EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Including patient preferences and patient-reported outcomes in global development programmes, submissions and labels

5th Industry Stakeholder Platform on R&D support

16 November 2020

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Involving patients - a progressive journey

1995
EMA created

1996
Dialogue with patients

2000
Patients become **Committee** members

2003
Working group with patients

2005
Framework of interaction with patient & consumer organisations

2006
Patient & Consumer **Working Party** (PCWP)

2014
Public Engagement **Department**

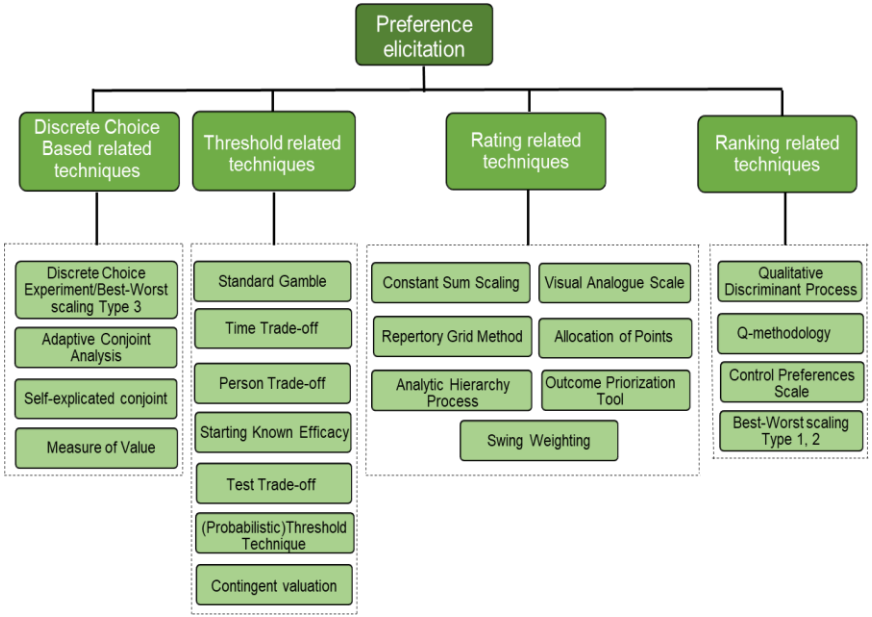
2017
Public **Hearings**

Involving young people

Today…
More systematic inclusion of patient input along medicine lifecycle

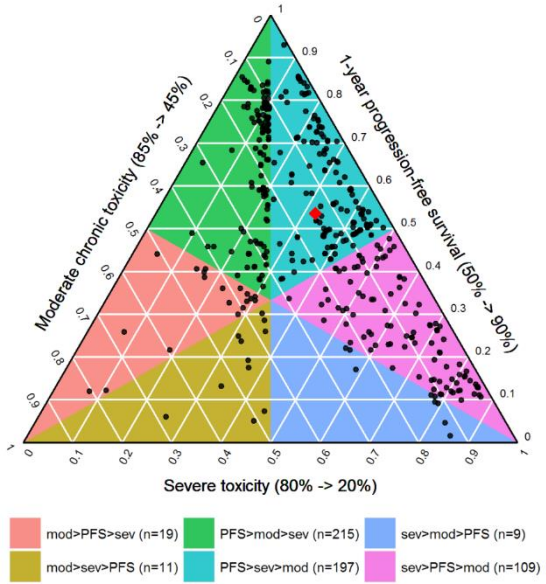
How to elicit preferences (trade-offs): old and new methods

- Key issues and concerns are being described (PREFER Project)
  - A description of commonly used and suitable methods
- Regulatory experience and guidance are currently lacking
- Impact for drug regulatory assessment and decisions?
  - Well suited for quantitative benefit-risk assessment



