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Inclusion of PROs in Dose-Finding Oncology Trials

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Primary goals of an early phase dose-finding oncology trial (DFOT)

(1) Evaluate the safety and tolerability of a new intervention,
(2) Determine the recommended dose(s) for further testing.

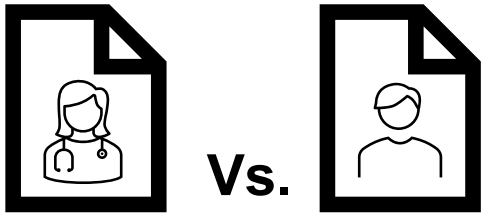
Defining tolerability

Standard definition from the International Conference on Harmonization (ICH)[1]:

“the degree to which overt adverse effects can be tolerated by the subject”

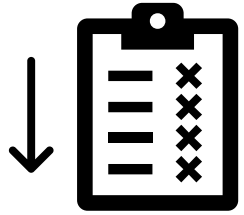
[1]Group IEEW. Ich harmonised tripartite guideline: Statistical principles for clinical trials. *Stat Med*. 1999;18(15):1905-1942.

Broadening tolerability definition and assessment



Differential reporting between clinicians and patients.[2]

"Hard to observe" side effects **not adequately characterised.**[3]



Physicians may **underreport** severe side effects.[2]

Broadening of the definition by Friends of Cancer Research[4]:

"A complete understanding of tolerability should include direct measurement from the patient on how they are feeling and functioning while on treatment."

[2]Di Maio M, Gallo C, Leighl NB, et al. Symptomatic toxicities experienced during anticancer treatment: Agreement between patient and physician reporting in three randomized trials. *Journal of Clinical Oncology*. 2015.
[3]Veitch ZW, Shepshelovich D, Gallagher C, et al. Underreporting of symptomatic adverse events in phase i clinical trials. JNCI: Journal of the National Cancer Institute. 2021.
[4]Basch E, Campbell A, Hudgens S, et al. Broadening the definition of tolerability in cancer clinical trials to capture the patient experience. 2020.

Current Patient-reported Outcome (PROs) landscape in dose-finding oncology trials

Current Use

- PRO use in dose-finding oncology trials is increasing.[5]

Quality Gaps

- 86% of DFOT papers reporting PROs lack clear PRO objectives.
- Considerable variability exists in PRO analytical approaches.[6]

"There is vast heterogeneity in the way PROs are analysed and subsequently presented within publications, this prevents comparison across study findings. Urgent improvement is needed."

[5]Lai-Kwon J, Yin Z, Minchom A, Yap C. Trends in patient-reported outcome use in early phase dose-finding oncology trials - an analysis of clinicaltrials.Gov. *Cancer Med*. 2021.
[6]Alger E, et al. Statistical methods and data visualisation of patient-reported outcomes in early phase dose-finding oncology trials: A methodological review. *eClinicalMedicine*. 2023

OPTIMISE (Incorporating Patient-Reported Outcomes in Dose-Finding Trials)

OPTIMISE-Research Objective Recommendations (ROR)

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

OPTIMISE-Analysis Recommendations (AR)

Identify appropriate statistical methods and data visualisation approaches to report PRO research objectives as per OPTIMISE-ROR.

OPTIMISE-Research Objective Recommendations

1. Methodological review
2. Two round Delphi survey
3. Consensus meeting

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International Consensus-Driven Recommendations for Patient-Reported Outcome Research Objectives in Early Phase Dose-Finding Oncology Trials: OPTIMISE-ROR

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Finalised OPTIMISE-ROR guidance

Recommendation 1: Critical PRO concepts recommended for assessing tolerability of investigational treatments:

(i) Overall Side Effect Impact
(ii) Symptomatic Adverse Events
(iii) Overall Health-Related Quality of Life

Recommendation 2: Utilise PROs to assess the tolerability of an investigational treatment across all DFOT settings, including:

(i) Dose escalation (with expansion cohort if applicable)
(ii) Expansion cohort(s)
(iii) Dose optimisation

Recommendation 3: Define PRO-based endpoints over defined time period and at each dose level/dosage.

Finalised OPTIMISE-ROR guidance

Recommendation 4: Utilise PRO measurements at final analysis to inform and support the selection of the recommended dose or dose range.

