathematician by training.

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Rachael Lawrance

Senior Director, Adelphi Values (UK)

Rachael leads a team of statisticians at Adelphi Values Patient Centered Outcomes group, (a specialist consultancy company) and is involved in many aspects of strategy, analysis and interpretation of PRO data in clinical programmes. Prior to Adelphi, Rachael was a clinical trial statistician at AstraZeneca. Rachael has particular expertise in oncology and interest in the topic of estimands, and co-chairs the PSI/EFSPI PFDD SIG and contributes to the SISAQoL-IMI consortium initiatives. Rachael was previously the Events Director on the Board for PSI, and is still involved in the PSI Events Committee.

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Konstantina Skaltsa

Director, Statistics and Psychometrics, IQVIA (Spain)

Dr Konstantina is a statistician with 15+ years experience in advanced statistical analysis in the HEOR area. She holds a PhD from the University of Barcelona, where she is also teaching. In her day-to-day job, she advises clients on optimizing their PRO strategy from the instrument selection and validation stage to the actual efficacy analysis, spanning from regulatory to payer/HTA interactions.

konstantina.skaltsa@iqvia.com

Talk 1

Implementing Patient Reported Outcomes to Capture Tolerability in Early Phase Clinical Trials

Devin Peipert, University of Birmingham

Implementing Patient Reported Outcomes to Capture Tolerability in Early Phase Clinical Trials

Devin Peipert
125th Anniversary Chair & Professor of Health Outcomes Research

Centre for Patient Reported Outcomes
BHP Centre for Regulatory Science & Innovation

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Overview: Treatment Tolerability

- In addition to their efficacy, tolerability of treatments is a key consideration for regulatory approval and prescribing
- In clinical trials and in routine care, inability to tolerate treatment leads to non-adherence, discontinuation, delays, and dose reductions
- Tolerability and safety are primary concerns of early phase clinical trials

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Defining and Assessing Tolerability: A Standard Definition

- Standard definition from the International Conference on Harmonization (ICH) "***the degree to which overt adverse effects can be tolerated by the subject***"
- An adverse event is a "disease, sign, or symptom" caused by the treatment (ICH)
- Primarily, tolerability is measured in terms of clinician-rated adverse events or clinical events like treatment discontinuation or hospitalization

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ICH Harmonised Tripartite Guideline. *Statistical Principles for Clinical Trials.* February 5th 1998.

Shouldn't We Hear from the Patient Too?

- In many cases, tolerability is something that comes from the patient, especially when it concerns symptomatic adverse events
- Updated definition of tolerability from Friends of Cancer Research:

The tolerability of a medical product is the degree to which symptomatic and non-symptomatic adverse events associated with the product's administration affect the ability or desire of the patient to adhere to the dose or intensity of therapy. A complete understanding of tolerability should include direct measurement from the patient on how they are feeling and functioning while on treatment.

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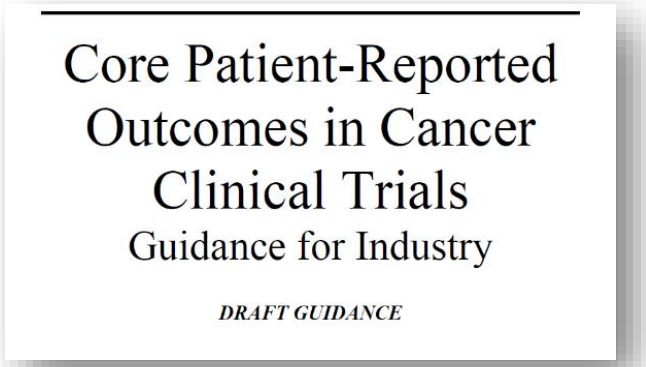
Basch E, Campbell A, Hudgens S, et al. *Broadening the Definition of Tolerability in Cancer Clinical Trials to Capture the Patient Experience.* Washington, DC: Friends of Cancer; 2020.

FRIENDS of CANCER RESEARCH

US FDA: Core PRO Concepts



FDA

Disease-related symptoms

Directly Focused on Tolerability

- Symptomatic adverse events
- Overall side effect impact summary measure

Indirectly Focused on Tolerability

- Physical function
- Role function

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United States Food and Drug Administration. *Core Patient-Reported Outcomes in Cancer Clinical Trials Guidance for Industry. 2024. October 24th.*

Recent Tolerability-Based FDA Drug Label

Patient-reported overall side effect impact results were supported by a lower incidence of treatment discontinuation adverse reactions for RETEVMO (4.7%) compared to cabozantinib or vandetanib (27%) in patients who received at

Table 22. Descriptive Summary of Patient-reported Overall Side Effect Impact While on Treatment in LIBRETTO-531

	RETEVMO (N=145)	Cabozantinib or Vandetanib (N=77)
Mean proportion of time with high side effect bother (95% CI)	8% (4.8%, 10%)	24% (17%, 31%)

Revised September 2024

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https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/213246s011s013lbl.pdf, Accessed 24/04.2025

FDA Project Optimus

Purpose: To reform the dose optimisation & selection paradigm

Overall Goal: "[…] move forward with a dose-finding and dose optimization paradigm across oncology that emphasizes selection of a dose or doses that maximizes not only the efficacy of a drug but the safety and tolerability as well"

Specific Goal: "Develop strategies for dose finding and dose optimization that leverages nonclinical and clinical data in dose selection, including randomized evaluations of a range of doses in trials."

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https://www.fda.gov/about-fda/oncology-center-excellence/project-optimus

Integrating PROs into Early Phase Tolerability Assessments

Health Policy

eClinicalMedicine
Part of THE LANCET *Discovery Science*

Advancing patient-centric care: integrating patient reported outcomes for tolerability assessment in early phase clinical trials – insights from an expert virtual roundtable

Christina Yap,[a,*] Olalekan Lee Aiyegbusi,[b,ab,ac,ad,ae] Emily Alger,[a] Ethan Basch,[c,af] Jill Bell,[d] Vishal Bhatnagar,[e] David Cella,[f] Philip Collis,[b] Amylou C. Dueck,[g] Alexandra Gilbert,[h] Ari Gnanasakthy,[i] Alastair Greystoke,[j] Aaron R. Hansen,[k,ag] Paul Kamudoni,[l] Olga Kholmanskikh,[m] Bellinda L. King-Kallimanis,[n] Harlan Krumholz,[o] Anna Minchom,[p] Daniel O'Connor,[q] Joan Petrie,[r] Claire Piccinin,[s] Khadija Rerhou Rantell,[t] Saaeha Rauz,[u,ah] Ameeta Retzer,[v,ai] Steven Rizk,[w] Lynne Wagner,[x] Maxime Sasseville,[y] Lesley K. Seymour,[r] Harald A. Weber,[z] Roger Wilson,[aa] Melanie Calvert,[b,ab,ac,ad,ae] and John Devin Peipert[f]

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Research Themes

Theme 1

The need and feasibility of establishing a universal set of PRO core concepts for tolerability assessment:

- Is it feasible and is there a need to develop a PRO Core Outcome Set (COS) to assess tolerability in phase I and II trials?
- If yes, would there be major differences between the COS needs for:
  - Phase I and phase II? How?
  - Oncology and non-oncology trials? How?

Patient advocate	2 (9%)
Regulator	4 (18%)
Clinical trialist	5 (23%)
Pharmaceutical representative	4 (18%)
Patient-reported outcomes methodologist	7 (32%)

***Table 1*: Expert roundtable participants (N = 22).**

Theme 2

Practical considerations for incorporating PROs in trial design for tolerability assessment:

- How and for what purpose should PROs be used in early phase settings?

Key prompts

  - How should PROs be used to guide trial design, whether for dose escalation, dose optimisation, or general tolerability assessment to inform PRO strategy in later phase trials?
    - Interim vs end-of trial analysis (and if they should be analysed formally or descriptively)
    - Real time reporting and response (utilising PROs to inform adverse event grading or independent PRO assessment)
    - Standardised vs ad hoc reporting
- What should be the role of PROs in regulatory decision-making in early phase trials?

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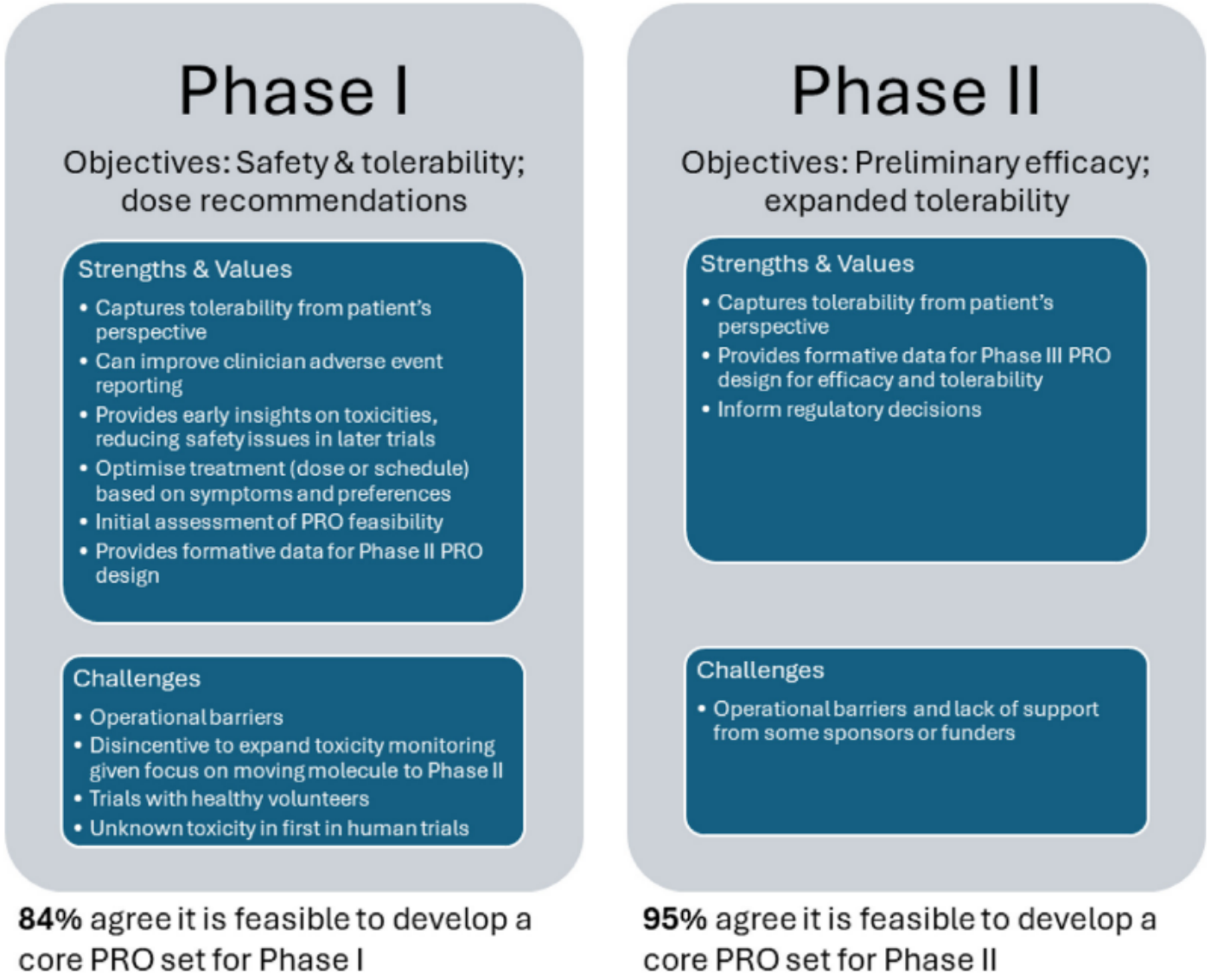
Overall: Identified Benefits & Challenges



