The Role of Patient-Reported Outcomes in Marketing Authorization Applications and Product Labelling (2018-2020)

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SAMENVATTING

ACHTERGROND

Weinig is bekend over de rol die Patient-Reported Outcomes (PROs) spelen binnen de belangrijkste klinische studies in een registratiedossier, en welke invloed zij hebben op de baat-risicoverhouding en product labeling

METHODE

Wij hebben de European Public Assessment Reports (EPAR's) van nieuw goedgekeurde en geweigerde producten (tussen 1 januari 2018 en 31 december 2020) geëvalueerd. De primaire en secondaire eindpunten van de belangrijkste studies, baat-risicoverhouding, effecttabellen (resultaten die een sterke invloed op de beoordeling hebben) en SmPC (voor besluitvorming over patiëntenzorg) werden geëvalueerd voor elke vermelding van een PRO.

RESULTATEN

In totaal voldeden 149 producten aan onze criteria. Hiervan noemden 84 (56,40%) PRO's. PRO's werden significant meer gebruikt als secundair eindpunt en waren significant meer gebruikt bij de besluitvorming voor medicatie voor chronische behandelingen in vergelijking met acute en preventieve behandelingen. Bovendien speelde de ziektecategorie een belangrijke rol in PRO-gebruik en PRO-bijdrage. Bij aandoeningen van de luchtwegen waren PRO's bijvoorbeeld in 100% van de effecttabellen en SmPC opgenomen. In tegenstelling tot infectieziekten, waar PRO's respectievelijk 5% en 0% terecht kwamen in de effecttabellen en SmPC. Bovendien was de bijdrage van PRO's uit geblindeerde onderzoeken significant meer bij aan de besluitvorming over patiëntenzorg in vergelijking met open-label onderzoeken 3.836 (95% CI 1.802-8.167, p <0.01).

CONCLUSIE

Verschillende productdeterminanten kunnen een rol spelen bij het gebruik en de bijdrage van PRO's aan de beoordeling en besluitvorming over patiëntenzorg. Over het algemeen is er een geleidelijke toename te zien in de bijdrage van PRO's ter ondersteuning van het verlenen van vergunningen voor geneesmiddelen. Ze wegen steeds meer mee bij de afweging van de baten-risicoverhouding.

ABSTRACT

BACKGROUND

Little is known about the role Patient-Reported Outcomes (PROs) play in, the main clinical studies, the benefit-risk assessment, product labelling, and which determinants play a role herein.

METHOD

We evaluated the European Public Assessment Reports (EPARs) of new medicinal agents with a regulatory decision (approved or refused) by the EMA between January 1, 2018 and December 31, 2020. The primary and secondary endpoints of the main studies, benefit-risk balance, effect tables (results that have a strong influence on the assessment) and SmPC (for patient care decision-making) were evaluated for any mention of PROs.

RESULTS

A total of 149 products met our criteria. From these, 84 (56.40%) mentioned PROs. PROs were used significantly more as a secondary endpoint and contributed significantly more to patient care decision-making by chronic treatment compared to acute and preventive treatment. Furthermore, the disease category played a significant role in PRO use. For example, by respiratory conditions, PROs weighed in on 100% of the effect tables and SmPC. In contrast to infectious disease, where PROs weighed in on 5%, and 0% of their effect tables and SmPC, respectively. Moreover, PROs from blinded studies contributed significantly more to patient care decision-making compared to open-label studies 3.836 (95% Cl 1.802-8.167, $p < 0.01$).

CONCLUSION

In conclusion, different product determinants play a role in the utilization and contribution of PROs to the assessment and patient care decision-making. Overall, more PRO claims are being approved by the EMA and a gradual increase is seen in their contribution to support drug licensing. They are weighing in more and more on the benefit-risk balance assessment.

INTRODCUTION

Medicine is developed to help patients with their disease-related problems. After development and before marketing, pre-clinical and clinical testing is performed to address any concerns surrounding the benefit-risk balance of the new medicinal agent. (1) In the past, mainly objective outcomes, such as tumour size, were measured. However, a complete evaluation of the effectiveness and safety of a medicinal agent is impossible without direct input from the patients' perceived benefit. This input is also known as Patient-Reported Outcomes (PROs). (2)

Taking the patient voice into consideration, PROs assess the patient perspective concerning disease and the impact of treatment. These outcomes come directly from the patient without being interpreted by others e.g., the patient's clinician. (3-6)These are subjective outcomes and reflect how patients feel. PROs help to clarify the extent a patient is suffering and their level of satisfaction with the treatment. (3-7) Furthermore, they translate the effect seen in objective outcomes (e.g., tumour shrinkage) in terms of clinical relevance (4, 5, 7). PROs reported in product labelling provide clinicians access to relevant treatment information, as perceived by patients. Also, it may add to patient care decision-making. (8, 9) Considering the patient is at the centre of health care, it is within reason to assume that these outcomes are as essential as outcomes reported by clinicians. (3)Additionally, PROs may support claims made by the marketing authorisation holder in product labelling. (2, 3, 6, 7, 10)

According to DeMuro et al., 47% of medicinal agents approved between 2006-2010 had a minimum of one PRO-related claim approved by the European Medicines Agency (EMA) and 19% by the Food and Drug Administration (FDA). (11) A constructive ClinicalTrials.gov review, found PRO use in clinical trials has increased from 14% to 27% between 2004-2007 and 2007-2013, respectively. (12) Regardless, little information is available about, 1) how often PROs are utilized in the main studies of a clinical development plan of an agent, 2) the role they play in the benefit-risk assessment leading to product licensing 3) their contribution to product labelling, and 4) which determinants play a role herein (e.g., treatment type).

In this research, we aimed to evaluate if PROs were utilized as a primary- and/or secondary endpoint and if these results contributed to the benefit-risk balance assessment, and their contribution to product labelling. Second, we aimed to evaluate variables (e.g., disease condition) that may determine PRO use.

We suspect that PROs play an essential role in drug licensing of new products. Furthermore, that they are less popular among some disease categories (e.g., CVS vs. CNS) because objective outcomes are easier to measure. We also assume PROs are more important among chronic treatments compared to short-term treatments. We assume this because in short term treatments the focus is usually curing the disease (e.g., infectious diseases). Lastly, the study design (e.g., open label versus double-blind studies) may hamper the trustworthiness of PROs and prevent their contribution to product labelling.

METHOD

STUDY DESIGN

In this review, we evaluated whether medicinal agents submitted to and assessed the European Commission (EMA) between January 1, 2018 and December 31, 2020 utilized PROs as a primary- and/or secondary endpoint and if these results contributed to the benefit-risk assessment and product labelling. Excluded were medicinal without an authorisation status, veterinary products, generic products, biosimilars, vaccines, and diagnostic agents. **(See Appendix A)**

DATA SOURCES

EPAR-PUBLIC ASSESSMENT REPORT

In Europa, every medicinal agent (approved or refused for marketing authorization) has a detailed European Public Assessment Report (EPAR). *The selected EPARs were retrieved from the table of EPARs for human and veterinary use excel sheet* found *on the EMA website* (13). The EPAR-Public Assessment Report contains detailed, useful, transparent and straightforward information concerning the evaluation process of the product. (13, 14) In this report the main studies in support of a Marketing Authorization as summarized. (15) The benefit-risk balance section of the EPAR contains regulatory considerations/discussions, evaluating the sought-after benefits of a product compared to the risks of unwanted side effects. (13). The benefit-risk discussion is complemented with the effect table, which presents the most essential results for the approval or refusal of the product. So, if a PRO is mentioned in the benefit-risk section of the EPAR and especially in the effect table, this suggests that the PRO has an impact in the decision-making. Note that each EPAR is specific for one medicinal agent/product. So EPAR and product are used as interchangeable terms i.e., in the results we mention products.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

If a medicinal agent is approved, they have an SmPC. The SmPC reflects the conditions of the licencing (e.g., how product should be used). The SmPC contains detailed information for clinicians. (13) Specifically we looked at section 5.1 of the SmPC. Important results from the main studies are included in section 5.1 to help clinicians to determine if their patient resembles the patients in the studies and what to expect from the treatment. If PROS are mentioned here, they contribute to the patient care decision-making.

MAIN STUDIES

Main studies in the EPARS were evaluated for PRO use as primary and/or secondary endpoint. To identify the main studies, the term pivotal was used as a search term. For practical reasons only the term main studies will be used. Furthermore, if a EPAR had more than four main studies, we restricted the evaluation to four studies chosen at random.

OUTCOMES

PRIMARY OUTCOMES

For each medicinal agent it was determined If PROs were used a primary- (yes/no) and/or secondary endpoint (yes/no) **in any** of its main studies. If PROs were mentioned in the benefit-risk balance (yes/no), contributed to the effect table (yes/no), and were mentioned SmPC (yes/no). Lastly, if they were mentioned in any of the above (yes/no).

SECONDARY OUTCOMES/DETERMINANTS FOR PRO USE

Second, we aimed to evaluate variables (e.g., disease condition) that may be determinants for PRO use. Variables determined were treatment type (acute- (yes/no), chronic- (yes/no), or preventive treatment (yes/no)), orphan design (yes/no), authorization (yes/no), disease category, if the main studies were blinded (yes/no), randomized (yes/no). Further, the duration of the study design and the duration of the double-blind were also determined. The PRO collection method (interview (yes/no), diary/electronic method (yes/no)), PRO instrument(s) used, and novel instrument (yes/no) were also collected. **(See Appendix A)** Furthermore, we determined if a product was for acute, chronic, or for preventive treatment based on its indication, dosage, and the duration of the treatment. Chronic were defined as long-term illness (e.g., heart disease, diabetes) and acute as short-term treatment (e.g., treating a urinary tract infection). Preventive was defined as a treatment used to prevent or avoid disease or its sequelae (secondary prevention) (e.g., hypertension). **(See Appendix A)**

POSITIVE CONTRIBUTION

In our protocol a positive contribution of a PRO was defined as PROs mentioned in the effect table and benefit-risk assessment and benefit-risk discussion. However, during our analysis, we decided that a PRO mentioned in effect table carried the most weight because these were the most essential results used to evaluate the sought-after benefits of a product compared to the risks of unwanted side effect to support product licensing. **(See Appendix A)**

KEY TERMS

Terms used for data extraction were scale, diary, electronic, satisfaction, questionnaire, QoL, Hrqol, VAS, measure, open-label, blinding, randomized, randomization, duration, outcomes, endpoints, duration, a secondary endpoint, the primary endpoint, quality of life, health outcome, health-related quality of life, health-related. PRO, the patient reported, patient-reported, pain, main studies, main study, and main, pivotal.