Recommendation 5: Utilise PROs in dose-finding oncology trials to inform the selection of PRO−related endpoints in the follow−on study (e.g. Phase II).

Recommendation 6: Define each PRO-related research objective in a dose-finding oncology trial, to guide the appropriate analytical approach, as either:

(i) Descriptive/exploratory,
(ii) Statistically powered.

OPTIMISE- **Analysis Recommendations**

OPTIMISE-Analysis Recommendations (AR)

Identify appropriate statistical methods and data visualisation approaches to report PRO research objectives as per OPTIMISE-ROR.

1. Literature review

2. Extract approaches and assess for relevance

3. Refine for clarity and ensure DFOT suitability

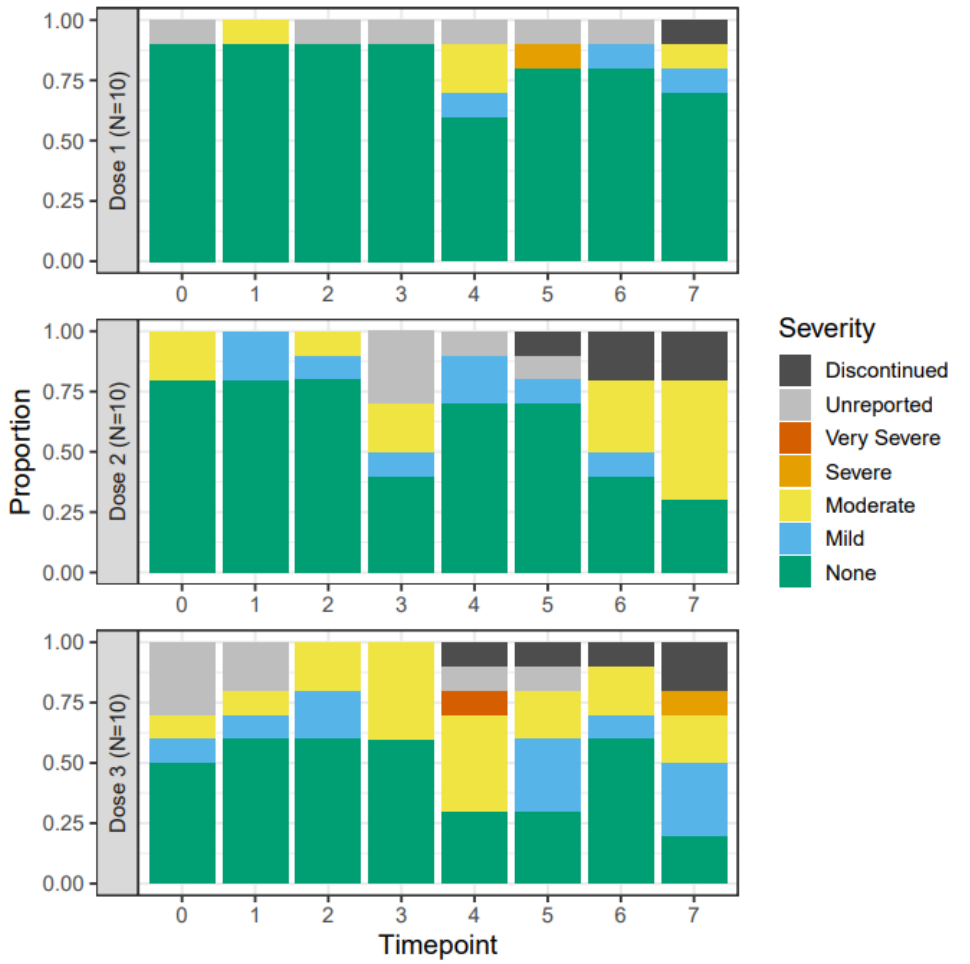
THE LANCET Oncology

A practical toolkit with recommendations for analysing and visualising patient-reported outcomes in early phase dose-finding oncology trials (OPTIMISE-AR)

Emily Alger, Antoine Regnault, Amylou C Dueck, Madeline Pe, Michael J Grayling, Melanie J Calvert, Aaron R Hansen, Olga Kholmanskikh, Julia Lai-Kwon, J Jack Lee, Anna Minchom, Yu Qiao, Khadija Rerhou Rantell, Jessica Roydhouse, Claire Snyder, Stefan N Symeonides, Nolan A Wages, Roger Wilson, Christina Yap

Example 1

- ✓ Suitable for critical PRO tolerability concept - symptomatic adverse events,
- ✓ PROs are visualised at defined doses and time points,
- ✓ Descriptive labels and traffic light colours indicate score meaning,
- ✓ Patients with missing data or intercurrent events are indicated,
- ✓ Figure presented in a clinical format with methodological rigour.