Soekhai et al., 2019, Value in Health & PREFER report

Trade-offs in benefit-risk assessment

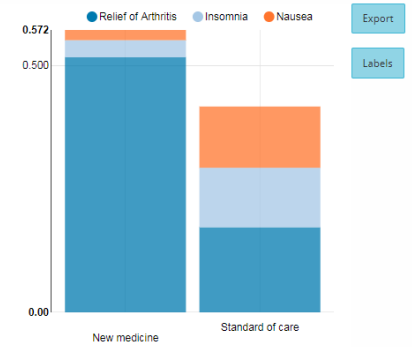


New medicine	Standard of care
0.572	0.417

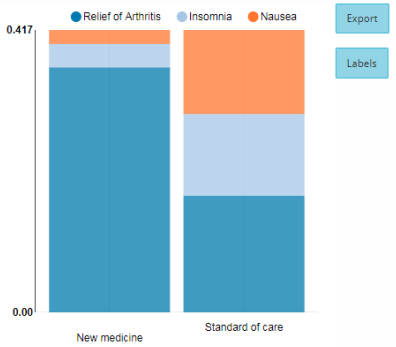
New medicine	Standard of care
0.417	0.417

Value profiles

Base case



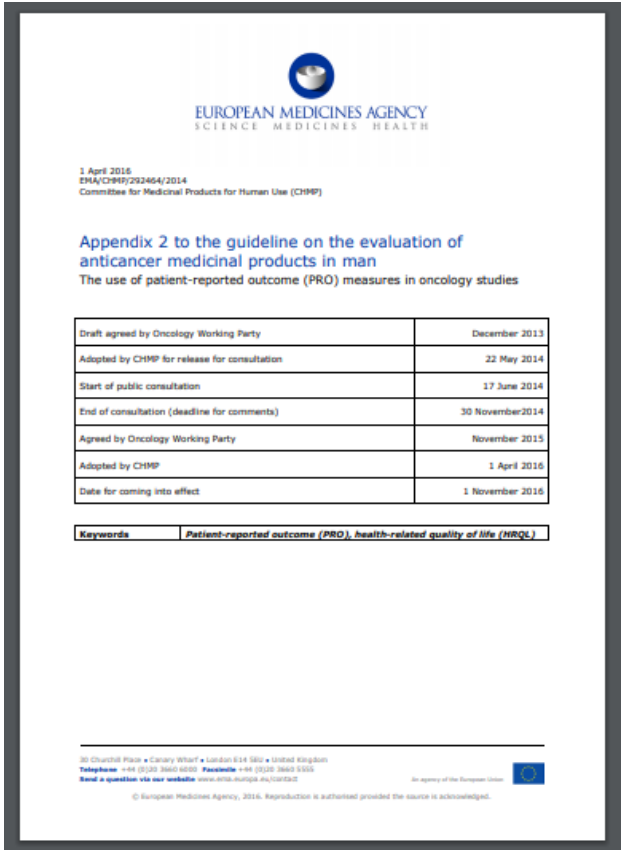
Recalculated case



Postmus et al. The Oncologist 2018; ADDIS 2, IMI Get Real

PROs in cancer drug applications

- Usefulness of describing patient utilities about treatments in oncology is increasingly recognised (CHMP anticancer guideline)
- PRO analyses are often included in pivotal clinical trials as secondary or exploratory endpoints
- Claims about the effect of a medicinal product on PROs, either positive effect or lack of negative effect, are often proposed



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1 April 2016
EMA/CHMP/292464/2014
Committee for Medicinal Products for Human Use (CHMP)

Appendix 2 to the guideline on the evaluation of anticancer medicinal products in man
The use of patient-reported outcome (PRO) measures in oncology studies

Draft agreed by Oncology Working Party	December 2013
Adopted by CHMP for release for consultation	22 May 2014
Start of public consultation	17 June 2014
End of consultation (deadline for comments)	30 November2014
Agreed by Oncology Working Party	November 2015
Adopted by CHMP	1 April 2016
Date for coming into effect	1 November 2016

Keywords	*Patient-reported outcome (PRO), health-related quality of life (HRQL)*

Possible guiding principles for assessment and labelling

- Claims in the SmPC will depend on:
  - Reliability and validity of the PRO effects described (scientific standards)
    - Adequacy of tools
  - Usefulness of knowledge of PRO effects and uncertainties for doctors and patients
    - May vary depending on the clinical setting
- Internationally agreed regulatory standards are needed
- Important ongoing initiatives standards: SISAQOL-IMI