ANALYSIS

Descriptive statistics were used to present how many and the percentage of products that used PROs, as a primary and/or secondary endpoint in any main study, in the benefit-risk balance, effect table, SmPC. We explored if and which other endpoints also contributed to the effect table or SmPC. How many and mean percentage of treatment types, disease categories, instruments, and collection methods were calculated. The Chi-Square test was used to explore possible association between these determinants and PRO use and their contribution to the benefit-risk, effect tables and SmPC. Binary logistic regression was used to explore if orphan design and authorization

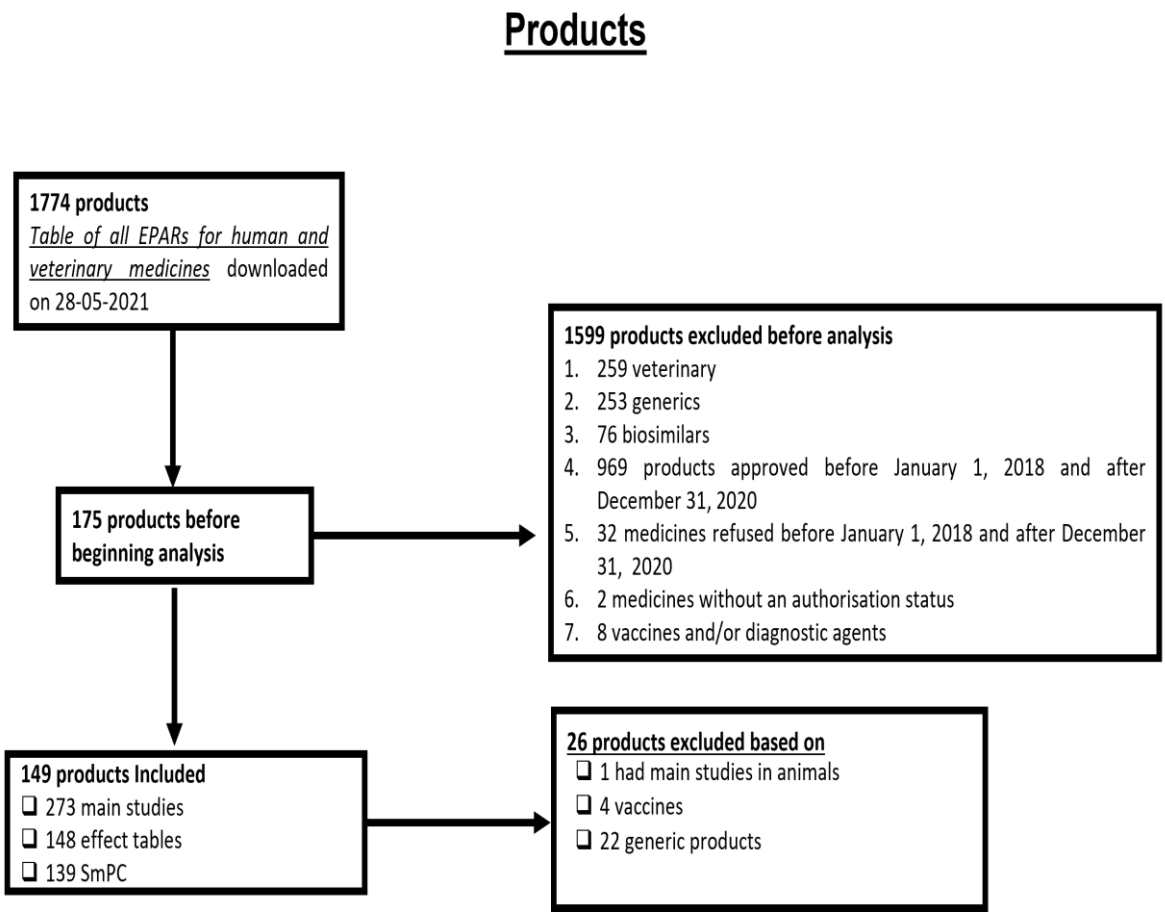

Figure 1 shows the product extraction process used and the number of products included in this study. A total of 1599 products were excluded. This was done by narrowing down the table of EPARs using steps 1-7.

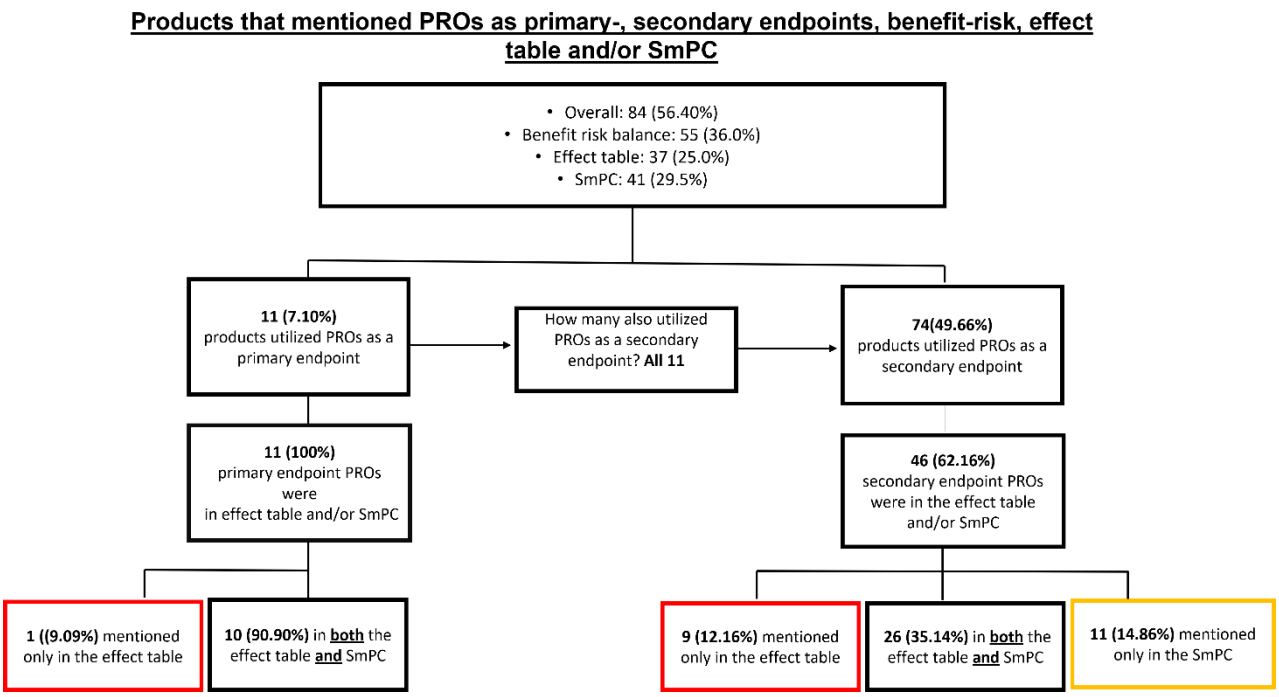

Figure 2 Illustrates the number of our products that mentioned PROs and also how often they were mentioned in the benefit-risk, effect tables, and SmPC. Furthermore, this figure shows how many PROs were used as primary/secondary endpoints, and how many of these contributed to effect tables and SmPC.

status were determinants associated with PRO use and their contribution to the benefit-risk, effect table, and SmPC. Possible associations between sample size, blinding, randomization, duration of the double-blind, duration of the study design and PRO use were analysed. With Binary logistic regression, the odds ratios (OR) and 95% confidence intervals (Cls) were calculated, and a $p \leq 0.05$ was considered statistically significant. Our analysis was done using spss Statistics 20 (IBM SPSS Inc.). **(See Appendix A)**

RESULTS

PRODUCTS

The table of EPARs for human and veterinary use contained 1774 products for screening. A total of 149 products between January 1, 2018 and December 31, 2020 met our inclusion/exclusion criteria, 10 of which were refused. The products had a total of 273 main studies, 148 effect tables, and 139 SmPC **(Figure 1)**.

OUTCOMES

PRIMARY OUTCOMES

In total 84 (56.40%) products utilized PROs. Overall, 37 (25%) and 41 (29.50%) products mentioned PROs in the effect table and SmPC, respectively **(Figure 2)**. In three effect table exploratory endpoint PROs were mentioned. In the SmPC, 6 products mentioned PRO endpoints from: exploratory endpoint (3), tertiary endpoint (1), non-main study (1) and other endpoint (1).