PRO-CTCAE symptom items severity scores at each timepoint for three doses with ten patients allocated to each dose. Category "Unreported" indicates patients with no PRO-CTCAE at baseline or post-baseline timepoints.

Example 2

Statistical Modelling Approach	Brief description	Key considerations for implementation and analysis in early-phase dose-finding trials		Exemplar use in published literature
		Strengths	Limitations	
(Generalised) linear models (GLMs)	Linear models estimate the relationship between a normally distributed response variable and covariates. Linear models can be extended to GLMs to allow for PRO response data to be of other data types.	GLMs provide a simpler alternative to GLMMs when comparisons between tolerability are only required between two time-points.[1]	GLMs do not support analysis across timepoints and are best suited to cross-sectional or study-defined fixed timepoint endpoints.	Within the Phase I setting, GLMs have been utilised to compare baseline-adjusted PRO scores at month 3 for two doses.[18]

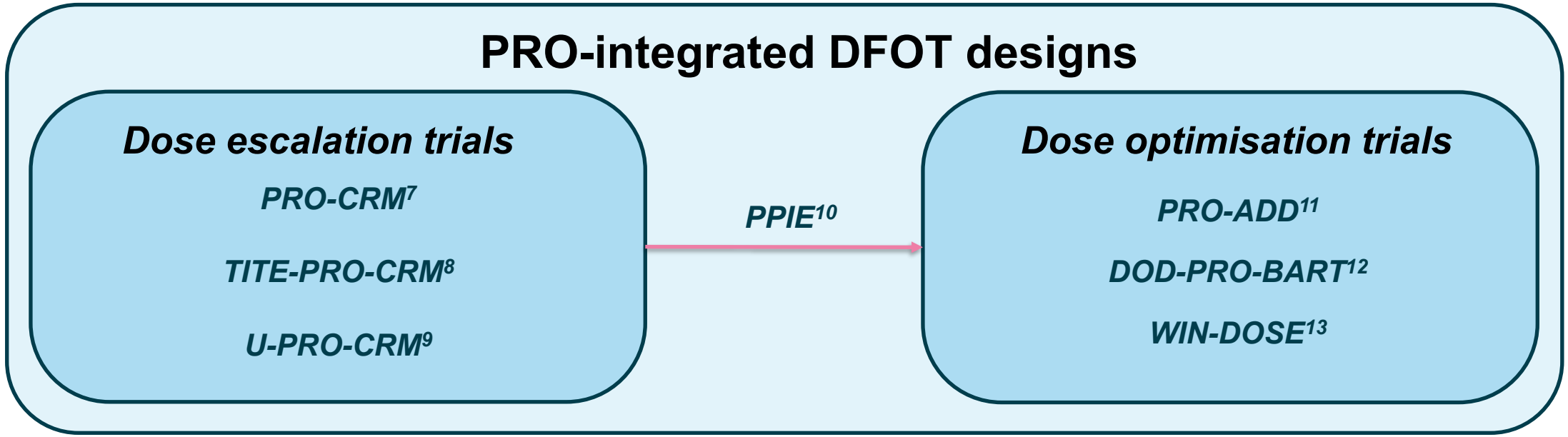
- ✓ Each analysis approach is evaluated with its strengths and limitations in the DFOT context,
- ✓ Approaches are assessed for relevance in exploratory and inferential settings,
- ✓ Existing evidence supporting their use in PRO analyses within DFOTs is referenced,
- ✓ Guidance is provided for exploratory and inferential analyses and PRO-informed dose-finding decision.

General considerations for statistical inference in DFOTs

PROs for exploratory analysis, estimation, and hypothesis testing

- ✓ More complex models can support statistical analysis, with clinically actionable inferences reported in more interpretable terms.
- ✓ If trialists use hypothesis testing, they should state whether it is exploratory or confirmatory.
- ✓ A trialist should clearly define research objectives so exploratory statistical analysis can help determine a recommended phase 2 dose.
- ✓ It is generally advisable to report not only p-values or point estimates, but also measures of uncertainty such as CIs or credible intervals in line with good reporting standards.