84% agree it is feasible to develop a core PRO set for Phase I

95% agree it is feasible to develop a core PRO set for Phase II

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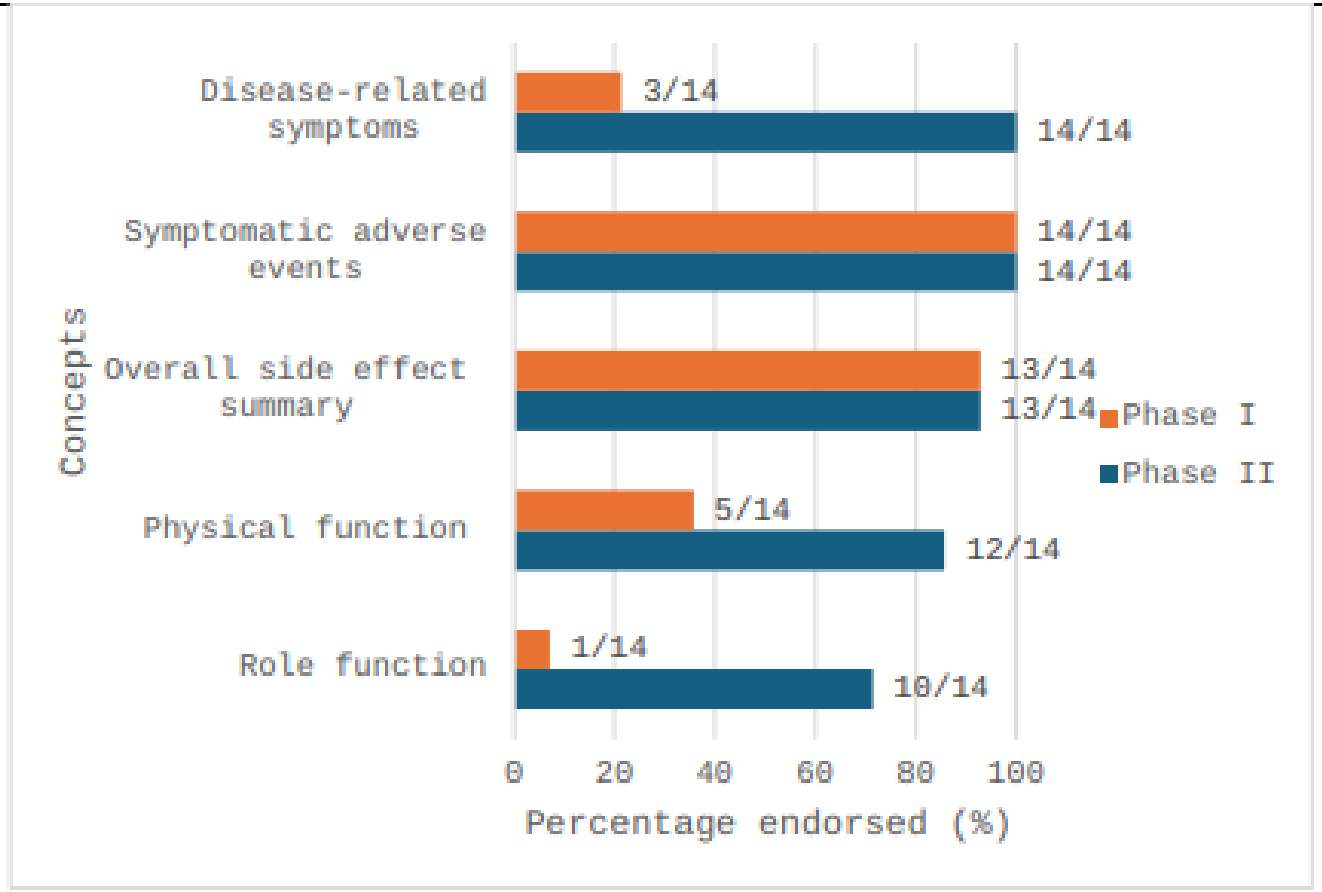
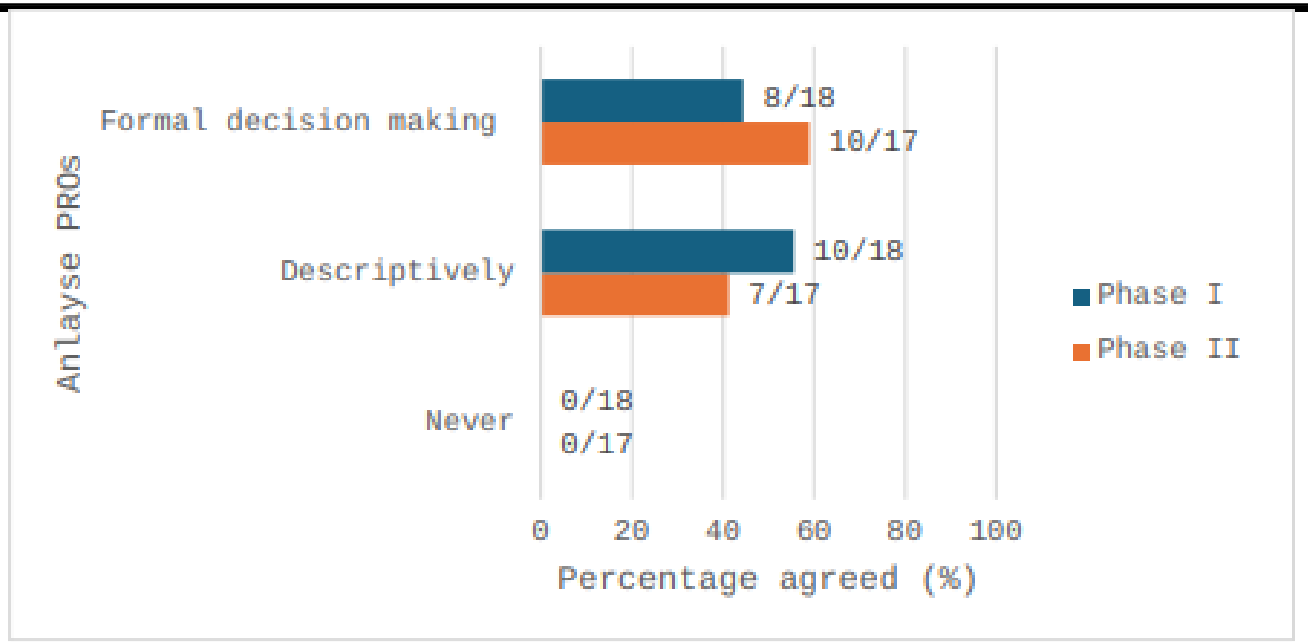
Theme 1 Results

Question	Results	Agreement
Participants' Endorsement of Concepts for Inclusion in a Minimum PRO Set for Early Phase Trials		For Phase I trials, participants endorsed the inclusion of symptomatic adverse events and overall effect summary concepts in a minimum PRO set for Phase I trials. They also agreed that disease-related symptoms and role function should not be used. No agreement was reached on the use of physical function. For Phase II trials, participants endorsed the inclusion of disease related symptoms, symptomatic adverse events, overall effect summary, physical function and role function concepts in a minimum PRO set for Phase II trials.

Theme 2 Results

Question	Results	Agreement
Formally vs Descriptively Should PROs be used…		No agreement was reached on whether PROs should be used for formal decision making or descriptively in Phase I and Phase II trials.
(2) Use PROs in a more formal way (independently) to assess patient-rated intolerability alongside investigator-rated CTCAE grading.		independently to assess patient-rated intolerability alongside investigator-rated CTCAE grading.

Recommendations & Actions

Recommendations	Actions
Promote PRO collection in phase I & I trials	Foster collaboration and communication between early and late-stage therapeutic development programs
	Educate & raise awareness about the significance of PROs in early phase trials
	Involve patients and patient advocacy groups in the design and conduct of early phase trials
	Encourage targeted funding for early phase trials that prioritise PRO integration in early phase study designs

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Recommendations & Actions

Recommendations	Actions
Adopt the FDA core PRO concepts as initial PRO measures set	Phase I: overall side effect impact, symptomatic adverse events
	Phase II: overall side effect impact, symptomatic adverse events, physical function, role function, and disease symptoms
	Develop PRO core outcome sets for phase I and II trials, and consider appropriateness for oncology and non-oncology settings

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Recommendations & Actions

Recommendations	Actions
Conduct additional research into multiple aspects of integrating PROs into early phase trials	Pilot feasibility studies across differing trial settings, implementation challenges potentially encountered by clinical teams when PROs are implemented in real time and ad hoc, with or without real-time alerts
	Additional consensus-building work with diverse stakeholders, including clinical trialists and methodologists, patients, PRO researchers, and regulators

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OPTIMISE-AR: Incorporating Patient-Reported Outcomes in Dose-Finding Trials - Analysis

ICR The Institute of Cancer Research

[Part 1] Determine the PRO research objectives which could be considered for use in the context of dose finding oncology trials.

[Part 2] Identify appropriate statistical methods and data visualisation techniques to support analysis and presentation of PRO endpoints to answer (or matched with) PRO research objectives in Part 1.