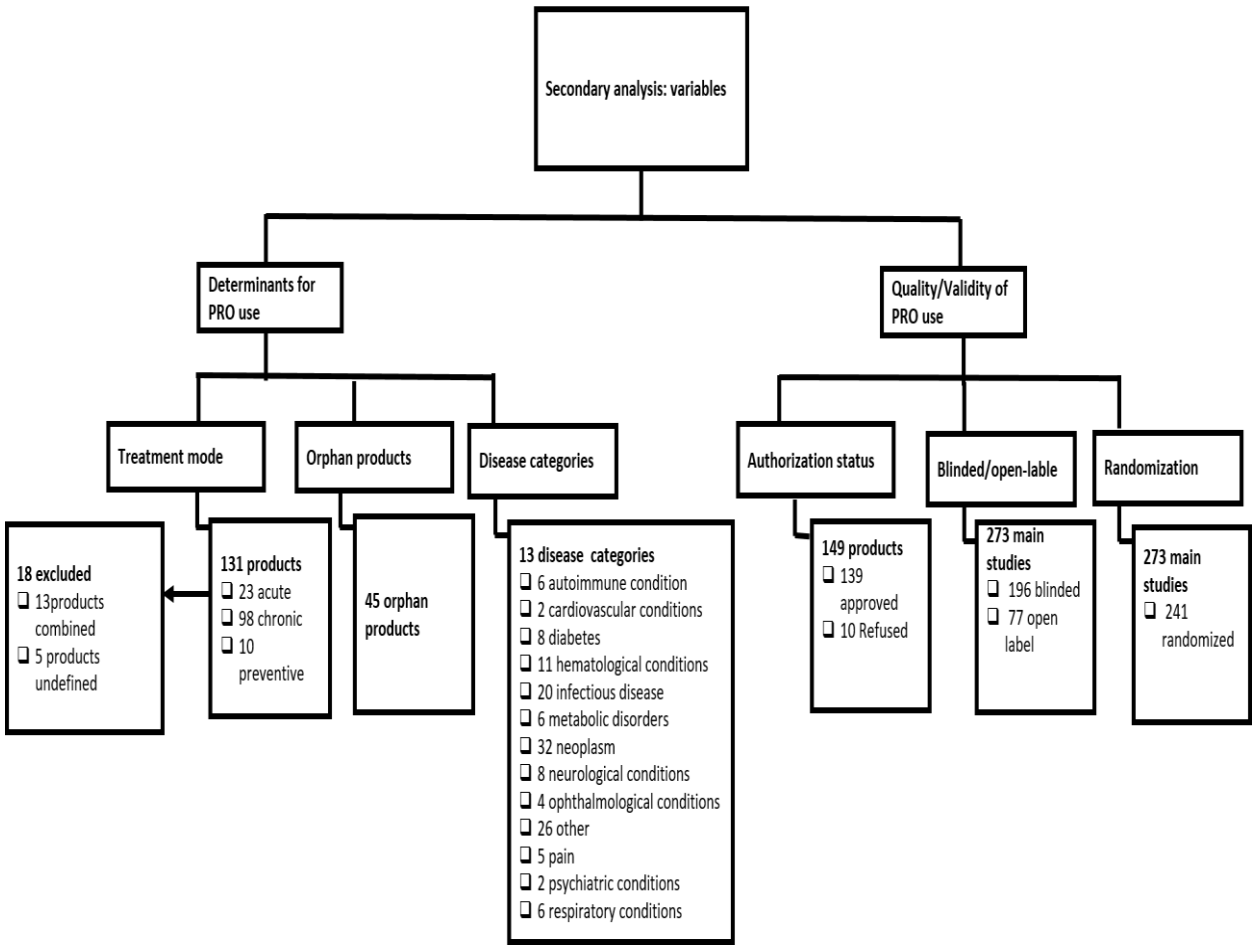

Figure 3 Shows the different variables that may determine PRO use and its validation.

TREATMENT TYPE

For the treatment type**,** 131 medicines were included (98 chronic-, 23 acute, and 10 preventive treatments). No significant difference was found between the treatment type and PRO use as a primary endpoint ($\chi2$ (2) = 1.815, p < 0.404), and their contribution to the benefit-risk balance ($\chi2$ (2) = 3.032, p < 0.220) and effect tables ($\chi2$ (2) = 3.655, p < 0.161). PROs were used significantly more as a secondary endpoint ($\chi2$ (2) = 13.490, p <0.001) and in the SmPC ($\chi2$ (2) = 8.428, p < 0.015) by chronic- compared to acute- and preventive treatment **(Figures 3-4)**.

ORPHAN AND AUTHORIZATION

149 products were orphan. The design was not associated with PRO as a primary endpoint, 1.190 (95% CI 0.299- 4.726, p < 0.805), secondary endpoint, 0.938 (95% CI 0.464-1.896, p < 0.857) and their contribution to the benefit-risk balances, 1.119 (95% CI 0.538-2.329, p < 0.764) effect tables, 1.257 (95% CI 0.545-2.898, p < 0.592) and SmPC, 1.118 (95% CI 0.504-2.479, p < 0.783).

AUTHORIZATION

Overall, 139 products were authorized and 10 were refused. For one refused product, the benefit-risk assessment and effect table

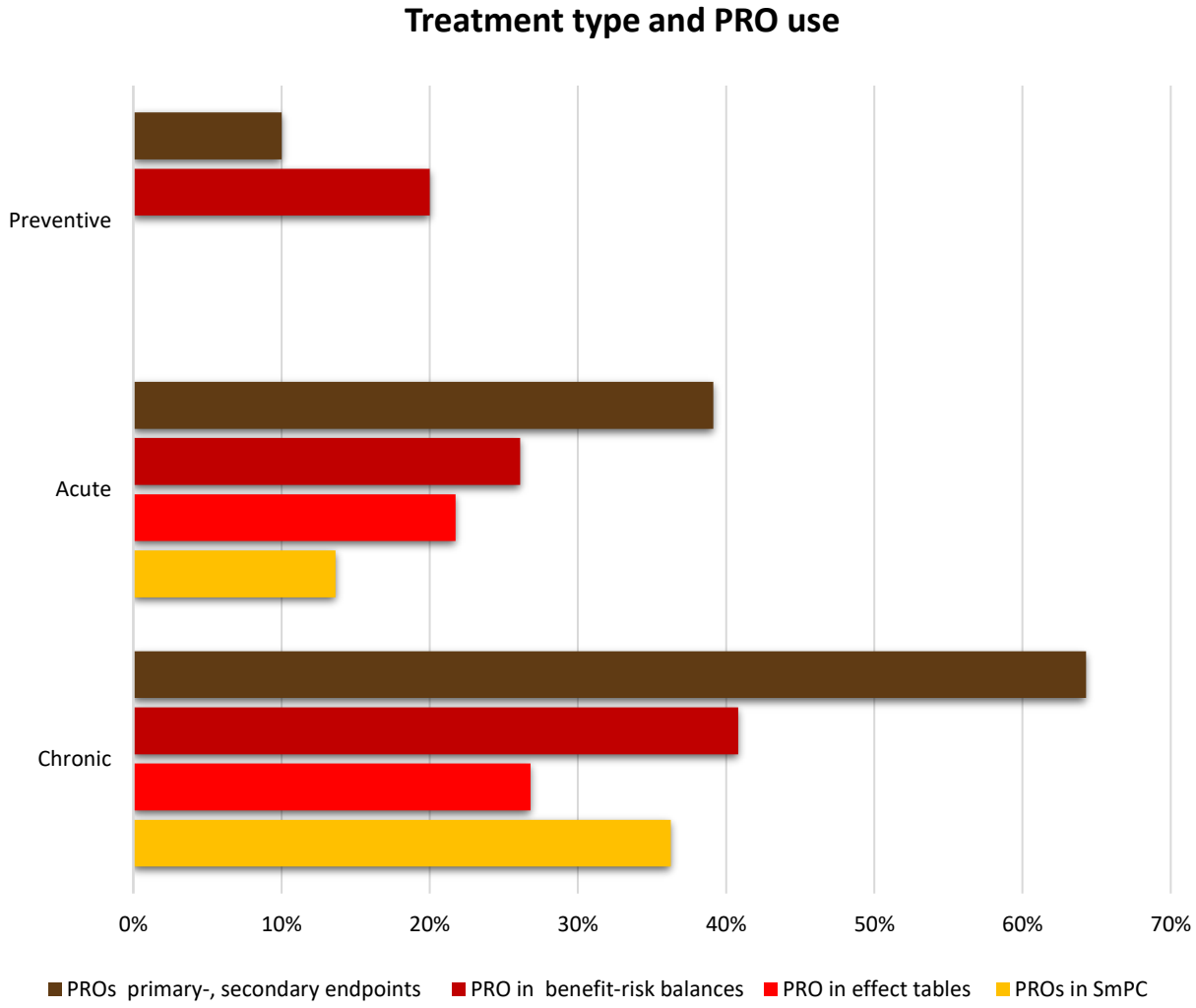

Figure 4 shows PRO use in acute, chronic, and preventive treatment. Further, the impact on decision-making is presented and in product labelling.

presented methodology deficiencies in the PRO collection method. These results were mentioned in the benefit-risk assessment and effect table. For another refused product, it was mentioned in the benefit-risk assessment that PROs were not measured, and therefore the clinical benefit of the drug in patients could not be fully established.

No significant association was found between PRO use as a primary endpoint, 1.373 (95% CI 0.157-12.020, p < .774) secondary endpoint, 1.008 (95% CI 0.278- 3.647, p < .991) its contribution to the benefit-risk balance, 1.698 (95% CI 0.467-6.173, p <0.421) and effect table, 788 (95% CI 0.155-4.007, p < 0.774) and the authorization status of the products.

DISEASE CATEGORY

In total, 136 products which included a disease category and total of 13 different disease categories were found (**Figure 3, 5**). A significant difference was found between PRO use as a primary endpoint ($\chi2(13) = 26.841$, $p<0.013$), secondary endpoint ($\chi2$ (13) $=38.030$, $p < 0.001$) and the disease category. A significant difference was found in the number of PROs presented in the benefit-risk balances ($\chi2$ (13) = 43.986, $p < 0.001$), effect tables ($\chi2$ (13) = 44.880, $p < 0.001$), SmPC ($\chi2$ (13) = 46.395, $p <0.001$) in different disease categories. For example, autoimmune conditions utilized PROs in 67 %, 33%, and 67% of their benefit-risk balances, effect tables, and SmPC, respectively.

