PRO Data Generation in Practice

A review of patient-reported outcomes used for regulatory approval of oncology medicinal products in the European Union between 2017 and 2020

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Disclaimers

- I declare having no conflict of interest.
- The views expressed in this presentation are the personal views of the author and may not be understood or quoted as being made on behalf of or reflecting the position of the Portuguese Authority for Medicines and Health Products (INFARMED), the European Medicines Agency (EMA) or any of its committees or working parties/groups the author is affiliated with.
- Research conducted at the University of Lisbon/Faculty of Pharmacy (Master in Regulation and Evaluation of Medicines and Health Products).

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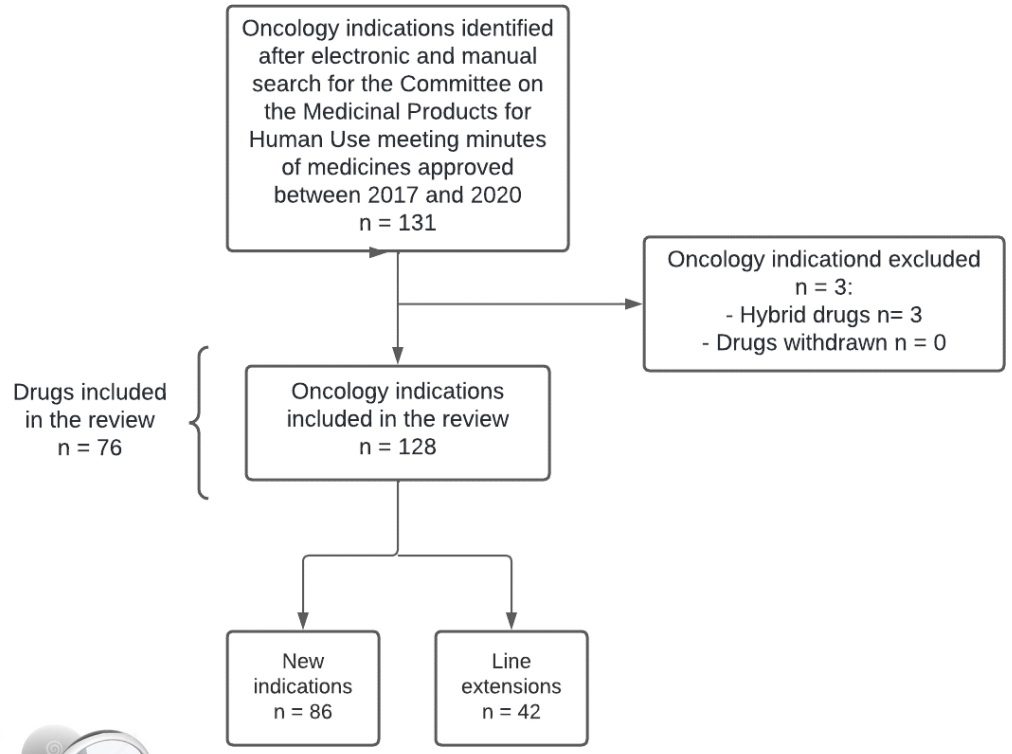
Background & objectives

- **Cancer diseases**, and **their respective treatment regimens**, are associated with significant **negative symptoms**, **side effects** and **functional limitations**.

- Collection of patient-reported outcomes (PRO) in clinical trials gained special interest and is recommended by regulatory authorities. **PRO may provide evidence** to **support medicines approval, labelling and marketing claims**.

- To analyse the **data based on PROs of new oncology indications granted a market authorization by the European Commission following a positive opinion by EMA** between **2017 and 2020** and to **identify PRO related label claims granted**.

Methodology & studies that included PRO



EPAR and SmPC were reviewed to identify use PRO and PRO claims

100 (78.1%) oncology indications included PRO in the confirmatory clinical trials:

- 37 indications supported by double-blinded RCT.
- 63 indications supported by open-label trials.
- Out of 104 confirmatory trials, PRO defined as a secondary endpoint in 60 studies (57.7%), exploratory in 31 (29.8%) and as both in 13 (12.5%).