1. Methodological review

2. Delphi survey

3. Consensus meeting

4. Expert roundtable

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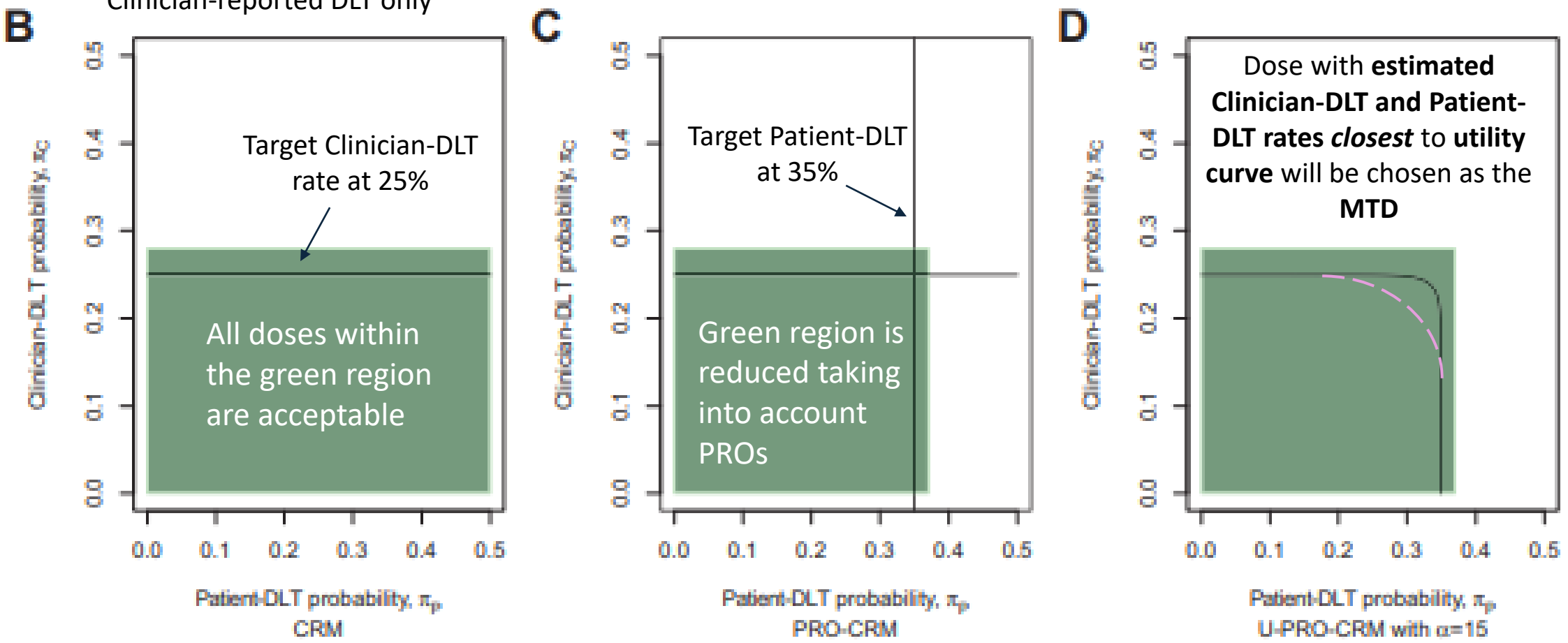
Dose-selection incorporating PROs

Maximum Tolerated Dose (MTD) is chosen based on Clinician-reported DLT only

MTD is chosen based on Clinician-DLT and patient–DLT



DLT: Dose Limiting Toxicity

PRO-CRM: Lee SM, Lu X and Cheng, Stats Med, 2021

U-PRO-CRM: Alger E, Lee SM, Cheung K & Yap C, ESMO Op

Take Home Points

- Patient-centricity is critical in the evaluation of new treatments' tolerability; standard safety evaluation is not sufficient
- Stakeholders agree that including PROs in early phase trials is important; more refinement of objectives and implementation approaches are emerging
- Statistical methods for PRO-supported dose-finding are available

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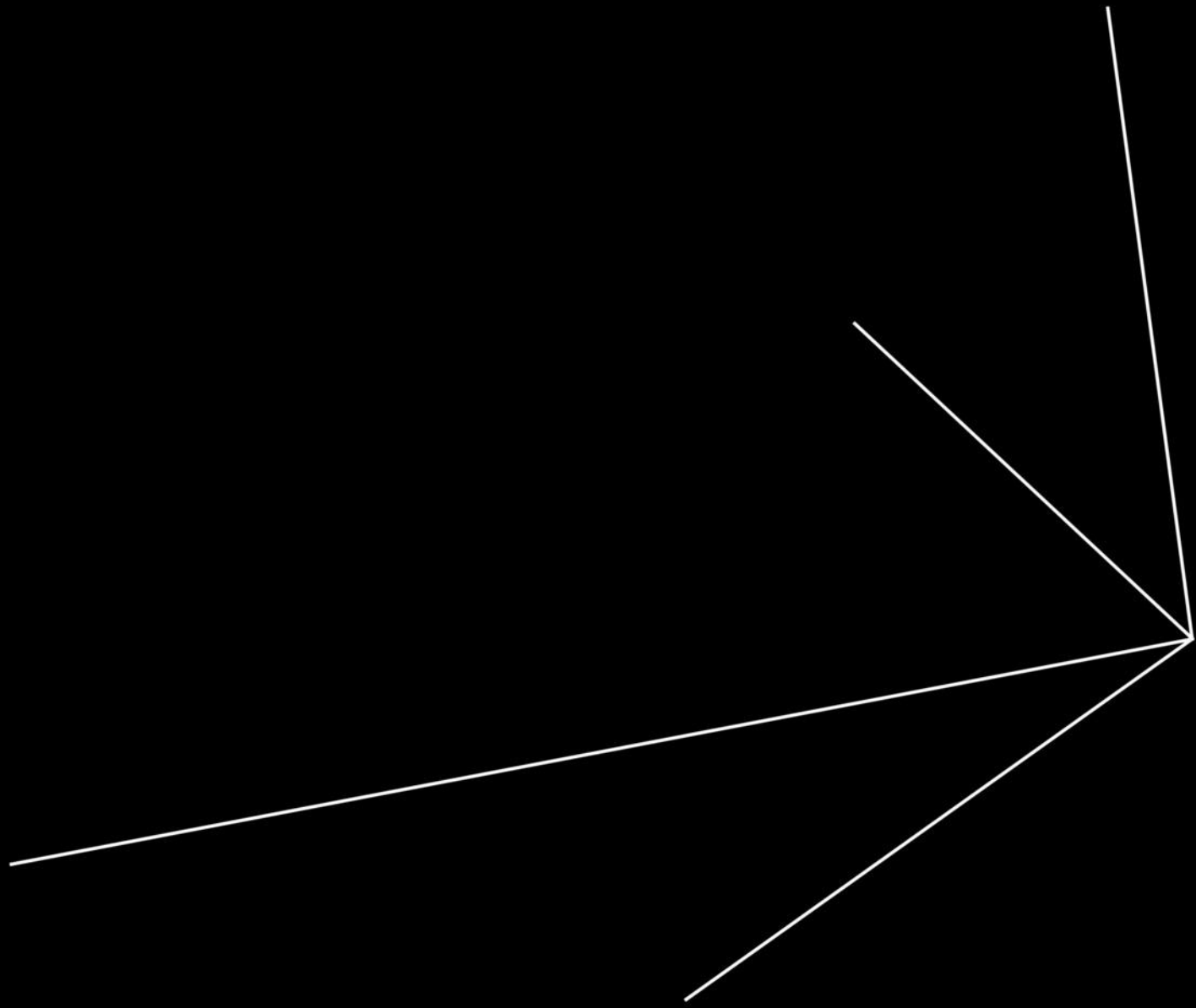
Thank you!
Questions?



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Talk 2

Project Optimus in Action: A Multistate Modelling Approach for Benefit-Risk Assessment in Oncology Dose Finding

Alexandra Lauer, Boehringer Ingelheim

Boehringer Ingelheim

Project Optimus in Action

A Multistate Modeling Approach for Benefit-Risk Assessment in Oncology Dose Finding

Alexandra Lauer | June 9th, 2025 | PSI 2025 Conference, London

Life forward

Disclaimer

This presentation is based on secondary use of data from the Brightline-1 Study (NCT05218499). The results are derived from a subset of the full analysis set used in the CTR analyses, excluding patients who withdrew informed consent.

Results therefore differ from published references.

All views are my own.

Boehringer Ingelheim

Agenda

01 Introduction: FDA’s Project Optimus and the role of Tolerability

02 Traditional Analysis Approach – PFS with a dash of Tolerability

03 Multistate Modeling and Time Spent in State Comparisons

04 Outlook

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Introduction

FDA’s Project Optimus and the role of Tolerability

Boehringer Ingelheim

FDA's Project Optimus

Purpose

The Oncology Center of Excellence (OCE) Project Optimus is an initiative to reform the dose optimization and dose selection paradigm in oncology drug development. Too often, the current paradigm for dose selection—based on cytotoxic chemotherapeutics—leads to doses and schedules of molecularly targeted therapies that are inadequately characterized before initiating registration trials.

Patients may be receiving these novel therapeutics for longer periods of time to maximize the benefit of a drug, which ideally includes not only longer survival but also an improved quality of life.

Poorly characterized dose and schedule may lead to selection of a dose that provides more toxicity without additional efficacy, severe toxicities that require a high rate of dose reductions, intolerable toxicities that lead to premature discontinuation and missed opportunity for continued benefit from the drug, and potentially persistent or irreversible toxicities that limit the options for receiving benefit of subsequent therapies—to name a few examples.

Project Optimus | FDA

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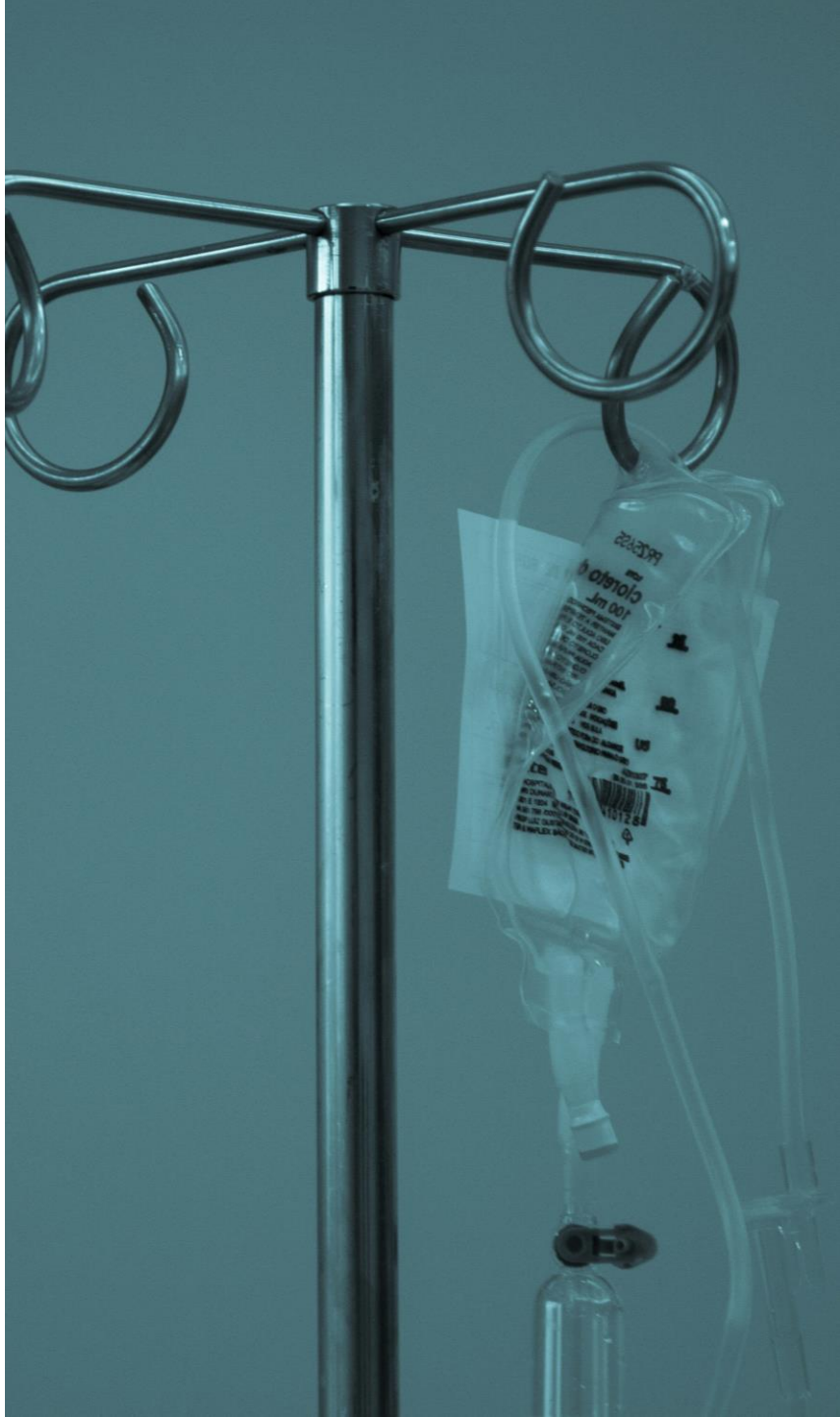

Tolerability – Definition and Instruments

Tolerability - Definition

Degree to which symptomatic & non-symptomatic AEs associated with a drug administration affect the **ability/ desire of patients** to adhere to the **dose or intensity** of the therapy.