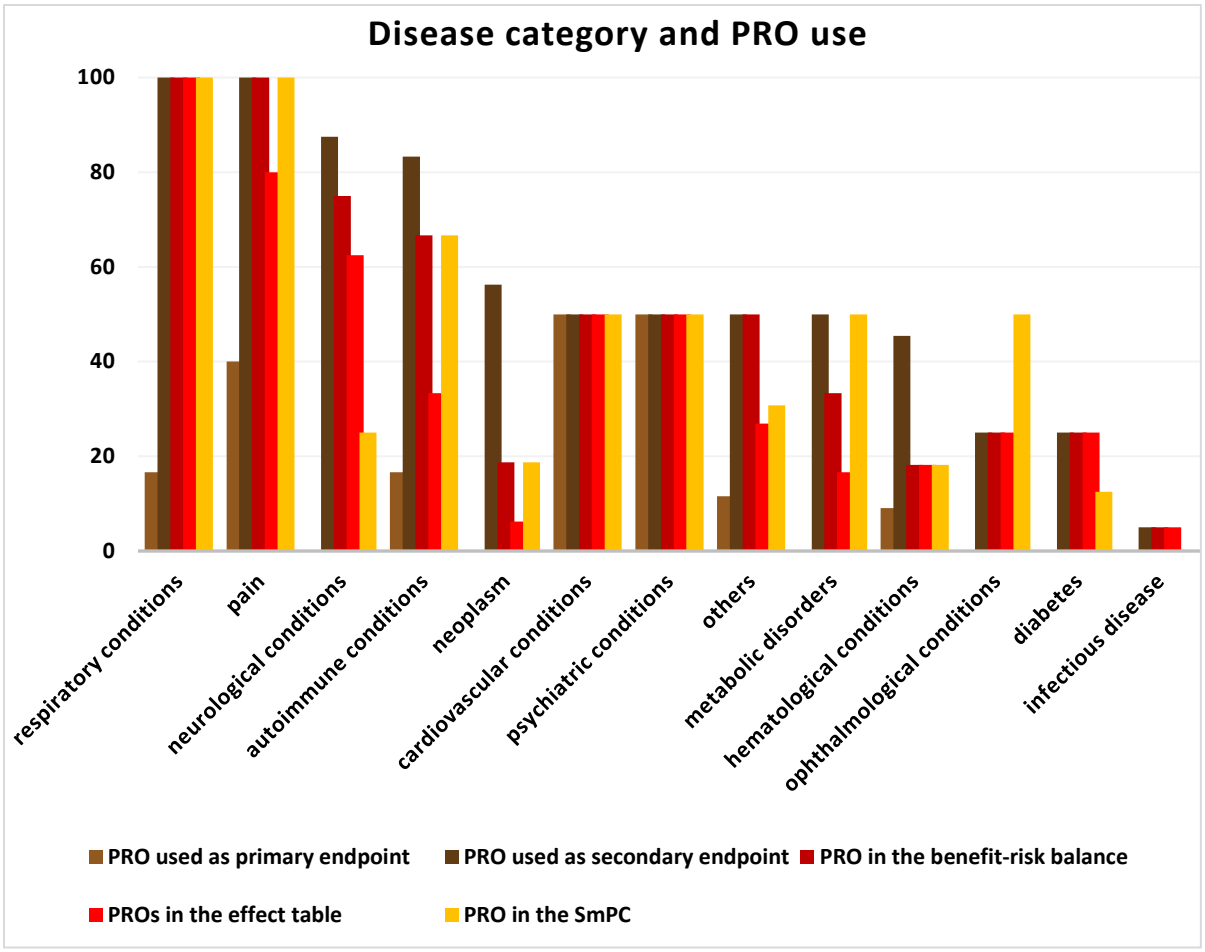

Figure 5 Illustrates PRO use in different disease categories. The table shows in bold, the disease categories that used PROs significantly more.

Whereas infectious disease utilized PROs in 5%, 5%, and 0% of their benefit-risk balances, effect tables, and SmPC, respectively. Neoplasm diseases used a significant number of PROs as a secondary endpoint. However, as seen in **figure 5** PROs are infrequently mentioned in the effect tables and SmPC. For psychiatric conditions there was a one-on-one relationship between the PRO and its contribution to the effect tables and SmPC. In contrast with the neurological conditions, PROs were mentioned less in the effect table and SmPC, despite being often being used in the main studies (**Figure 5)**.

Surprisingly, only 40% of the pain products utilized PROs as a primary endpoint whereas the evaluation of pain depends on the patients reporting. This is explained in the migraine products, where the number of migraines was the primary endpoint.

COLLECTION METHOD AND DISEASE CATEGORY

From the 84 products that utilized PROs, 12 (15%) and 16 (19%) mentioned collecting PROs via an interview and diary/electronic, respectively. The one neoplasm product that collected PROs via a dairy/electronic method, had results contribute to both the effect table and SmPC (**Figure 5**).

PRO INSTRUMENTS

A total of 98 different tools were used to collect PROs. All instruments were well established. 74 Instruments were only mentioned in the main studies of one product and did not contribute to the effect table and/or SmPC. Some instruments were utilized less, but always contributed to the effect table and SmPC. Some instruments only contributed to the SmPC and not the effect table. The EORTCQLQC3 (a quality-of-life cancer questionnaire) was the instrument most

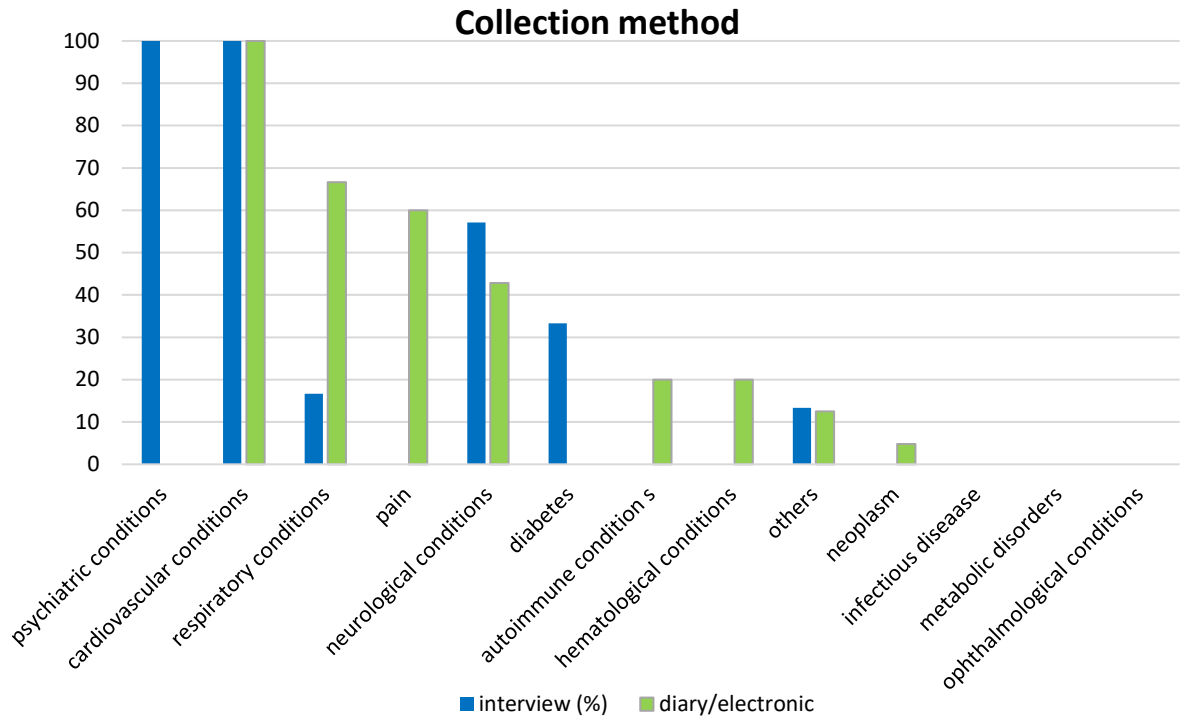

Figure 6 shows the different methods of used to collect PROs in different disease categories.

used. No significant difference was found between the type of instrument(s) used and PROs contribution to the SmPC and effect tables, 1.004 (95% CI 0.994-1.014, p < 0.443) and 1.015 (95% CI 1.003-1.026, p < 0.011) respectively.

SECONDARY OUTCOMES QUALITY/VALIDITY

Overall, 2(2.60%) and 28 (36.36%) open-label studies utilized PROs as a primary- and secondary endpoint, respectively. Further, 21 (11%) and 88 (45%) blinded studies utilized PROs as a primary- and secondary endpoint, respectively. Moreover, 14 (18%) and 9 (12%) of open-label studies presented results in the effect tables and SmPC respectively. For blinded studies, 49 (25%) and 66 (34%) presented results in the effect tables and SmPC, respectively. The OR of PRO use as a primary endpoint and PROs contribution to the SmPC was significantly higher in blinded studies compared to open-label studies, 4.500 (95% CI 1.029-19.678, p < 0.046) and 3.836 (95% CI 1.802-8.167, p < 0.01), respectively **(Table 1)**.

sample size, randomization, duration of the double-blind, and duration of the study design were not variables associated with PRO utilization and their contribution to the effect table and SmPC (Table 1).

DISCUSSION

This paper gives an overview of PROs used in new medicinal agents and their role in the benefit-risk assessment, drug licensing, and product labelling in the last 3 years.