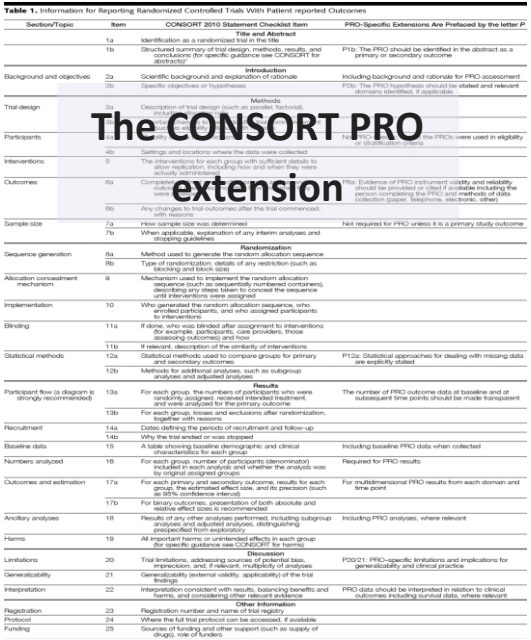


Table 1. Information for Reporting Randomized Controlled Trials With Patient-reported Outcomes

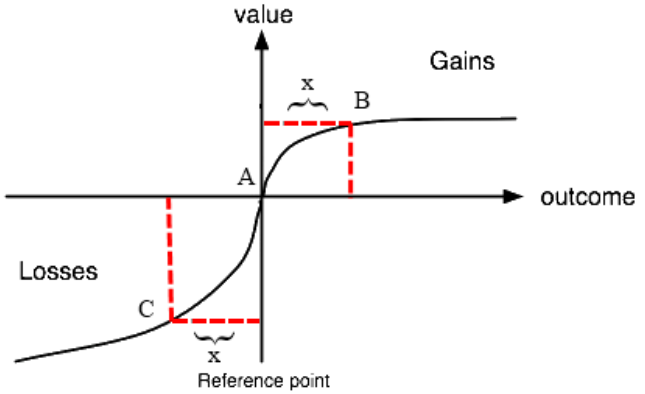
Section/Topic	Item	CONSORT 2010 Statement Checklist Item	PRO-Specific Extensions Are Prefaced by the letter P
		Title and Abstract	
	1a	Identification as a randomized trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)*	P1b: The PRO should be identified in the abstract as a primary or secondary outcome
		Introduction	
Background and objectives	2a	Scientific background and explanation of rationale	Including background and rationale for PRO assessment
	2b	Specific objectives or hypotheses	P2b: The PRO hypothesis should be stated and relevant domains identified, if applicable
		Methods	
Trial design	3a	Description of trial design (such as parallel, factorial), including allocation ratio	
Participants	4a	Eligibility criteria for participants	Number of missing PROs or stratification criteria
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	P6a: Evidence of PRO instrument validity and reliability should be provided or cited if available including the person completing the PRO and methods of data collection (paper, telephone, electronic, other)
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	Not required for PRO unless it is a primary study outcome
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
		Randomization	
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomization; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	P12a: Statistical approaches for dealing with missing data are explicitly stated
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
		Results	
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	The number of PRO outcome data at baseline and at subsequent time points should be made transparent
	13b	For each group, losses and exclusions after randomization, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Including baseline PRO data when collected
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Required for PRO results
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, the estimated effect size, and its precision (such as 95% confidence interval)	For multidimensional PRO results from each domain and time point
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	Including PRO analyses, where relevant
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
		Discussion	
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	P20/21: PRO-specific limitations and implications for generalizability and clinical practice
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	PRO data should be interpreted in relation to clinical outcomes including survival data, where relevant
		Other Information	
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

The CONSORT PRO extension

Calvert et al. *JAMA* 2013

The risk of "methodology aversion" in drug regulation

- Fear that toolboxes may turn into black boxes
- Uncritical adoption may lead to false conclusions and patient harm
- *Not* to use novel, robust methodologies has equally detrimental consequences
- Need to evaluate and validate methodologies ("qualify"): prospectively, well controlled, and according to a pre-agreed plan



Bauer et al. NRDD, 2014; Eichler et al. CPT, 2020

Take home messages

- Great opportunity for drug regulators to become more **systematic** about collecting patient trade-offs and utilities, and using them in the assessment or to inform doctors and patients
  - Well-suited for quantitative benefit-risk assessment methods
- Many types of new data and approaches: **validation** and **evaluation** ("qualification") are needed before **confidence** in methods and regulatory **guidance** can be produced