Overall Side Effect Bother/ Burden (FACT-GP5/ EORTC IL46)

GP5 (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

		Not at all	A little bit	Somewhat	Quite a bit	Very much
GP5	I am bothered by side effects of treatment.....	0	1	2	3	4

[Generic]

Symptomatic Adverse Events (PRO-CTCAE 124 items, 78 symptomatic AEs)

1a. In the last 7 days, how OFTEN did you have NAUSEA?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
1b. In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

[Specific]

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Traditional Analysis Approach

PFS with a dash of Tolerability

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The Brightline-1 Study

Trial Title/ Rationale

A Phase II/III, randomized, open-label, multi-center study of brigimadlin compared to doxorubicin as first line treatment of patients with advanced dedifferentiated liposarcoma (DDLPS), comparing two doses of brigimadlin to doxorubicin

Schedule of Assessments

	Week										
	0	1	...	6	...	12	...	15	18	...	48
FACT-GP5* PRO-CTCAE*	x	x	x	x	x	x	x	x	x		x
Tumor Assessment				x		x			x		x

*Weekly until Week 15, then every 3 weeks to Week 48 or PD (whichever occurs first)

Demographic summary

	Brigimadlin 30 mg q3w (n=88)	Brigimadlin 45 mg q3w (n=87)
Age [Years] - Mean (SD)	62 (11.6)	66 (10.2)
Sex [n (%)]		
Male	54 (61.4%)	60 (69.0%)
Female	34 (38.6%)	27 (31.0%)
Baseline ECOG [n (%)]		
0	58 (65.9%)	52 (59.8%)
1	30 (34.1%)	35 (40.2%)

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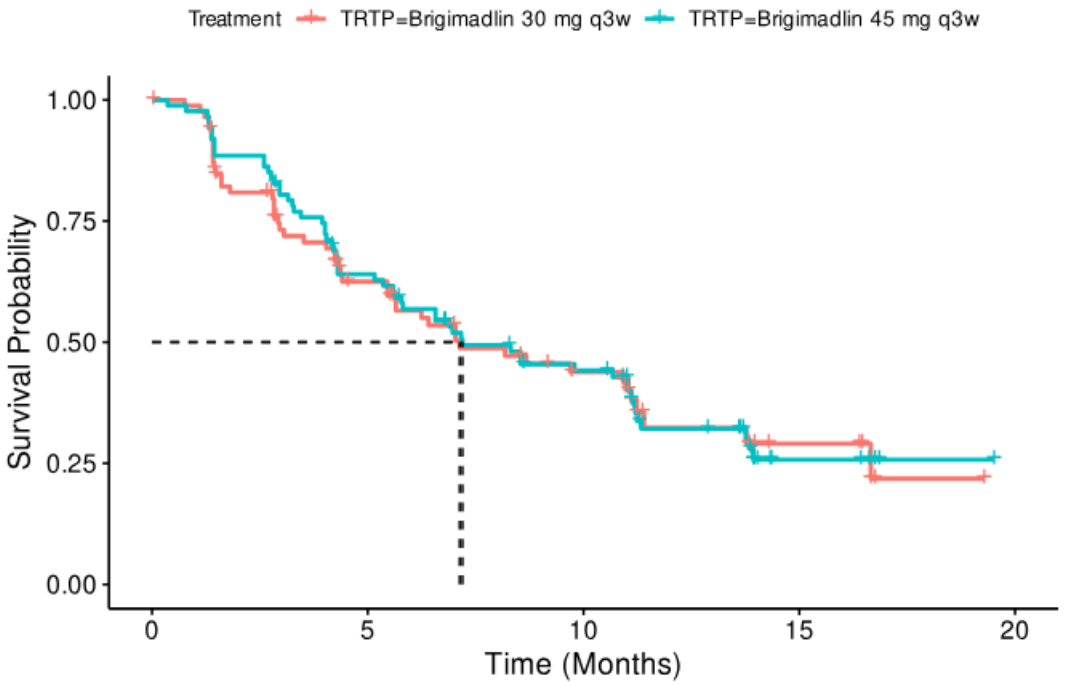
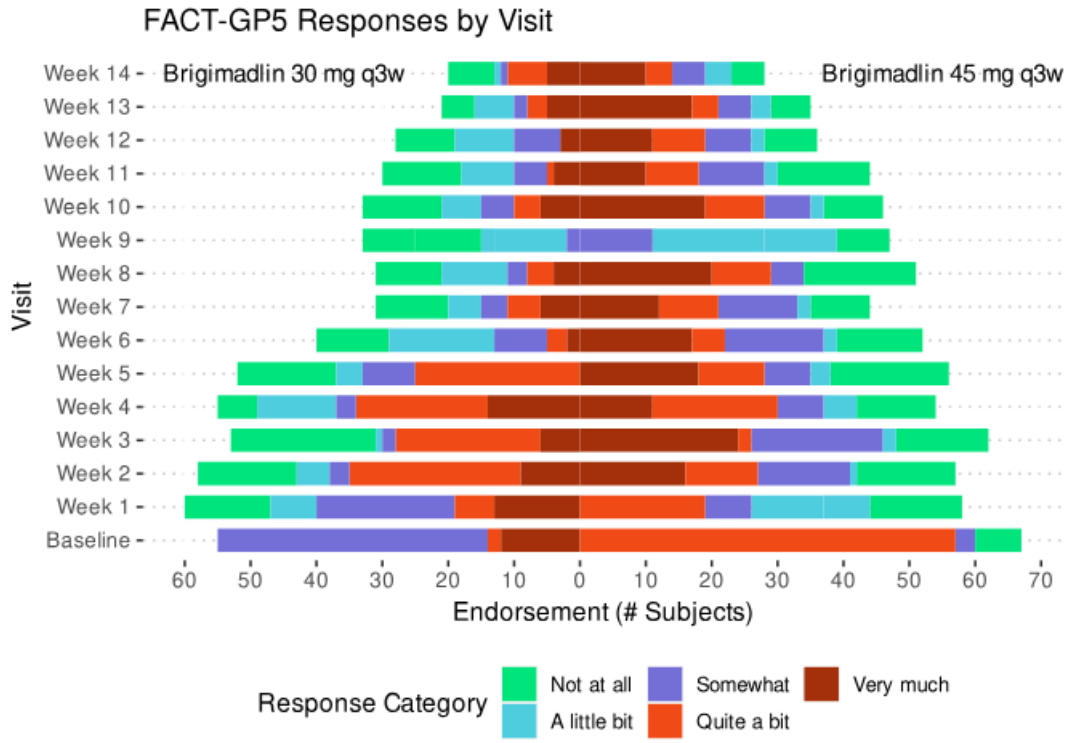
Traditional Analysis Approach

Progression-Free Survival



Tolerability



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Caveats in the context of the B/R Assessment

Benefit-Risk Assessment

"Are 11 months of PFS with 40% toxicity preferable over 9 months of PFS with 20% toxicity?"

Caveats

- No understanding longitudinal profile of side effect burden
- Preference-based with no inclusion of patient experience

https://www.ema.europa.eu/en/documents/presentation/presentation-enhancing-benefit-risk-assessment-integrating-survival-data-longitudinal-patient-reported-outcome-data-d-postmus_en.pdf

D. Postmus:

"Enhancing Benefit-Risk Assessment: Integrating Survival Data and Longitudinal PRO Data"

(2024 EMA and EORTC workshop: How can PRO and HRQoL data inform regulatory decision making?)

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Multistate Modeling and Time Spent in State Comparisons

Time Spent in Tolerable State

Classical B/R Assessment

"Are 11 months of PFS with 40% toxicity preferable over 9 months of PFS with 20% toxicity?"

Time with Acceptable Tolerability

"Are 11 months of PFS with high side effect burden followed by 2 months with acceptable side effect burden preferable over 9 months of PFS with acceptable side effect burden?"

https://www.ema.europa.eu/en/documents/presentation/presentation-enhancing-benefit-risk-assessment-integrating-survival-data-longitudinal-patient-reported-outcome-data-d-postmus_en.pdf

D. Postmus:

"Enhancing Benefit-Risk Assessment: Integrating Survival Data and Longitudinal PRO Data"

(2024 EMA and EORTC workshop: How can PRO and HRQoL data inform regulatory decision making?)