Overall, primary- and secondary endpoints PROs have the strongest influence on the assessment. Primary endpoint PROs are always considered relevant and therefore always contributed to drug licensing assessments, and product labelling. More than half (62%) of secondary endpoint PROs contributed to the assessment and product labelling. It should also be pointed out that, non-primary and non-secondary endpoints, also may contribute to the benefit-risk assessment and patient-care treatment-related decision. Half (56%) of the medicinal agents approved between 2018-2020 mentioned PROs. Compared to the DeMuro et al. study (47%), a gradually increased is seen in recent years. To ensure important patient-centred perceived benefits are not ignored, we recommend that

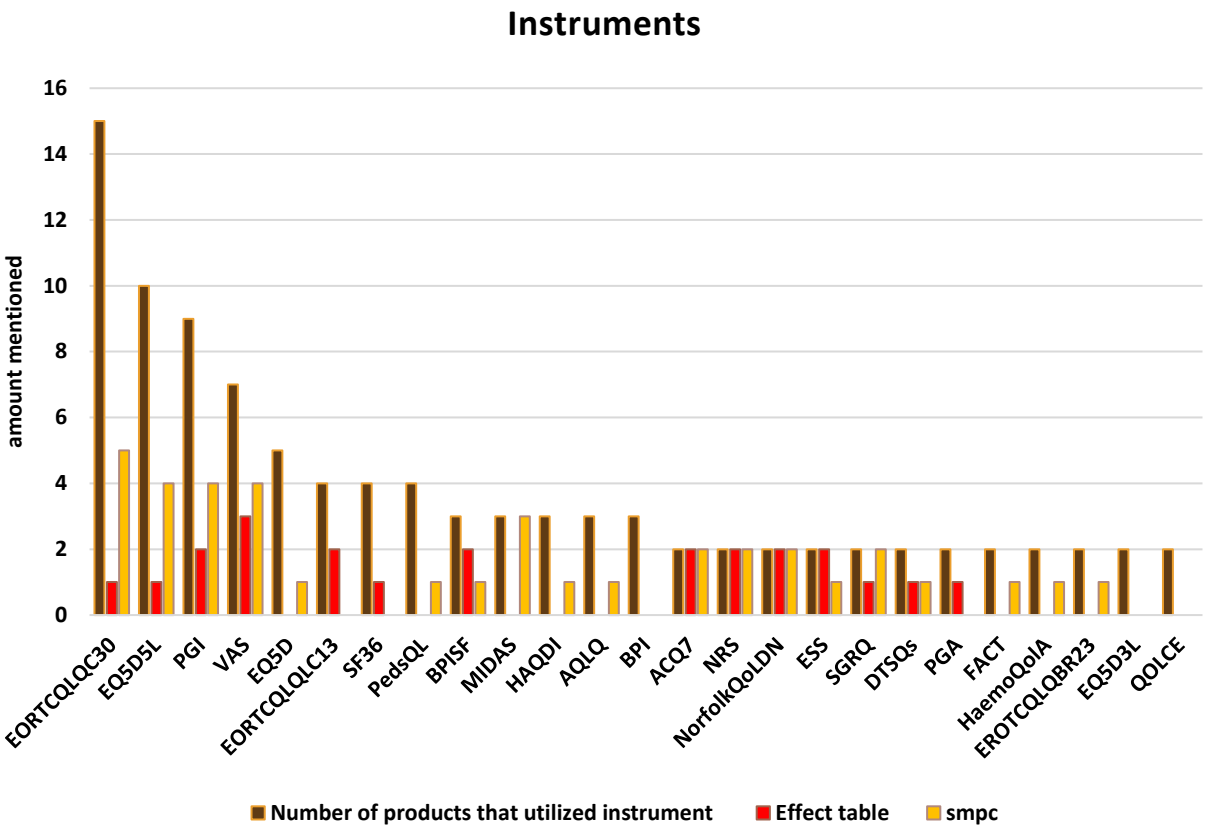

Figure 7 This figure illustrated the 24 instruments utilized. These instruments were mentioned more than once overall.

PROs are incorporated more often, at least as a secondary endpoint.

This study shows that some variables influence the role PROs play in the assessment and in product labelling. Outcomes from open-label and non-randomized design studies are considered less reliable. PROs from open-label studies were infrequently mentioned in the effect tables, and often mentioned in the SmPC. Apparently, they are less important for regulatory decision-making than patient care decisions. Even though medicinal agents of blinded studies are more likely to present results in the effect table than open-label studies, the open-label design also played a role in product labelling. Therefore, we recommend that these studies include PROs endpoints. If included in product labelling, they will give clinicians access to valuable results.

Additionally, some disease categories and treatment types valued PROs less than other disease categories and treatment types. Therefore, PROs from these studies barely made it to the product assessment and labelling. PROs are being used less than expected in preventive therapy. This might be explained by the fact that patients may not have complaints that can be reported. However, PROs could be used for reporting adverse events. Products used for the same indication are comparable with respect to the safety profile. Therefore, we recommend that PROs be utilized more in preventive therapy because this may improve the safety issues related to the use of preventive therapy.

In our products, PROs were always evaluated for respiratory condition medicinal agents. Respiratory PROs utilized as a primary or secondary endpoint always contributed to the benefit-risk assessment. They had a strong influence on the assessment and product labelling. Clinicians prescribing newly approved products for respiratory conditions, always have access to PROs in the SmPC to help with patient-care decision-making.

As expected, PROs use was valued by CNS (neurological and psychiatric conditions) products. Interestingly, neoplasm products utilized PROs significantly more as a secondary endpoint compared to other disease categories (e.g., infectious diseases). However, PROs from these medicinal agents rarely made it to the assessment and product labelling.

Only two from the 18 neoplasm products that utilized PROs, had results contribute to the effect tables and therefore, had a sound influence on the benefit-risk assessment and product licensing. From these two products, one collected PROs via a diary/electronic method. By neoplasm, clinical testing usually focuses more on objective outcomes than on subjective outcomes like PROs. These studies are often times open label, which makes the results less reliable. Moreover, PRO burden may limit its use in cancer patients. For these patients, it may be better to consider collecting PROs using another method, like an interview or diary/electronic method. This may be interesting to investigate in future research.

When we looked at the different instruments utilized, EQRTCQLQC3 was the most utilized PRO instrument between 2018-2020. This is a questionnaire developed to evaluate the quality of life in cancer patients. Its frequency is probably because we had many cancer products. PROs captured using this instrument oftentimes did not contribute to the benefit-risk balance assessments and effect tables. They contributed more to the SmPC (1/3) than to the product assessment. EQRTCQLQC3 was used 12 times by neoplasm as a secondary endpoint, and the product(s) that contributed to the effect and SmPC using this instrument were products for neoplasm. This instrument is validated; therefore, we assume that its results did not have a strong contribution to the benefit-risk assessment because of the open-label design in neoplasm and not instrument's untrustworthiness.

Further, the benefit-risk assessment was independent of the products authorization status. This means that PROs also play an essential role in approving and refusing products.

STRENGTHS AND LIMITATIONS

This paper gives an overview of PRO use in the benefit-risk assessment, drug licensing and product labelling. The structure of the EPAR (main studies-benefit-risk balance assessment-effect table) allowed for an evaluation of the impact of PROs on regulatory decision-making. Next to its strengths, this study had some limitations. First, we did not take into consideration that some products only had one or two endpoints. Therefore, this may have also played a role in the contribution of PROs to the assessment and product labelling. Products with fewer endpoints may be more likely to use PRO results in the assessment and product labelling because few endpoints were measured. We also didn't discriminate between the different types of PRO instruments and their aim, which may differ.

CONCLUSION

In conclusion, a gradual increase is seen in PRO claims. They are weighing in more and more on the benefit-risk balance assessment and in supporting drug licensing. The relationship between PRO for regulatory and patient care decision-making is not one-on-one. Overall, we recommend that PROs are more frequently incorporated in clinical development plans, product assessment and labelling.

Tabel 1 This table shows the different factors related to the validation of PROs.

PRO use in main Studies- Factors								
Primary Endpoint	**B**	**S.E.**	**Wald**	**df**	**Sig.**	**OR**	**95% C.I. for OR**	
							Lower	**Upper**
Sample Size	.001	.001	2.732	1	.098	1.001	1.000	1.002
Randomization	.359	.765	.220	1	.639	1.432	.320	6.415
Blinding	1.504	.753	3.992	1	.046	4.500	1.029	19.678
DurationOfDoubleBlind	.020	.010	3.878	1	.049	1.020	1.000	1.040
DurationOfStudyDesign	.008	.004	3.558	1	.059	1.008	1.000	1.017
Secondary endpoint	**B**	**S.E.**	**Wald**	**df**	**Sig.**	**OR**	**95% C.I. for OR**	
							Lower	**Upper**
Sample Size	.000	.000	.120	1	.729	1.000	1.000	1.000
Randomization	.388	.394	.968	1	.325	1.474	.681	3.192
Blinding	.355	.277	1.640	1	.200	1.426	.828	2.454
DurationOfDoubleBlind	.000	.003	.006	1	.937	1.000	.994	1.007
DurationOfStudyDesign	-.001	.001	1.803	1	.179	.999	.997	1.001
Effect table	**B**	**S.E.**	**Wald**	**df**	**Sig.**	**OR**	**95% C.I. for OR**	
							Lower	**Upper**
Sample Size	.000	.000	.412	1	.521	1.000	1.000	1.000
Randomization	.548	.510	1.157	1	.282	1.730	.637	4.699
Blinding	.419	.339	1.533	1	.216	1.521	.783	2.953
DurationOfDouble Blind	.005	.004	1.197	1	.274	1.005	.996	1.013
DurationOfStudyDesign	-.001	.001	1.803	1	.179	.999	.997	1.001
SmPC	**B**	**S.E.**	**Wald**	**df**	**Sig.**	**OR**	**95% C.I. for OR**	
							Lower	**Upper**
SampleSize	.000	.000	1.643	1	.200	1.000	1.000	1.000
Randomization	1.073	.553	3.765	1	.052	2.924	.989	8.640
Blinding	1.344	.386	12.158	1	.000	3.836	1.802	8.167
DurationOfDouble Blind	.001	.003	.106	1	.745	1.001	.994	1.008
DurationOfStudyDesign	.001	.001	.234	1	.629	1.001	.998	1.003