PRO measures selected

- A total of 54 different measures were used, of those 41 (75.9%) were disease-specific measures.
- 82.7% of the trials used >=1 PROM (a total of 240 PROM were used across the 100 indications with PRO data)

Patient-Reported Outcome Measure	Number of times used (n, %)
Euroqol-5 Dimension Index	**70 (29.2%)**
Other Generic measures	18 (7.5%)
European Organisation for Research and Treatment of Cancer (EORTC) modules	**99 (41.3%)**
EORTC QLQ-C30 with EORTC disease-specific module	32 (32.3%)
EORTC QLQ-C30 without EORTC disease-specific module	30 (30.3%)
Functional Assessment of Chronic Illness Therapy (FACIT) measures	**41 (17.1%)**
FACT-G with FACT disease-specific measure	3 (7.3%)
FACT-G without FACT disease-specific measure	2 (4.9%)
Other Disease-specific measures	12 (5.0%)
Total	240 (100%)

SmPC claims & EPAR reviewers' commentaries

- 128 approved oncology indications (2017-2020)
  - 100 (78.1%) oncology indications included PRO in confirmatory trials
    - 22 (17.2%) indications included label claims in the SmPC (the majority corresponding to solid tumors).
      - 11 (50%) were supported by randomised open-label studies, 10 (45.5%) by double-blind RCT and 1 (4.5%) was by an open-label single arm trial study.
      - PRO was selected as a secondary endpoint in 16 studies (72.7%), as exploratory in 4 (18.2%) and as both secondary and exploratory in 2 (9.1%).
    - 76 indications had EMA reviewers' comments provided on PRO included in the EPAR.
      - EMA reviewers' comments provided possible **reasons for not included PRO data in the SmPC** for **34 (44.7%) indications** (for a total of 20 indications no reason for claim refusal was identified).

EPAR reviewers' commentaries

Reasons for PRO label claims exclusion identified in EPAR reviewers' comments	Number of indications (n,%)
Study conduct	
Data should be interpreted with caution as there was no blinding of the study treatment	1 (1.3%)
Potential bias in PRO data as a result of blinding failure	2 (2.6%)
Interpretability of QoL results and therefore their **clinical relevance is unclear/limited**	**8 (10.5%)**
Rational for timing and frequency of PRO collection was not fully described with regard to population, disease and/or treatment regimen	4 (5.3%)
PRO analysis was not robust enough or did not even exist	4 (5.3%)
PRO analysis was considered exploratory	4 (5.3%)
PROM selection	
PROM selected was not considered optimal	4 (5.3%)
Missing data	
Handling missing data was not included and/or sufficient	2 (2.6%)
Reliability of the results was hampered due to **missing data**	**5 (6.6%)**
Study design	
Value of data was questionable and caution in interpretation is needed when **using open-label design**	**16 (21.1%)**
No firm conclusion could be drawn from the QoL data of single arm trials	2 (2.6%)

**A comment may include one or more reasons for PRO label exclusion; percentage calculated for the total of EPAR reviewers' commentaries*

Conclusion

- Despite **growing recognition on the value of PRO data** for the development of improved cancer therapies, PRO implementation remains challenging.

- Between 2017-2020, EMA granted **PRO labelling to 22 (17.2%) out of 128 oncology indications**. **78.1% included PRO data in confirmatory trials**.

  - **Gnanasakthy *et al*** (Value in Health, 2019): Between 2012-2016, EMA granted PRO labelling to 21 (32.8%) out of 64 oncology indications approved. **70% included PRO data in confirmatory trials**.

- Several key concerns were identified regarding PRO implementation including the **rationale**, **study conduct** (data collection, training, management and analysis), influence of **study design**, **missing data** and **PROM selection**.

Take-home message

- While **PRO implementation remains challenging**, **there is added value benefits in their use**, namely for both **research and clinical practice**, contributing to **share decision-making processes**, supporting HTA decisions, and ultimately **enhancing healthcare systems.**

  - But **methodological robustness, consistency of outcome reporting** and **early dialogue with regulatory agencies** are paramount.

Thank you!