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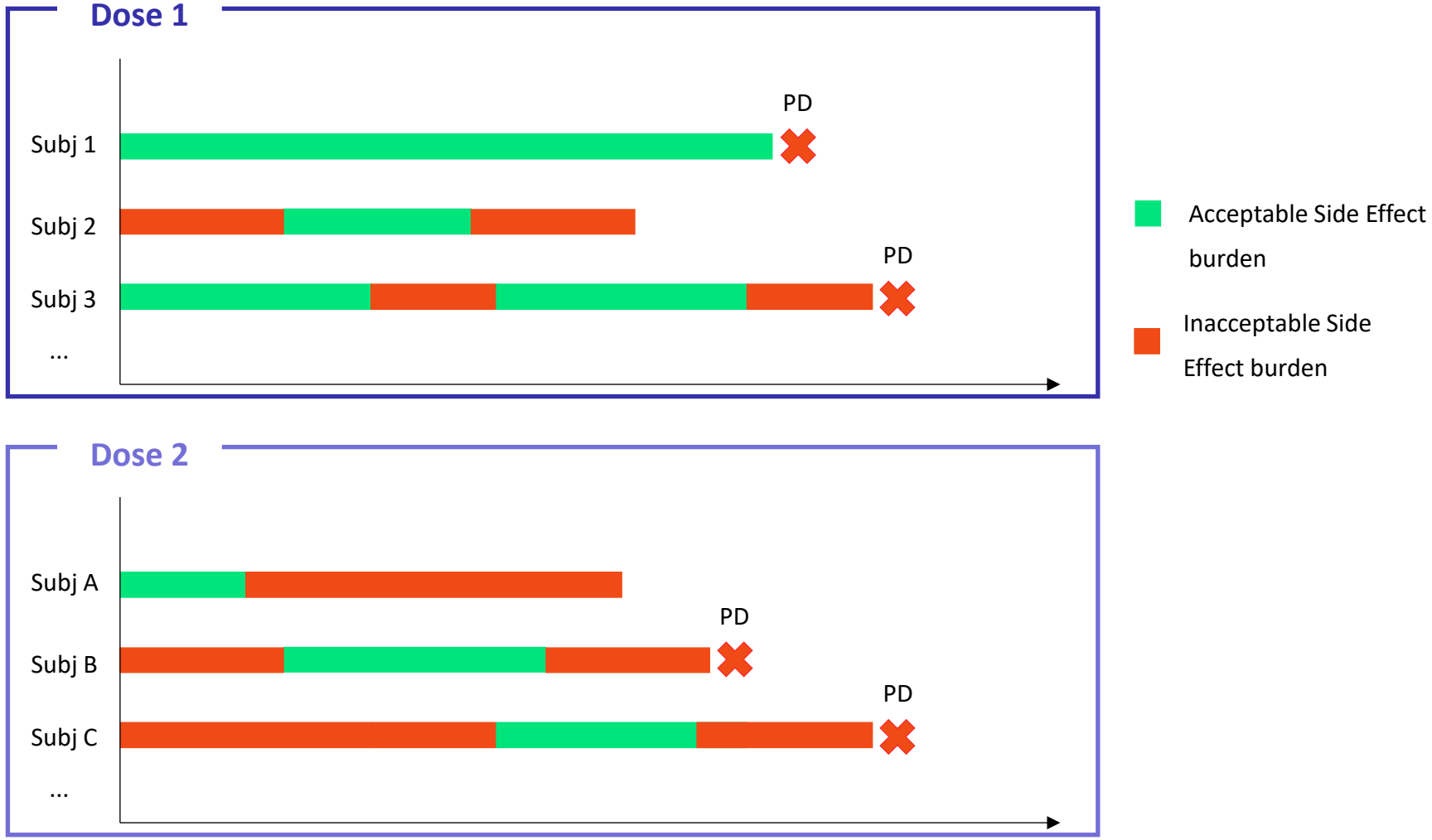
Motivation for Multistate Modeling



→ Need to longitudinal modeling between different side effect burden states

→ States are **not** continuous (no MMRM)

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Multistate Modeling – Stepping away from time to first event

	Classical Survival Analysis	Multistate Models
Focus	Single event of interest	Transitions between multiple states over time
Assumption	Transition into single (absorbing) state will eventually occur	Subjects can transition between multiple states over time
Analysis	Single hazard function	Transition-specific hazard function
Example	PFS, OS	Length of time with adequate side effect burden prior to tumor progression/ death

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Modeling Transitions – Problem formulation and a dash of maths

Let $(X_t)_{t\geq 0}$ be a time-inhomogeneous Markov process modeling an individual's state at time t, with state space

$$X_t \in \{1, 2, 3\}, \quad t \geq 0.$$

Events are modeled via transitions between states. Let

$$p(s,t) \coloneqq \left(p_{l,j}(s,t)\right)_{l,j\in\{1,2,3\}},$$

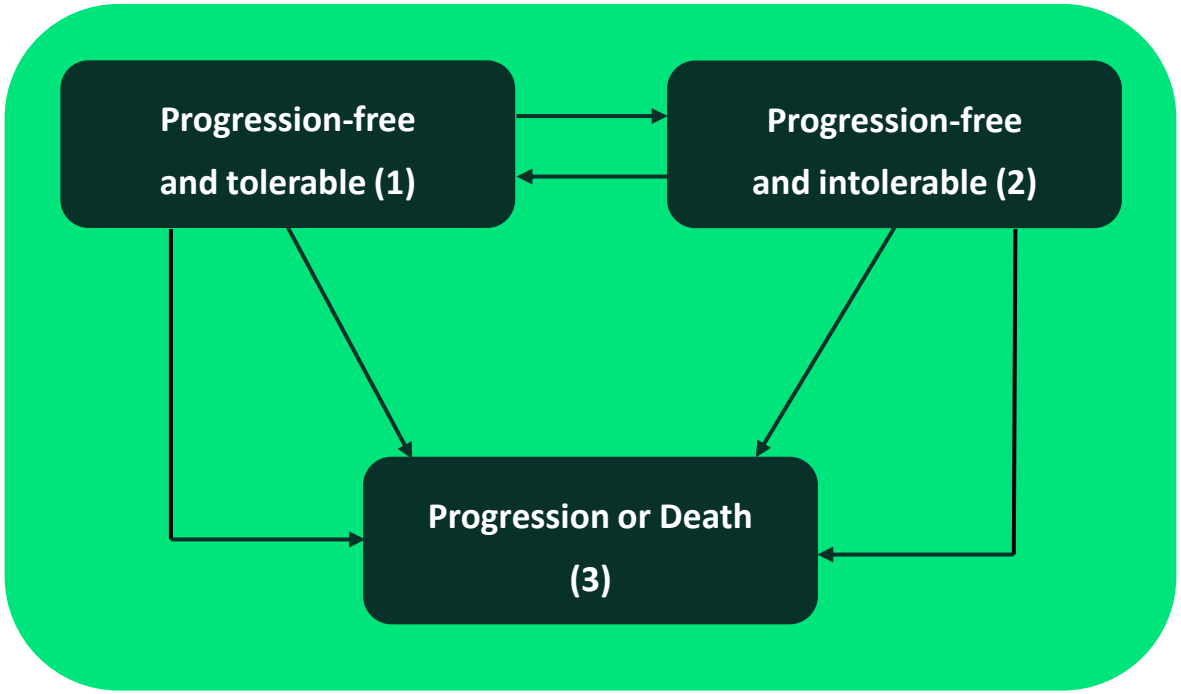
be the matrix of transition probabilities, where

$$p_{l,j}(s,t) \coloneqq \mathbb{P}[\{X_t = j\} \mid \{X_s = l\}], \qquad s,t \geq 0.$$

Transition hazards and cumulative transition hazards are

$$\alpha_{l,j}(t)\, dt \coloneqq \mathbb{P}\left[\left\{X_{(t+dt)-} = j\right\} \,\middle|\, \{X_{t-} = l\}\right],\ l \neq j,$$

$$A_{l,j}(t) \coloneqq \int_0^t \alpha_{l,j}(u)\, du\,.$$



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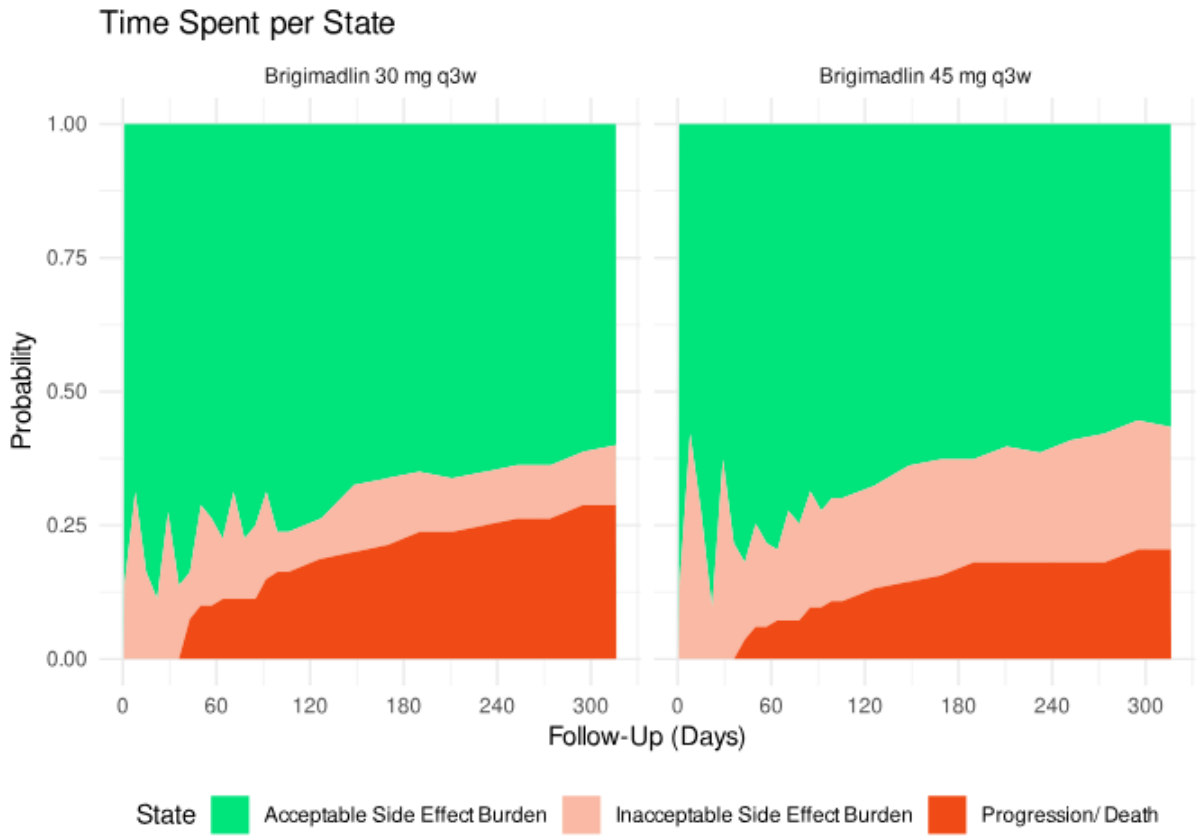
Comparison of time spent in tolerable state

Time Spent in State per Dose over 335 Days

	Brigimadlin 30 mg q3w	Brigimadlin 45 mg q3w
PFS and Acceptable Side Effect Burden	232	218
PFS and Inacceptable Side Effect Burden	40	72
PFS/ Death	63	45

- Lower dose: **less** time spent in inacceptable side effect burden state
- Higher dose: benefit in PFS comes at cost of **increase** side effect burden



Boehringer Ingelheim

Outlook

Summary and Caveats

Pros

- Comprehensible combination of traditional survival and longitudinal PRO data
- Results can be communicated to patients to solicit preferences and inform the B/R profile

Cons

- Model complexity increases with additional states
- Time spent in state estimation is prone to bias in the presence of intermittent missingness
- Choice of landmark timepoint for comparison needs justification

Boehringer Ingelheim

Thank you!