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APPENDIX A PROTOCOL

The role of Patient-Reported Outcomes in Marketing Authorization Applications and product labeling (2018-2020): Research Protocol

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COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

CBG MEB

MEDICINES EVALUATION BOARD

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SECTION 1: GLOSSARY

PRO: Patient-Reported Outcome

HRQL: Health-Related Quality of Life

EPAR: European Publication Assessment Report

EMA: European Medicines Agency

CHMP: medicines by the Committee for medicinal product for human use

CVMP: Committee for Medicinal Products for Veterinary Use

CNS: central nervous system

CVD: cardiovascular diseases

SmPC: Summer of Product Characteristics

PGWBI: Psychological General well-Being Index

PAI: Physical Activity Index

SEIQoL: Schedule for the evaluation of Individual quality of life

RAQoL: Rheumatoid Arthritis Quality of life questionnaire

McSad: Major unipolar depression

CAMPHOR: Cambridge Pulmonary Hypertension Outcomes Review

SECTION 2: INTRODUCTION

Medicine has been developed to help patients with their disease-related problems. Moreover, clinical testing is performed to address any concerns surrounding the benefit-risk balance of a new treatment. [16] Oftentimes a complete evaluation of the effectiveness of a medicine is impossible without input directly from the patient of interest. [12] Considering the patient is at the centre of health care, it is within reason to assume that these outcomes are as important, if not more essential than outcomes reported by clinicians. [3] This is where Patient-Reported Outcomes (PROs) come into play. PROs are results that assess the patient's perspective regarding their treatment(s) and disease. These outcomes come directly from patients without interpretation by anyone else, including clinicians. They are subjective outcomes that reflect how patients feel and they can help clarify the extent to which a patient is suffering. [1,2,3,6, 18] Moreover, they translate the effect seen in objective outcomes (e.g., tumour shrinkage) in terms of clinical relevance [1,2, 18]. PROs provide clinicians with access to valuable tools to help extract relevant information regarding the effect of treatment as perceived by the patient, which in turn may add to patient care decision-making. [7, 13] In addition, PROs may be used to support claims made by the marketing authorization holder in medical product labelling. Howbeit, the claim should be consistent with the documented evaluability assessments of the PRO concept measured, method, and instrument(s) used. [1,2]

Present-day marketing authorization holders, clinicians, and patients are acknowledging PROs more and more. [1,2,19] According to DeMuro et al. 47% of medicines approved between 2006-2010 had a minimal of one PRO-related claim approved by the European Medicines Agency (EMA) and 19% by the Food and Drug Administration (FDA). [23] In December of 2009, the FDA issued a formal guideline for the use of PROs to support labelling claims in the clinical development plan. [2] According to a constructive ClinicalTrials.gov review, the use of PROs in clinical trials has increased from 14% to 27% between 2004-2007 and 2007-2013. A clinical review conducted in New Zealand and Australia between 2005-2017 concluded that 45% of trials used PROs. [19]

However, little information is known about the degree to which PROs are being incorporated in the primary/secondary outcomes of pivotal studies. These are phase III studies that marketing authorization holders use to evaluate and confirm the efficacy and safety of a medicine. Furthermore, it is still unclear how often these PROs are included in product labelling, how this has changed over time, and which factors play a role herein.

SECTION 3: AIM

This study aims to clarify the extent to which marketing authorization assessment reports (EPARS) of recently approved medicines utilize PROs in their pivotal studies and If these outcomes contribute to supporting a positive benefit-risk balance and product labelling.

SECTION 4: METHOD

We will be performing a review about marketing authorization dossiers to determine how often and how PROs are being incorporated in the drug development process to support marketing applications in Europe.

4.1 PROS

The terms PRO instrument, PRO concept, and PRO method are defined below.

4.1.1 PRO CONCEPT

A PROs concept may be one-dimensional (e.g., signs and symptoms of allergic rhinitis and pain), or it can be multidimensional (e.g., health-related quality of life (HRQL). [3] This concept is the data that is being measured. [table 1]

Concept	Description	Questions
Symptoms	One-dimensional and are oftentimes the main objective of the treatment	What symptoms are you experiencing?
QoL	Multi-dimensional is often used in cancer care.	How often is the adverse event (e.g., vomiting) experienced? How often do you go out with friends?
HRQOL	A Multi-dimensional subset of PROs concept that encompasses the patient perspective on the impact of their disease and treatment(s) on their daily physical, psychological, social functioning, and well-being.	Would you say that your general health is: excellent, good, fair, or poor? Has this improved during your treatment?

TABLE 1: This table shows the different concepts that may be measured using the different PRO instruments. [1,2,3]

4.1.2 PRO INSTRUMENT

A PRO instrument is the tool used to collect PRO data. There are various novel PRO instruments. Some of them are simple (e.g., semi-structured questionnaire), dimension specific (e.g., Physical activity index PAI), others are Disease-specific (e.g., Rheumatoid Arthritis Quality of life questionnaire (RAQoL), etc. [4,5] Various instruments are being utilized to measure PROs in clinical trials. [2] These instruments are used as a means of evaluating the benefit-risk of treatment. [2] They often include signs and symptoms that patients may experience. [2] [table 2]

Instrument	Type	Description
Psychological General Well-Being Index (PGWBI)	Generic	This type is for a wide range of patient groups and measures aspects that pertains to health status and outcomes of illness.
Physical Activity Index (PAI)	Dimension specific	This is a health score based on measuring the impact of heart health on physical activity.
Schedule for the evaluation of Individual quality of life (SEIQoL)	Individualized	These tools allow a patient to select issues, worries, or domains that are of personal concern to them.
Rheumatoid Arthritis Quality of life questionnaire (RAQoL)	Disease-specific	This type of instrument measures the effect of rheumatoid arthritis on the quality of life of a patient.
Major unipolar depression (McSad)	Utility measures	This is like the generic type of measurement, with only one type of numerical evaluation of wellbeing.
Cambridge Pulmonary Hypertension Outcomes Review (CAMPHOR)	Region site-specific	This is specific to the region of the disease.

Table 2: This table describes different types of novel instruments used in clinical studies to collect PROs. [3,21]

4.1.3 PROS COLLECTION METHOD

Different methods can be used to collect PROs. The PRO concept using the instrument of interest can be collected using diaries, questionnaires, interview scripts, etc. this may also be done electronically. [2] [Table 3]

Collection Method	Description	Type of questions
Diary	Contains questions/answers written by the patient with regards to a task, symptom, etc.	How many times did you experience shortness of breath today?
Interviews	A structural conversation where the patient is asked questions related to the concept of interest.	How many times did you experience shortness of breath today?
Electronic	Data is collected using an electric method (e.g., electric diary, computer, or telephone).	How many times did you cough today?

Table 3: *This table shows some of the different methods used to collect the concept of interest. [3]*

4.2 OBJECTIVE

4.2.1 GENERAL OBJECTIVE

The general objective of this study is to identify in which EPARS of newly approved medicines are PROs being utilized in the clinical development plan. Furthermore, to evaluate if these outcomes contribute to supporting a positive benefit-risk balance and Summer of Product Characteristics (SmPC).

4.2.3 PRIMARY OBJECTIVE

This study has two primary objectives. The first is to determine the use of PROs in the primary/ secondary endpoints of pivotal studies. The second primary objective is to determine how often PROs are discussed in the benefit-risk balance and SmPC. In addition, it will be determined if PROs contributed to supporting a positive benefit-risk balance.

4.2.4 SECONDARY OBJECTIVE

The secondary objective of this study is to determine if PROs (used in the pivotal studies) were collected using novel instruments. It will be determined if there is an association between different factors (i.e., information regarding the type of treatment (acute, chronic, or preventive), randomization, blinding, the sample size, study duration, different PRO methods, PRO concepts, PRO instruments, therapeutic area and orphan design) and the inclusion of PROs in the benefit-risk assessment reports, SmPC and how this has changed over time.

4.2.5 SPECIFIC PRO RESEARCH QUESTIONS

1. How many newly approved medicines utilize PROs in the primary or secondary endpoints of pivotal studies
2. How often are these PROs results utilized in the benefit-risk balance of newly approved medicines per year?
3. Do PROs have a positive contribution to the benefit-risk balance?
    1. Does a positive contribution increase over time?
4. How often do these PROs results utilized in the SmPC of newly approved medicines per year?
    2. Does PRO incorporation increase over time?
5. Which Factors [drug/disease-related/dossier related/ PRO related] are associated with the use of PROs in SmPC and benefit-risk balance.
    A. Which PRO concept is measured?
    B. Which collection method is used to measure PROs?
    C. Which Instrument is used to measure PROs?
    D. Is the instrument a novel instrument?
    E. What is the study size?
    F. Is the study blinded?
    G. Is the study randomized?
    H. What is the therapeutic area?
    I. is the treatment acute, chronic, or preventive?
    J. Is it an orphan medicine?
    K. What is the duration of the study?

4.3 STUDY POPULATION

4.3.1 THERAPEUTIC AREAS

All therapeutic areas will be included in this study. However, extra attention will be given to three therapeutic areas. The therapeutic areas of interest are cardiovascular diseases (CVD), diseases of the central nervous system (CNS), and oncology. [3] CNS diseases, such as depression, are mental disorders associated with loss of appetite, sleep disturbance, fatigue, etc. This may affect factors such as physical, mental, and social health. Moreover, low quality of life among patients with cardiovascular disease(s) is a growing concern. [10] Further, next to the hindering symptoms, an economical burden and a lack of emotional wellbeing associated with cancer can affect a patient's quality of life. Products that fall under these therapeutic areas will be identified using the (ATC) classification.

