Learnings from…

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

Carla Torre
University of Lisbon | Faculty of Pharmacy

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- 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.
- Academic 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

- **Capturing patient's perspective** during clinical trials in the oncology setting is an **opportunity to collect** unique information on the **patient's experience of the disease, its treatment, including the impact on their quality of life (QoL > longevity)**.

- **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**.

Objectives

- 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**.

Methods

- Two independent investigators identified **new oncology indications**, **including line extensions**, granted a market authorization by the European Commission **between 2017 to 2020**. Medicinal products with one or more indications approved within study timeframe were included.

- For each each medicine/indication **EPAR and SmPC were retrieved**.

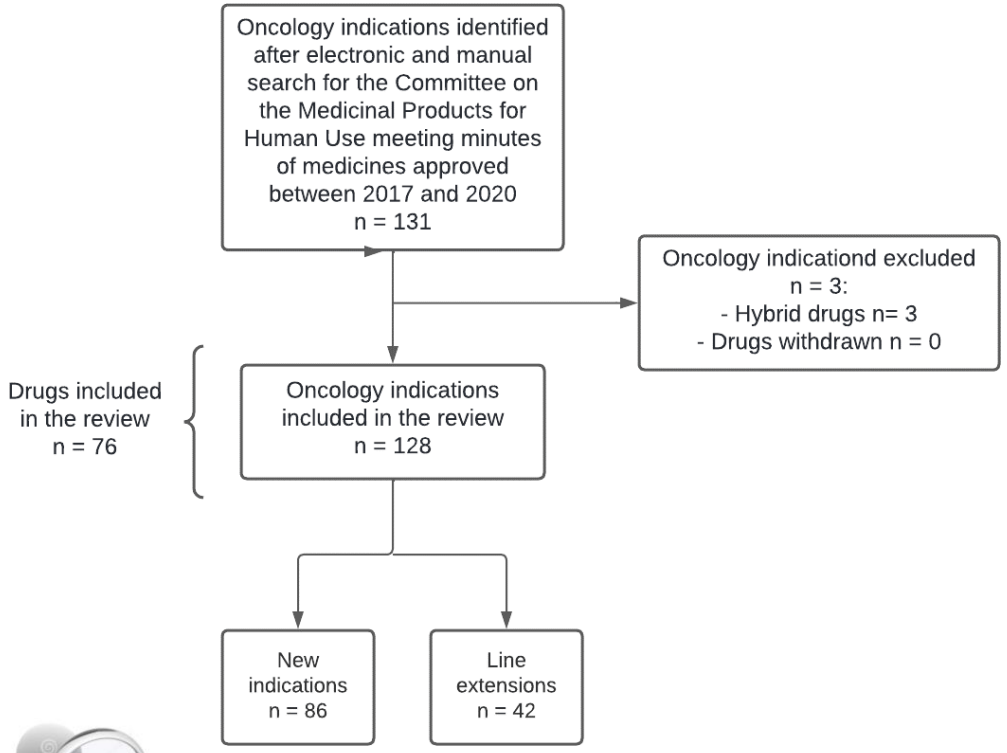
✓ <u>EPAR data extraction</u>

- Brand Name and International Non-proprietary Name (INN)
- Therapeutic Indication
- Marketing Authorisation Holder
- Main Study(ies) supporting submission
- Study Design
- Comparator(s)
- Number of Patients
- **Presence of PRO and PROM**
- **PRO endpoint status (primary, secondary and/or exploratory)**
- **PROM designation**
- **EPAR assessment comments were extracted to potential identify causes for inclusion and/or exclusion of SmPC label claims**

✓ <u>SmPC data extraction</u>

- 5.1 Pharmacodynamic Properties of the screened SmPC was reviewed for PRO label claims

Characterization of 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%).
      - Among the studies with SmPC claims granted, only one enrolled <200 patients
    - 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 could be identified).

EPAR reviewers' commentaries

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

**A comment may include one or more reasons for PRO label exclusion*

Strengths & limitations

- This review **only examined new oncology indications** approved by EC between **2017 and 2020**, hence **PRO use and PRO labelling claims** on oncology medicinal products, **cannot be fully characterized**.
- It was **inferred that when including a PRO in a clinical trial, a PRO label claim was intended**, which could have biased our result interpretation.
- Review based only on **available public information** (other documents such AR were not part of this study).

- ✓ Compared with previous reviews, this review provides a more **comprehensive overview of how PRO measures have been used to support regulatory decision–making (2017-20)**.
  - ✓ Identification **of potential causes for PRO claims not being granted**. Such insights provide an important perspective on the future challenges of using PROs in oncology clinical trials field.

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**.

Summary remarks

- 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!