Boehringer Ingelheim

Intro on talk 3

Measuring and defining endpoints for pain

Konstantina Skaltsa, IQVIA

Including pain improvement in the drug label is possible

- When **pain** is a concept of interest (CoI) in a disease, it is usually raised by patient as one of their most bothersome symptoms, and thus a target for improvement
- Sponsors with drugs that may **improve pain in conjunction with disease response** have the opportunity to pursue a label claim for pain improvement, i.e., include PRO data in the label (or SmPC for EMA)
- However, measuring pain, as well as defining meaningful and robust endpoints is not straightforward

Measuring and creating endpoints for pain requires careful consideration of several aspects

- Chronic or acute
  - e.g. fibromyalgia vs post-surgery pain)
- Stable or showing dynamic patterns
- Localized (e.g., at a tumor site) or general

- Different **aspects of pain** can be measured:
  - Intensity (most common)
  - Frequency
  - Duration
- Different scales exist for measuring pain
  - e.g., Brief Pain Inventory (BPI) **severity** and **interference** scales, with item #3 (worst pain) rated 0-10 commonly used

- Can be measured:
  - at regular intervals (recall-based)
  - at a daily level
  - multiple times per day (EMA)

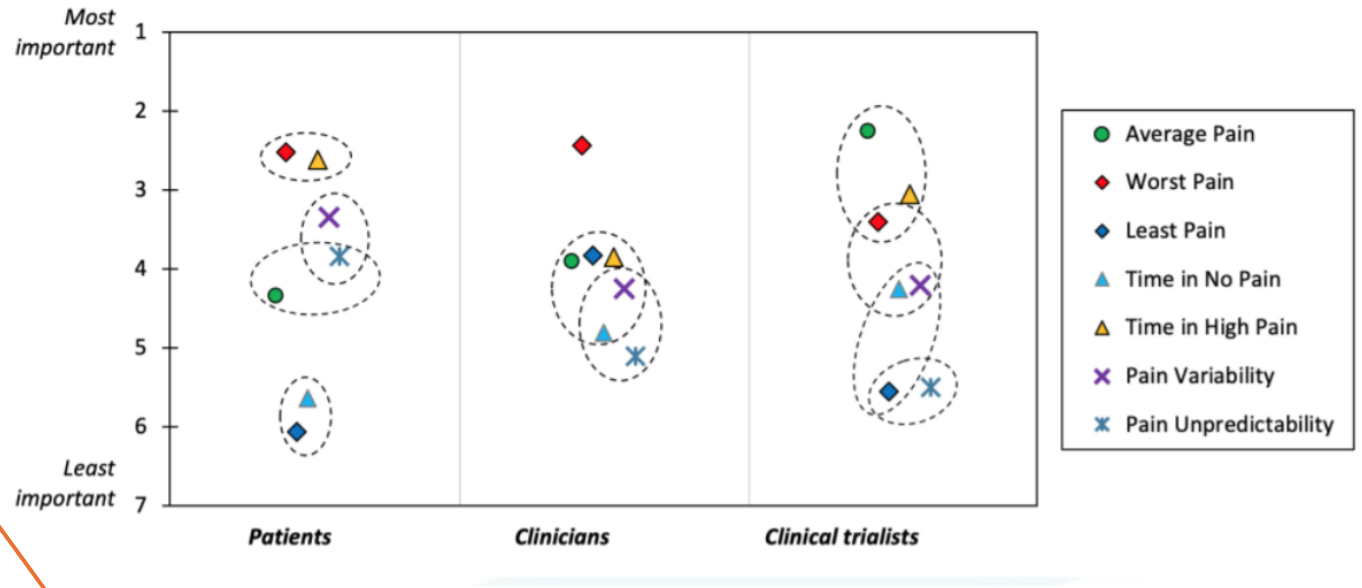
- **Rescue and concomitant medication** needs to be collected and accounted for in the analysis

EMA: Ecologic Momentary Assessment
https://www.ema.europa.eu/en/clinical-development-medicinal-products-intended-treatment-pain-scientific-guideline

Different endpoints may be considered when more frequent assessments are planned

- **Average** pain
- Least/**Worst pain**
- Time in low/high pain
- Pain variability
- Pain unpredictability
- Pain after wake-up

Used to be the norm



Is most commonly used to capture intensity
When measured daily or more frequent prompts: an average of the worst pain per day over a week is considered

Stone ISPOR 2019 and Stone et al 2021 (https://pubmed.ncbi.nlm.nih.gov/32947012/), Schneider et al 2021 (https://pubmed.ncbi.nlm.nih.gov/33203516/)

Antitumor drugs may also offer pain relief

An FDA perspective

- Pain **intensity** is usually assessed

- **Worst or average** pain (11-point NRS) with a 24h-recall period, i.e., diary

- **Analgesic use** should be collected with same recall
- A systematic approach is needed to define increase, stability, decrease

- Including a cohort experiencing pain attributable to cancer may be needed
- Most common **population**: baseline weekly average “worst pain in past 24 hours” scores of ≥3 or ≥4 on an 11-point NRS.

- **Missing data** are frequent and may be associated with pain status
- Non-responder imputation implying a composite approach when binary endpoint
- Extensive sensitivity analyses are needed

NRS: Numerical Rating Scale
Basch et al 2013 (https://pubmed.ncbi.nlm.nih.gov/24375398/)

Talk 3

Patient-Reported Pain & missing data: case-study example in sickle cell disease

Evgeniya Reshetnyak, Novartis

Global Health DU
Global Drug Development

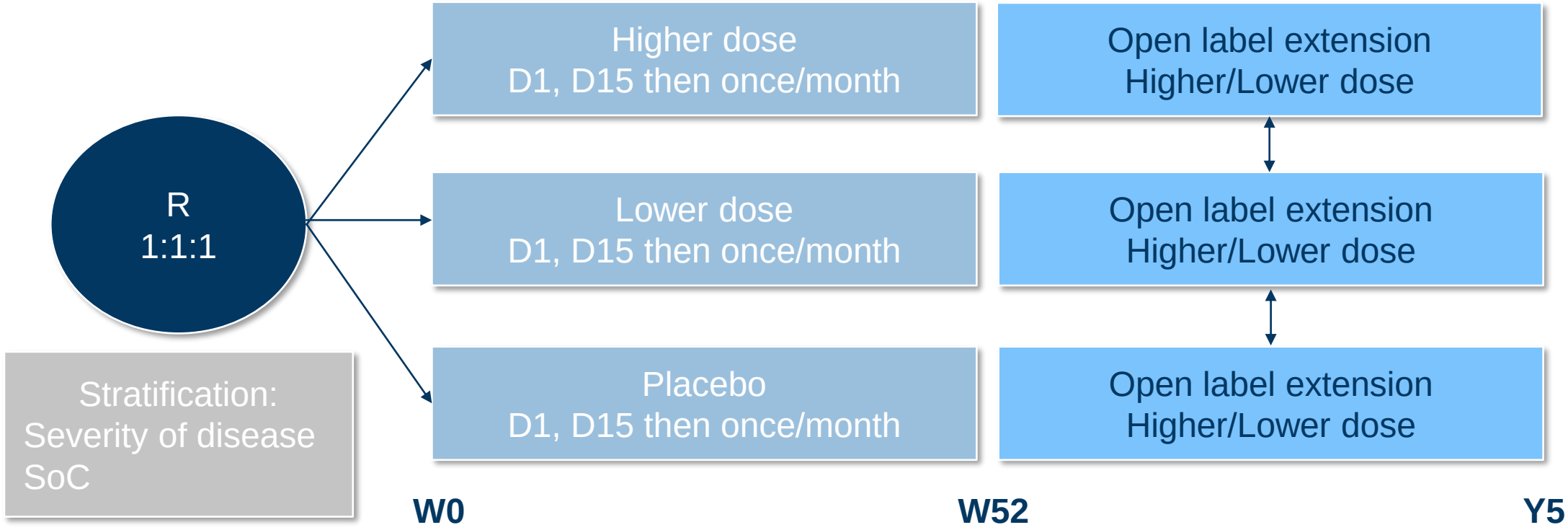
Case study: Phase III PRO Analysis

Evgeniya Reshetnyak, Statistician

NOVARTIS | Reimagining Medicine

Phase III Study Design

Phase III hematology/immunology placebo-controlled randomized double-blind study was designed to confirm efficacy and safety of a lower dose the compound and to assess safety and efficacy of a higher dose.



Phase III – ASCQ-Me tool

- **Hypotheses testing**: The study was not powered to assess specific PRO related hypotheses thus statistical analyses of these data were considered **exploratory** in nature.
- **Tool**: ASCQ-Me for patients aged ≥18 years
- **Data collected**: every 7 days up to 52-week treatment period; recall period – 7 days
- **Structure**: 5 short forms, containing 5 items each, measured on 5-point Likert scale

ASCQ-Me – Pain Impact SF

	Never	Rarely	Sometimes	Often	Always
In the past 7 days, how often did you have pain so bad that you could not do anything for a whole day?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
In the past 7 days, how often did you have pain so bad that you could not get out of bed?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
In the past 7 days, how often did you have very severe pain?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
In the past 7 days, how often did you have pain so bad that you had to stop what you were doing?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
In the past 7 days, how often did you have pain so bad that it was hard to finish what you were doing?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Forms: 4 administered short forms were used to capture of all relevant disease symptoms and impact concepts:

- ✓**pain impact (5 items)**
- ✓emotional impact (5 items)
- ✓sleep impact (5 items)
- ✓joint stiffness (5 items)