4.3.2 DATABASE

For this study, data will be collected using two different sources: The EPARs and the SmPC. The EPAR is the main web database containing detailed published information by the EMA on medicines by the Committee for medicinal products for human use (CHMP) and Committee for Medicinal Products for Veterinary Use (CVMP). It contains clear, straightforward, useful, and detailed information for public use. [9] The SmPC contains information for healthcare providers.

4.3.3 COLLECTING MEDICINES

Medicines included in this study will be collected using the **European public assessment reports (EPARs) of medicinal products for human and veterinary use** retrieved from documents from the European Medicines Agency (EMA) website.

4.3.4 EXTRACTING MEDICINES

Our medicines will be selected using **the table of EPARS for human and veterinary use** excel sheet on the EMA website. The exclusion criteria will be as followed:

i. Products without authorization,
ii. Veterinary drugs,
iii. Generic drugs,
iv. Biosimilars,
v. Products approved before January 2018 and after December 2020,
vi. Vaccines and diagnostic agents.

We will be excluding products that do not meet our inclusion criteria. Vaccines usually give a lifetime of immunity after only one or two administrations. They are used as primary prevention and patients do not have to the diseases. Diagnostics do not fall under treatment and therefore will not be included in this study. Generic drugs and biosimilars are drugs that are bioequivalent to the original medicine. For financial reasons, these products use the clinical studies of the original medicine dossier in their EPARS. Moreover, duplicate dossiers will be excluded because they contain the same active ingredient. Therefore, they are the same medicine but under a different name.

4.4 ADJUSTING THE EMA EXCEL SHEET

As mentioned above, the **table of EPARS for human and veterinary use** will be used to select the medicine products**.** This table will be downloaded and renamed (see **Data storage** for more detail). First, new columns will be added (e.g., sample size) to extract relevant data for this study. This process is explained further by section **4.7 Excel sheet**. Next, medicines that do not meet the in- and exclusion criteria will be hidden. Steps in Figure 1 by **step 1** will be followed to obtain our study population. Once the new columns have been added, and the medicines have been chosen the URL links in column AD will be used. Each row contains a URL link in column AD for the specific product in that row. This link leads to the EPAR of the medicine. The EPAR contains an overview, authorization details, product information, and assessment history of the product. Here, the assessment reports can be found using the EPAR-Public assessment report link under **Assessment history** and the SmPC can be found using the EPAR-Product information link under the **Product information**. We will evaluate the use of PROs in the primary or secondary endpoints of the main 'pivotal' studies which support the application. PROs information included in this section and the benefit-risk balance (section 3 of the EPARS) will be extracted.

Secondly, section 5.1 of the SmPC will be examined. All PRO information will be extracted. Section 5 of the SmPC contains results from the clinical study reports. [**Figure 1 and 2P]**.

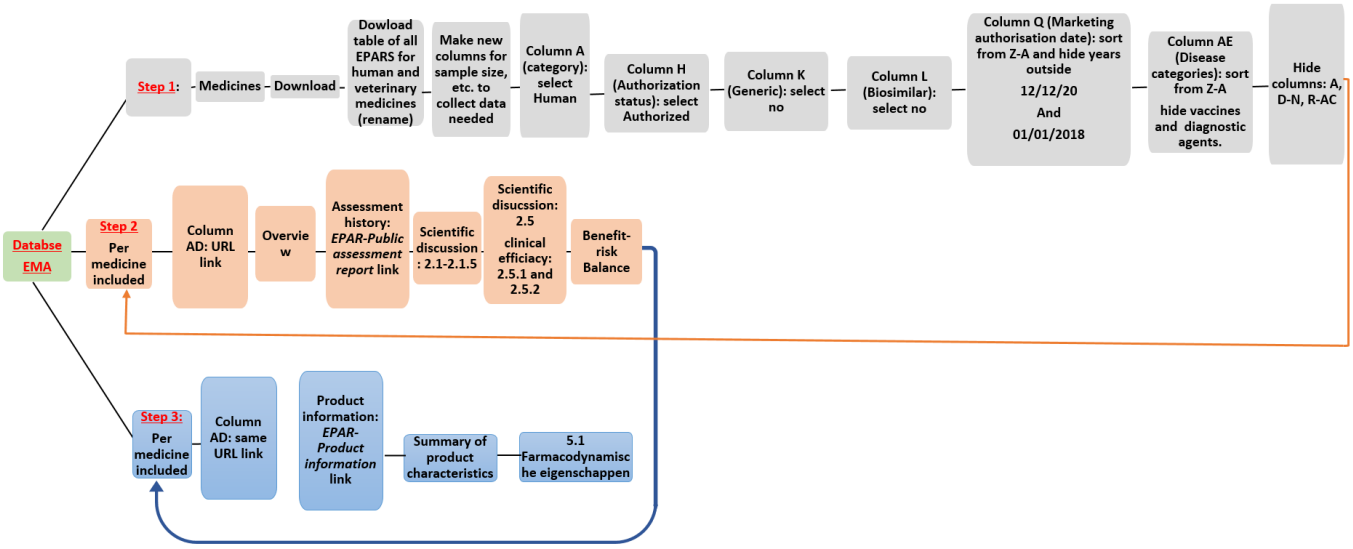

Figure 1: this figure visualizes how medicines and needed data will be collected in this study and the data source that will be used.

4.5 DATA COLLECTION

The EPAR will be used to collect data information. First**,** it will be determined if the treatment is acute, chronic, or preventive. This will be done using the dosage information and therapeutic area. This information can be found by the medicine overview and if needed the SmPC. Next, the list of abbreviations in the EPAR-Public assessment report will be examined for any PRO-related information. Further, the pivotal studies, usually found in section 2.5.2, contain information about the main studies, will be examined to determine study randomization, blinding, study size, and duration. PRO instrument, method, and concept terms/abbreviations found in the list of abbreviations will be used as search terms (see table 4) for more detail) and to determine if PRO were used in the primary or secondary endpoint(s). Then, we will examine if any PRO information is used in the benefit-risk balance. We will then determine if PROs have a positive contribution to the benefit-risk balance. We define a positive contribution as the use of PROs in the effect table (section 3.6) and the benefit-risk assessment and discussion (section 3.7).

Screenshots will be made of the primary and secondary endpoints, sample size, blinding, duration, all PRO data found. If PROs are included in section 3.7 screenshots will be made. If not, screenshots will not be made.

Lastly, section 5 of the SmPC for medicines that included PROs in the primary or secondary outcomes of their pivotal studies will be examined. PRO used in this section will be extracted. See **Figure 2**.

4.5.1 CHRONIC, ACUTE, AND PREVENTIVE TREATMENT

These treatments will be defined as followed: Chronic treatment is a treatment for a long-term illness (e.g., heart disease, diabetes). Acute treatment is a short-term treatment. It can be for a severe short turn illness (e.g., treating a urinary tract infection). [26] Preventive treatment is defined as a treatment used to prevent or avoid disease or its sequelae (secondary prevention) (e.g., hypertension). [27]

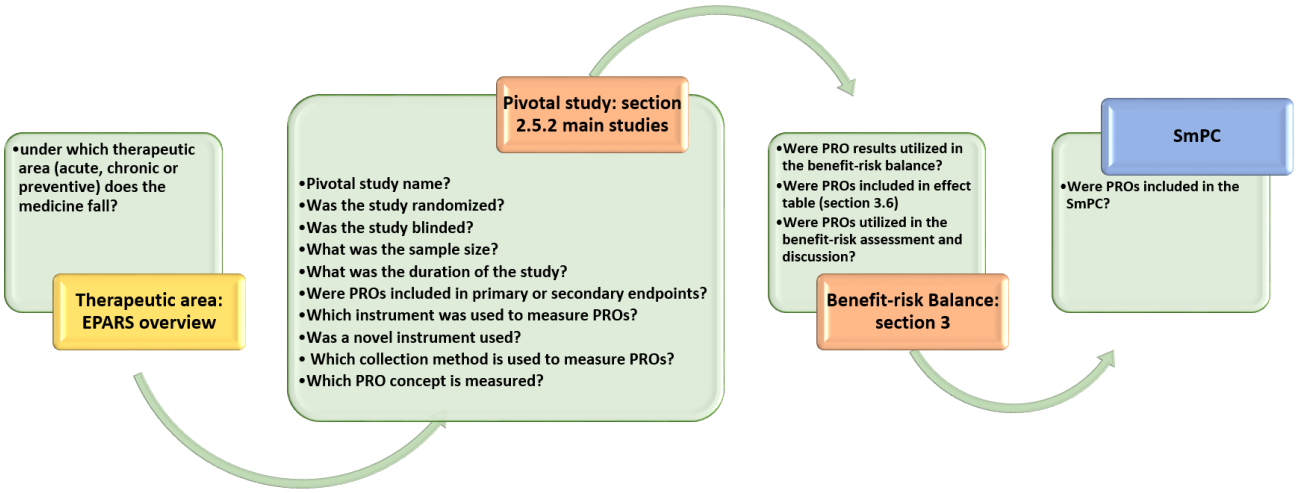

Figure 2: The process of collecting the data.