PROs embedded within dose-finding design for formal decision making



[7]Lee, S. M., Lu, X., & Cheng, B. (2020). Incorporating patient-reported outcomes in dose-finding clinical trials. Statistics in medicine, 39(3), 310-325.
[8]Andrillon, A., Biard, L., & Lee, S. M. (2025). Incorporating patient-reported outcomes in dose-finding clinical trials with continuous patient enrollment. Journal of biopharmaceutical statistics, 35(5), 839-850.
[9]Alger, E., Lee, S. M., Cheung, Y. K., & Yap, C. (2024). U-PRO-CRM: designing patient-centred dose-finding trials with patient-reported outcomes. ESMO open, 9(7), 103626.
[10]Alger, E., Van Zyl, M., Aiyegbusi, O. L., Chuter, D., Dean, L., Minchom, A., & Yap, C. (2024). Patient and public involvement and engagement in the development of innovative patient-centric early phase dose-finding trial designs. Research Involvement and Engagement, 10(1), 63.
[11]Alger, E., Mandrekar, S. J., Yin, J., & Yap, C. (2026). PRO-ADD: Patient-empowered dose-finding trials integrating safety, preliminary efficacy and patient-reported outcomes for optimal dose selection. Statistical Methods in Medical Research, 09622802261435969.
[12]Chung, Y. C., Zhao, Y., Liu, M., Lin, J., & Liu, R. (2025). Dod-pro-bart: Dose optimization design incorporating patient-reported outcomes via machine learning with bayesian additive regression trees. Statistics in Biopharmaceutical Research, 17(3), 347-356.
[13]Alger, E., Lin, R., Lee, J. J., Yuan, Y., & Yap, C. (2026). Generalized Pairwise Comparisons in Dose Optimization Oncology Trials: Beyond Safety to Multi-outcome Dose Selection. Clinical Cancer Research, OF1-OF10.

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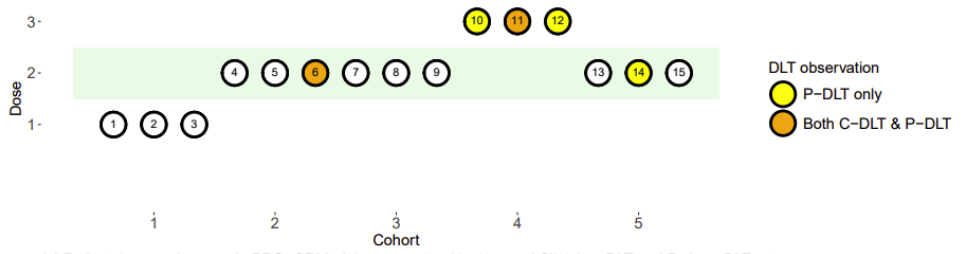
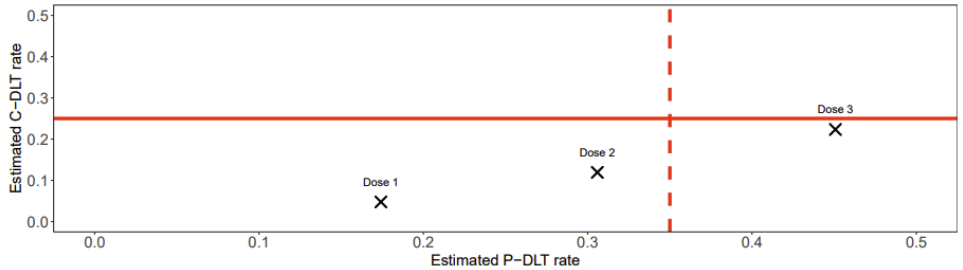


(a) Patient dose assignment in PRO−CRM trial case study with observed Clinician−DLT and Patient−DLT outcomes.