Phase III – PRO analysis

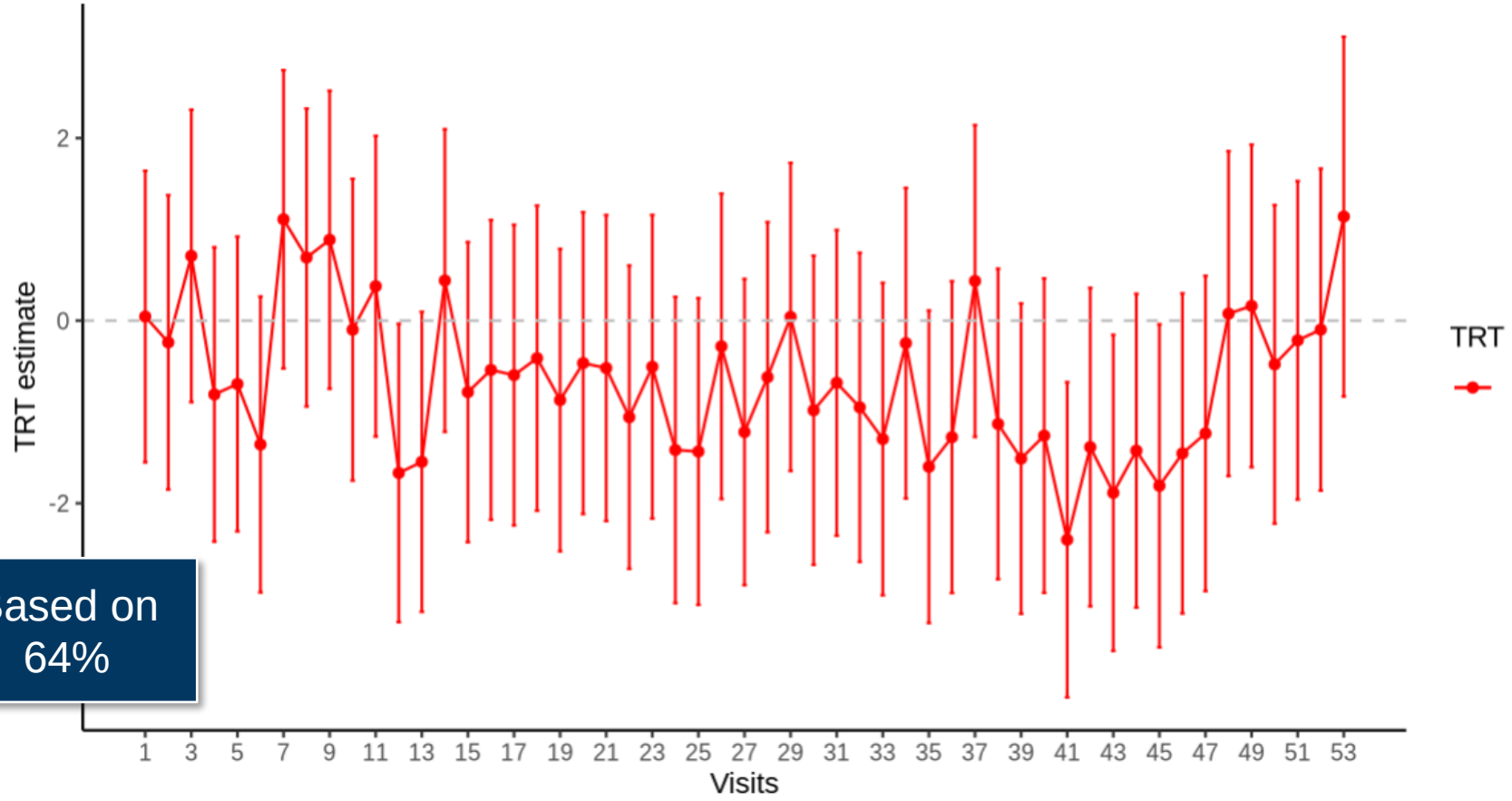
- **Metric**: T-scores; higher scores indicate better quality of life and less impact of the disease; sum of scores are analyzed by the short form, not the overall total score
- **Missing data**: At a given visit, for all Short Forms, all questions are mandatory, therefore a question within a Short Form cannot be missed, and the questionnaires are either complete or completely missing, and cannot be partially completed. No imputation was performed, complete case.
- **Endpoint**: change in T-scores from the baseline on the short forms and treatment arms.
- **Model**:
  - Short forms were analyzed separately
  - A repeated measurement analysis model for longitudinal data (linear mixed effect model, MMRM) was used to estimate differences in the T-scores of the short forms between treatment groups.
  - Model included terms for treatment group, the stratification factors, time, baseline value as main effects, and an interaction term for treatment group by time.
  - This analysis was restricted to patients with an evaluable baseline score and at least one evaluable post-baseline score.

Estimand Attributes

The PRO estimand is described by the following four attributes:

1. **Target population** adolescents and adults patients with ≥2 pain events leading to healthcare visit in the previous year, and not planning to start/discontinue SOC during first year
2. **Primary variables** Change in QOL T-scores on the short forms during the first year post randomization
3. **Intercurrent events** of interest in this study :
   a. Treatment discontinuation within the first year - **Hypothetical strategy**
   b. Pain both leading to healthcare visit and treated at home –**Treatment policy**
   c. Initiation or discontinuation of SOC – **Hypothetical strategy**
   d. intake of analgesic (including opioids) or ad hoc transfusions administered temporarily – **Treatment policy**
4. **Summary Measure –** adjusted mean difference

MMRM with available data



Based on 64%

N=252 (FAS)