4.6 KEY TERMS

The table below shows the different data that will be examined when collecting PRO data from the EPARs and SmPC. Keywords will be used to reduce time-consuming tasks (e.g., reading the entire pivotal study) and maximize the amount of relevant information collected. The list of abbreviations will be examined for any PRO-related information/terms (e.g., HAT-QoL). The PRO terms included in the abbreviation will be used as key terms to search the EPARS and SmPC. [Table 4]

Database	What to search	Terms
EPARs	Are PROs included in the list of abbreviations?	Qol, instrument, questionnaire, satisfaction, scale, Vas, measure
EPARS	Were PROs used in the pivotal studies?	Pivotal studies, pivotal, main studies, patient-reported outcomes, open-label, blinded, randomised, efficacy, study size, N=, duration, disease duration, months, outcomes, endpoints, primary endpoint, secondary endpoint, follow-up, signs, symptoms, quality of life, health outcome, subject reported, reported, scale, QoL, pain, measure, main studies, main study
EPARS	Were PROs included in the benefit-risk balance?	Effect table, improvement, importance of favorable and unfavorable effect, patient-report Patient report, Balance of benefits and risk,
SmPC	Were PROs included in the SmPC?	5.1

Table 4: Search terms used to extract data from the EPARS.

4.7 EXCEL SHEET

Raw data from this study will be collected manually using the **table of EPARS for**

human and veterinary use. As mentioned before, this table will be downloaded and renamed (See section **Data storage** for more detail). To help collect relevant data the following columns will be added: acute therapeutic area, chronic therapeutic area, preventive therapeutic area, pivotal study name (3x), randomization (3x), blinding(3x), sample size(3x), duration of the study(3x), PROs included in the primary outcomes(3x), PROs included in the secondary endpoint(3x), Section 3: PRO results utilized in the benefit-risk balance, 3.6. effect table: PROs, 3.7 benefit-risk assessment, and discussion: PROs, section 5 of the SmPC: PROS, were PROs included in one of the following: primary or secondary outcomes of pivotal studies/ benefit-risk balance/SmPC, Novel instrument, Types of PRO instrument(s) utilized, which PRO is most important in case of more than one PRO this is the most important per study protocol (based on the EPAR), PRO concept, the method used to measure PROs, extra information, and Pdf file findings. Columns A, D-N, R-AC will be hidden.

	C	D	Q	R	AD	AE	AF
10	Medicine name	Therapeutic area	Orphan medicine	Marketing authorization	URL	Disease categories	Acute therapeutic area
11	(Name)	Breast Neoplasms	no	21-12-2018	https://www.ema.europ..	Neoplasms	no

	AG	AH	AI	AJ	AK	AL	AM
			Pivotal study 1				
10	Chronic therapeutic area	Preventive therapeutic area	Pivotal study name 1	Randomization	Blinding	Sample size	Duration of the double-blind
	Yes	No	Study433	No	Yes	250	12 months

	AN	AO	AP	AQ	AR	AS	AT
	EPARS: for our primary results	EPARS: for our primary results	Pivotal study 2				
10	PROs included in the primary endpoint	PROs included in the secondary endpoint	Pivotal study name 2	Randomization2	Blinding2	Sample size	Duration of the double-blind
	No	Yes	Study455	Yes	No	330	12 months

	AU	AV	AW	AX	AY	AZ
	EPARS: for our primary results	EPARS: for our primary results	Pivotal study 3			
10	PROs included in the primary endpoint2	PROs included in the secondary endpoint2	Pivotal study name 3	Randomization3	Blinding3	Sample size3
	No	Yes				

	BA	BB	BC	BD	BE	BF	BG
		EPARS: for our primary results	EPARS: for our primary results	EPARS: for our primary results	EPARS: for our primary results	EPARS: for our primary results	EPARS: for our primary results
10	Duration of the double-blind	PROs included in the primary endpoint3	PROs included in the secondary endpoint3	Section 3: PRO results utilized in the benefit-risk balance	3.6. Effect table: PROs	3.7 Benefit-risk assessment and discussion: PROS	Section 5 of the SmPC: PROs
				Yes	No	no	no

Figure 3 on the left illustrates what the excel sheet will look like after extra columns are added to the ***table of EPARS for human and veterinary use*** excel sheet***. Columns*** A, D-N, R-AC will be hidden. This figure further illustrates how, and which data will be collected.

	BH	BI	BJ	BK	BL	BM
	EPARS: for our primary results					
	Were PROs included in one of the following: primary or secondary outcomes of pivotal studies/ benefit-risk balance/SmPC	Novel instrument	Types of PRO instrument(s) utilized	Which PRO is most important in case of more than one PRO this is the most important per study protocol (based on the EPAR)	PRO concept4	Interview
	Yes	No	EORTC QLC-C30 & EORTC QLQ-BR2 questionnaires	None	Health related quality of life	yes

	BN	BO
10	Extra information regarding findings.	Pdf file findings
		https://cbgmeb-my.sharepoint.com/personal/n_almugoter_cbg-meb_nl/Documents/Bureaublad.....

4.8 DATA STORAGE

All data will be collected using the College ter Beoordeling van Geneesmiddelen my workplace internet network. All data results will be collected on the Microsoft Excel database. Data extracted from studies for this research will be stored on the CBG-MEB's internal network. Backup versions of the lasted work (protocol, report, excel data will be saved. A folder called "Nora's work" on the desktop will contain separate folders called 'excel sheet', 'protocols' and 'pdf files; findings.' The 'pdf files; findings' folder will contain Microsoft word documents for each medicine included in this study. These Microsoft word documents will be used to store data found using the data collection method. Each medicine included in this study will have a designated word document in this "pdf files; findings" folder. The Microsoft word documents will be saved under the excel sheet row number of the and name of the medicine: #name medicine (e.g., 3Phesgo). pdfs of each of these word documents will also be saved in the same folder and under the same name. The 'excel sheet' folder will contain a folder called 'excel sheets 2' this folder will contain excel sheets of the raw data found during our analysis. The downloaded table of EPARS for human and veterinary use (with the added columns and study population that we will be using) will be renamed **ResultsEPARS**. Each week and copy of the most recent **ReusltsEPARS** excel sheet will be saved under **ResultsEPARS.v**.# (# will be the version number(e.g., ResultsEPARS.v.3)). Furthermore, within the folder called "excel sheets" a separate folder called "drug list" will be made. This folder will contain two Microsoft word documents, one that contains information regarding the drugs that will be excluded from the study after enrolment and the second will contain information about how we narrowed down drug products. Protocols will be saved in the 'protocol' folder under the version number (e.g., protocols.v.4). the 'protocol' will also contain a folder named 'feedback' which contains all protocol word document feedback received (e.g., protocol.v.1_Sdv_CAE_PM). 'Nora's work' folder will be private. Only NA will have access to this folder. Using a shared folder accessible only to NA, PM, AE SV, and on the CBG-meb internet network, study reports will be shared. Data collected from the original source will be anonymized in this study. At the end of this research everything (inclusive raw data) will be delivered to the CBG. It will be permanently stored by the program of science office on the PBW hard drive.

4.9 QUALITY CHECK

Weekly, the quality of the entered data will be verified. The excel data will be checked for consistency and completeness. This will be done by filtering data in the columns. This will be done separately per column and row. An example of inconsistency is if one pivotal study was used, but information about the sample size, duration of the study is not available in the connected cell. Another example is if the medicine is for CVD and the instrument used is RAQoL. This is inconsistent, meaning a mistake was made somewhere. If the pdf file drug name and number attached in Column BO is different than the medicine name and row number (e.g., a pdf of 15Ayvakyt is attached on row 14 for medicine Rekambys), a mistake would be indicated. Completeness of data will be checked to make sure all information (e.g., PRO method, PRO instrument, sample size) regarding medicines that included PROs are recorded.

These types of mistakes will be checked for errors during data entry.

The supervisors: AE, PM, and SV will have access to the shared folder and will check the data for possible errors. These checks will be performed at random to ensure the quality of the data.

4.10 STATISTICAL ANALYSIS

For this study data collected on an excel sheet will be analysed using the statistical package for the social sciences (SPSS). The primary and secondary data will be analysed separately.

(0= no, 1=yes, blank= no information)

4.10.1 PRIMARY ANALYSIS

For the first primary analysis, all medicines that met the inclusion and exclusion criteria requirements will be used to answer specific question 1. This is to determine how many of the medicines (e.g., 10 from 50) included PROs in their pivotal studies. The second primary analysis will be conducted on all medicines included answering specific questions 2-4. This is to determine how many of the medicines included PROs in their benefit-risk balance, and/or SmPC and if PROs contributed to a positive benefit-risk balance. The results that pertain to the specific questions 1-4 will be analysed using descriptive statistics. Were PROs included in the pivotal studies (yes/no), benefit-risk balance (yes/no), SmPC (yes/no). Further, a positive contribution of PROs to benefit-risk balance (yes/no). The amount per year will be calculated (in percentage) per specific question. A chart will be used to visually present the outcomes. The Y-axis will be the percentage and the x-axis will be the years. These findings will be compared to prior results found in the DeMuro et al. study.

4.10.2 SECONDARY ANALYSIS

The secondary analysis will be conducted on all medicines Using descriptive statistics, the secondary analysis will answer specific question 5 letters A-K. The results will be presented visually using pie charts, bar charts, and/or column charts. Factors such as the percent of studies where PROs had a positive contribution to the benefit-risk balance and study size will be presented. For example, a bar chat will have the study size on the x-axis and the percent with a positive benefit-risk balance on the y-axis. Another example is the therapeutic area on the x-axis and the percent that used a novel instrument on the y-axis.

We will perform a logistic regression analysis evaluating several dossiers, drug, and disease characteristics that are associated with the use of PROs. We will perform an explorative analysis to determine, characteristics that make PROs a success (e.g., larger studies, blinding).

4.10.3 ANALYSIS OF DRUG CHARACTERISTICS

The different drug characteristics will be analysed to better understand and compare different factors that may affect a difference in PRO use. For this part, the descriptive statistical method will also be used. The use of PROs in the pivotal studies, benefit-risk balance, and SmPC with regards to the therapeutic area and Orphan Medicine (orphan designation versus non-orphan) will be analysed.

SECTION 5: REFERENCES [i]

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