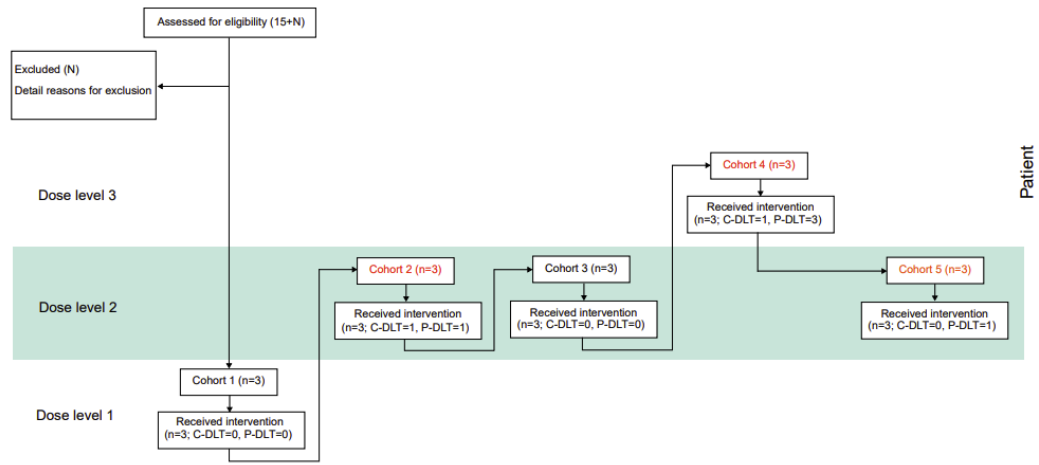


(b) Estimated P−DLT and C−DLT rate at final analysis.

B

	Clinician-DLTs				Patient-DLTs			
Dose	Prior C-DLT Rate	No. of Evaluable Patients	No. of C-DLTs	Estimated DLT rate (90% probability interval)	Prior P-DLT Rate	No. of Evaluable Patients	No. of P-DLTs	Estimated DLT rate (90% probability interval)
Dose 1	0.06	3	0	0.05 (0.01, 0.18)	0.10	3	0	0.17 (0.04, 0.39)
Dose 2	**0.14**	**9**	**1**	**0.12 (0.02, 0.30)**	**0.21**	**9**	**2**	**0.31 (0.11, 0.53)**
Dose 3	0.25	3	1	0.22 (0.07, 0.43)	0.35	3	3	0.45 (0.22, 0.65)

C



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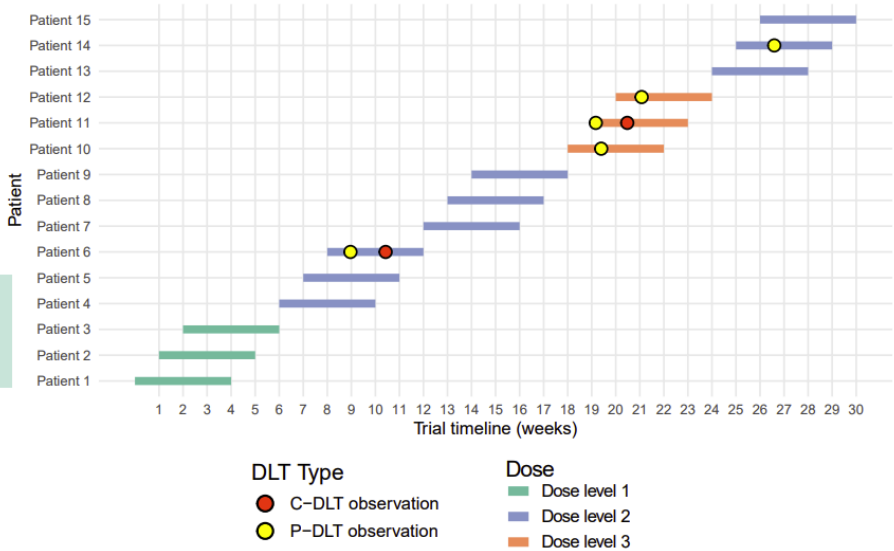

Conclusion

OPTIMISE-ROR provides consensus-based recommendations to support clearly defined PRO research objectives within early phase DFOTs.

OPTIMISE-AR provides a practical toolkit to support trialists in analysing and visualising PRO data in DFOTs, with implementation considerations and open-access R code.

As the importance of PROs in DFOTs continues to expand, OPTIMISE-ROR and -AR serve as foundation guidance and fit-for purpose resources

Empowering earlier, more impactful integration of patient voice in shaping tolerable, patient-centred decisions