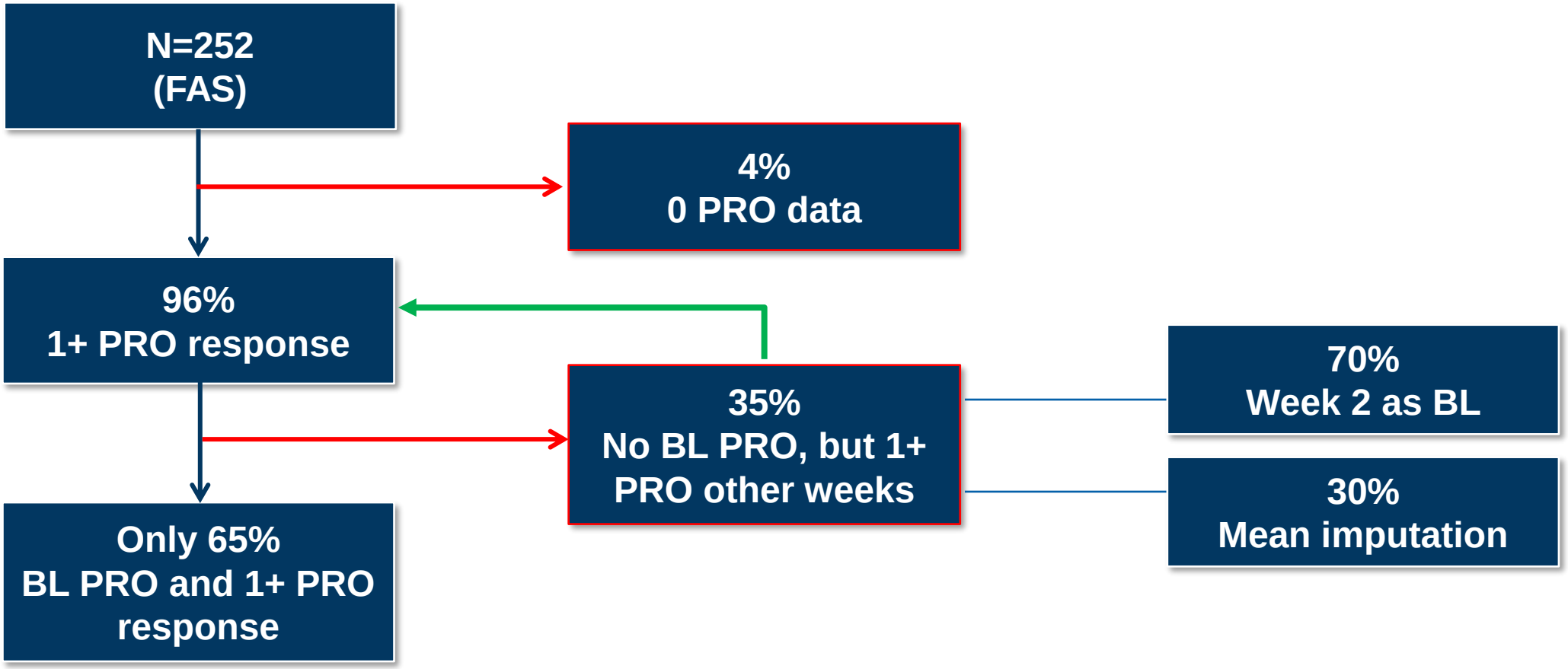
96% 1+ PRO response

Only 64% BL PRO and 1+ PRO response

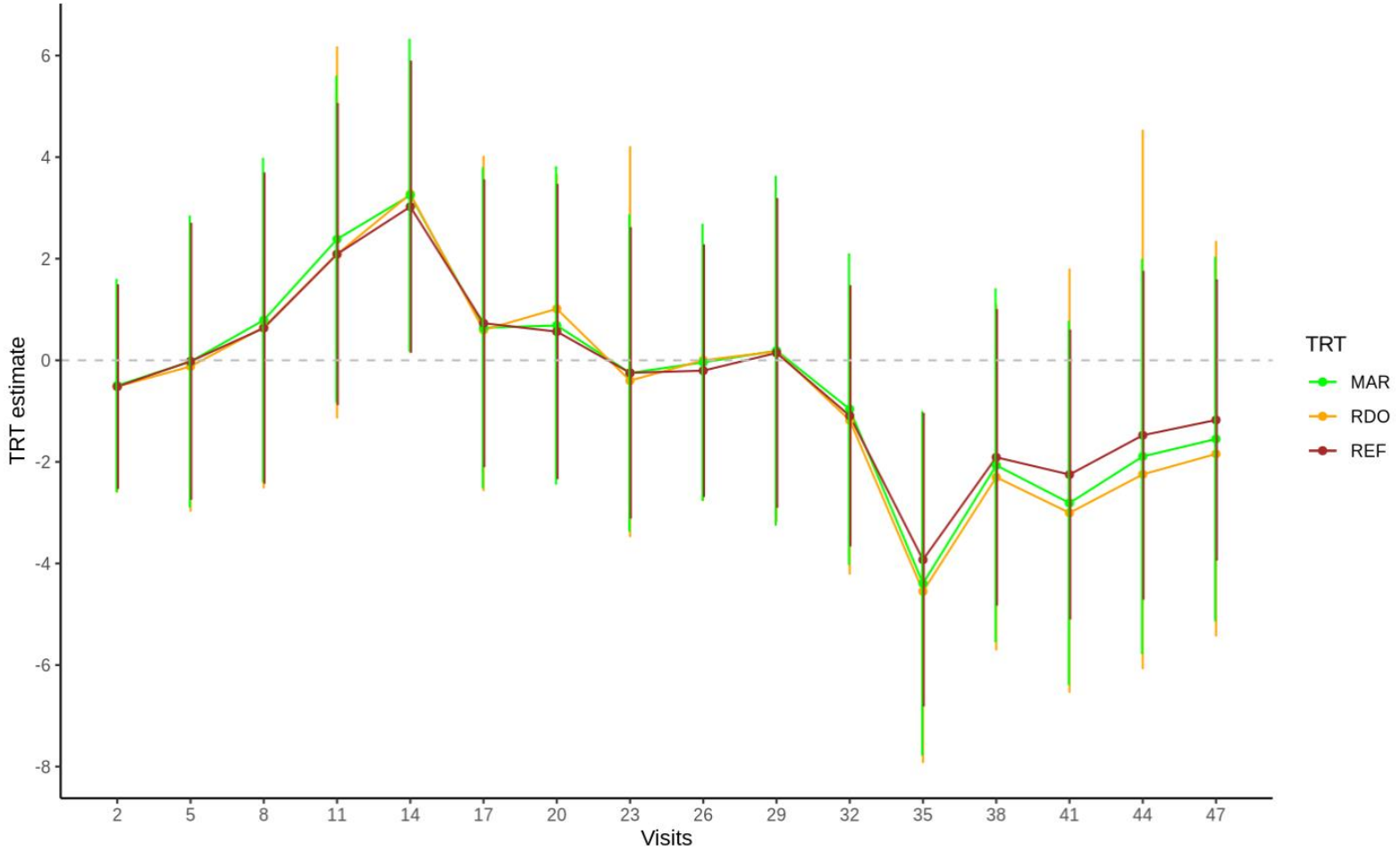
+ Easy to fit

- MAR is misaligned with estimand
- high missingness

Recover PRO baseline data

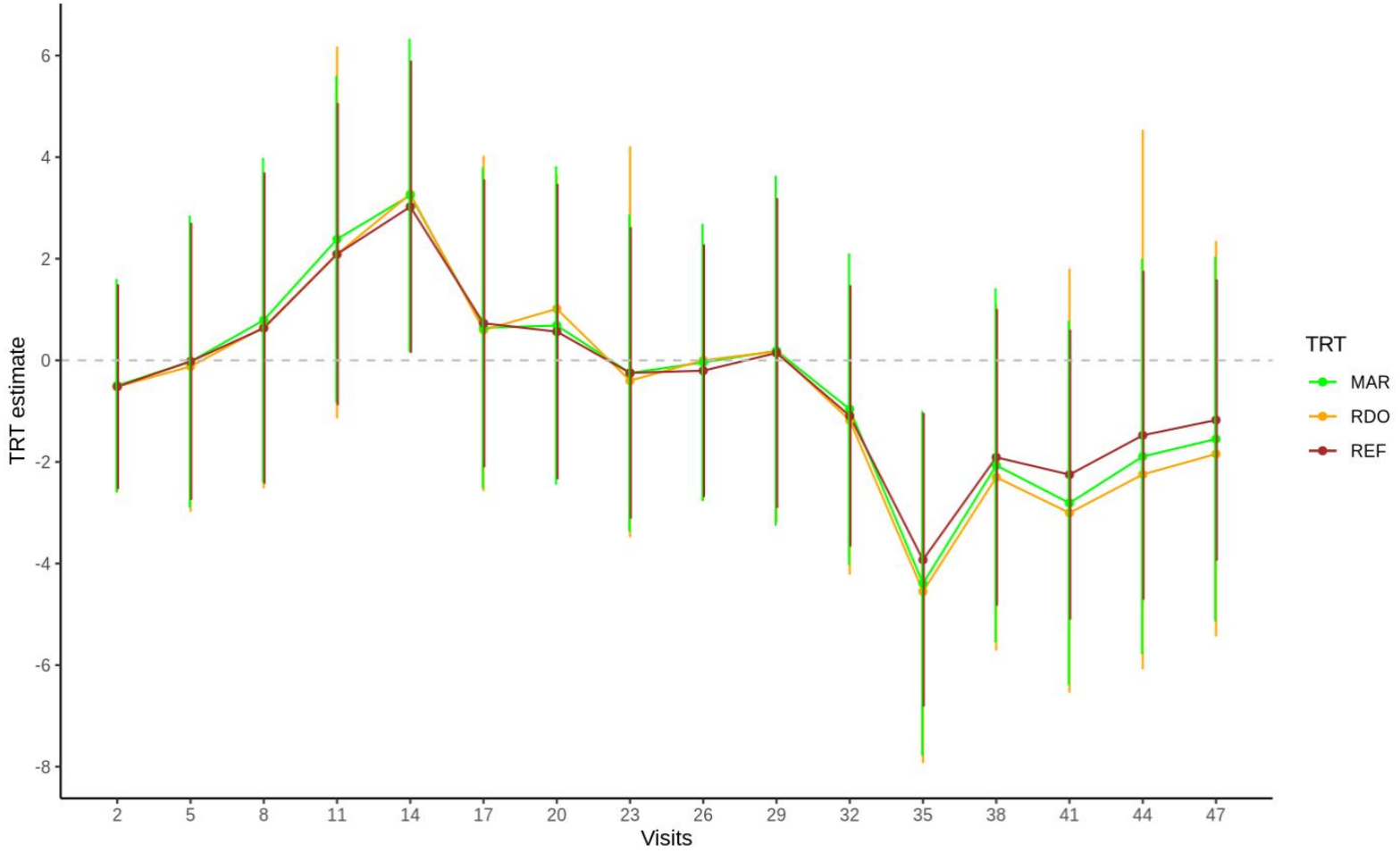


Alternative approaches – Pros and Cons



RDO:
+ Aligned with estimand
+ HA appropriate approach
- Dimensionality: `rbmi` Requires equivalent number of visits
- Challenging model fitting: covariance matrix and model terms
- High variance
- High dependence on low missingness
- Operationally challenging to plan at the design stage

Alternative approaches – Pros and Cons



MAR:
+ Easy implementation
- Misalignment with the estimand
- High variance

Reference-based:
+ Easy implementation and model fitting
+ HA appropriate
+ Alignment with the estimand
+ Lower variance
+ Similar performance to RDO
- May not be appropriate assumption for all ICE

Conclusions

- Goal – appropriately address missing data in a case study and align with estimand
- More advanced methods have more challenges:
  - may require higher quality of data - with less missingness and more dropout data
  - operational challenges at the planning stage
  - limitations of the software
- Recommendation: reference-based methods

Thank you!

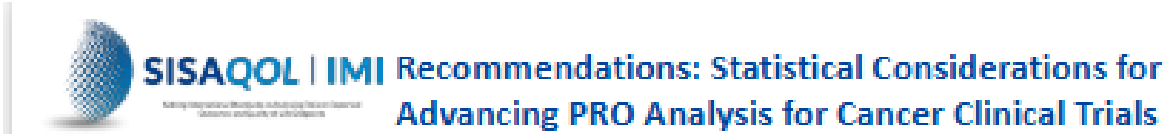
Hot Topics

Updates from our workstreams

- Knowledge Sharing – keeping up to date
- Structure Equation Modelling (SEM) approaches
  - Accepted as PSI poster
- Missing and aberrant PRO data in clinical trials – risk-based monitoring approach
- Diary data & intensive longitudinal data

Knowledge Sharing

- SISAQoL-IMI recommendations for PRO analysis in cancer clinical trials – see poster at PSI later today!



- FDA Core PROs in Cancer Clinical Trials
  - Final October 2024

- 2024 saw 1st two FDA labels with PRO tolerability information in the labels

Inavolisib/ITOVEBI – in breast cancer – PRO CTCAE and Modified bother item

Selpercatinib/RETEVMO – in thyroid cancer – FACT GP5 (side effects)

Knowledge Sharing

- Meaningful change/score interpretation – still in debate – 2025 publications
  - *FDA PFDD Guidance 4 still draft but in use and contains practical recommendations*
- COSMIN 2.0 guidelines for measurement properties of PROs published in March 2025
  - V1.0 was published in 2021 and well established; Version 2_0 is focused on


Quality of Life Research (2025) 34:151–160
https://doi.org/10.1007/s11136-024-03798-7

COMMENTARY

Conceptualizing meaningful between-group difference in change over time: a demonstration of possible viewpoints

Andrew Trigg[1] · Nicolai D. Ayasse[2] · Cheryl D. Coon[2]

Quality of Life Research
https://doi.org/10.1007/s11136-025-03952-9

COMMENTARY

Interpreting the meaningfulness of treatment effects estimated in parallel groups designs: comment on Trigg et al.

Kevin Weinfurt[1]

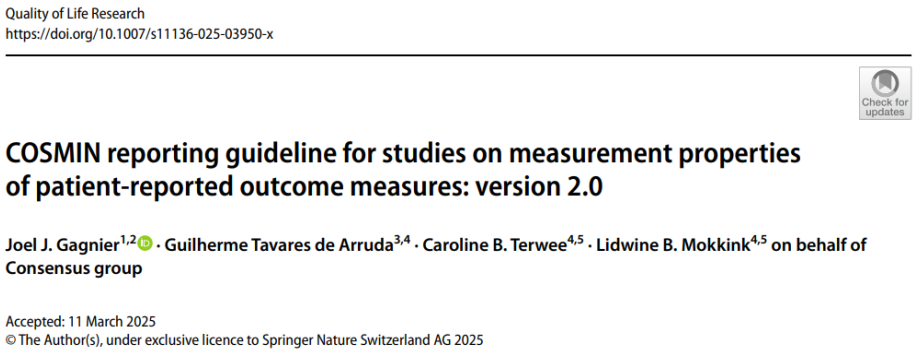
Pharmaceutical Statistics

WILEY

MAIN PAPER

Why "Minimal Clinically Important Difference" for Interpreting the Magnitude of the Treatment Effect Is Not Useful

Jitendra Ganju


Quality of Life Research
https://doi.org/10.1007/s11136-025-03950-x

COSMIN reporting guideline for studies on measurement properties of patient-reported outcome measures: version 2.0

Joel J. Gagnier[1,2] · Guilherme Tavares de Arruda[3,4] · Caroline B. Terwee[4,5] · Lidwine B. Mokkink[4,5] on behalf of Consensus group

Accepted: 11 March 2025

Note: PRO/COA key Guidance documents and summaries about them can be found on the PFDD SIG Webpage

Clinical Outcome Assessment (COA) data collection and monitoring is a Pharma Industry challenge

Ever-growing use of COAs in clinical trials becoming critical data: (co)primary or key secondary endpoints…
…But collecting, monitoring and analyzing COA data lead to challenges[1]

Increased requirements in SPONSOR RESPONSIBILITIES for oversight & review of audit trail data to ensure data integrity
ICH E6 Guideline for Good Clinical Practices (R3)on Risk-Based Monitoring[2] adopted on 6 Jan. 2025

Why monitoring COA data?

DETECTION	Detection of atypical sites	Detection of outlier at site level	Detection of trend (Region, Country, Site)	Detection of instruments structure issue or not well scored
IMPACT	investigation & trainings to sites, monitoring for next randomizations, stop recruitment in a site, data correction (central reviewer)	Impact on SAP: sensitivity analyses excluding atypical sites and /or participants	Impact on SAP: sensitivity analyses with stratification factor (region/site/country…)	Impact on the development plan: selection of COA for the indication, statistical analyses

Currently

Some quantitative risk-based monitoring tools are available but must be implemented with caution and appropriate safeguards

What may be the future?

Future tools may be extrapolated using more sophisticated methodologies to detect other types of issues (e.g. inconsistence of items, non-sense scores, ceiling and floor effects, intra- & inter-variability, threshold for outliers …)

[1]To know more about COA challenges:
- 4 FDA guidances about incorporation and evaluation of the patient's voice in drug development
- Several inter-industries and academics organizations dedicated to COAs: PFDD-SIG, DiMe, isoQoL, Mapi Research Trust…

[2]To know more about Risk-Based Monitoring (RBM) in general (non-COA related):
- Overviews: Risk-Based Monitoring in Clinical Trials: 2021 Update - PMC (nih.gov), Risk-Based Monitoring in Clinical Trials: Past, Present, and Future - PMC (nih.gov)
- Methodologies: Application of methods for central statistical monitoring in clinical trials - Amy A Kirkwood, Trevor Cox, Allan Hackshaw, 2013 (sagepub.com), https://www.lexjansen.com/phuse-us/2018/tt/TT13.pdf

Workstream:
Diary-data (Intensive Longitudinal Data (ILD))

Objectives of the ILD workstream

Context

Examples of ILD collected through:

- Diaries
- DHT

Types of ILD data encountered in drug development

Statistical methods for analyzing ILD

Thank you!

- Meet us all & find out more about joining our SIG during the conference
- Find us at the “SIG at the BAR” **Tuesday lunchtime**