HOW DO REGULATORS MANAGE UNCERTAINTY? A CLASSIFICATION OF UNCERTAINTIES AND COPING STRATEGIES

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Background

Uncertainty in the context of decision-making is **a feeling that blocks or delays decisions**. Effectively **communicating uncertainties and their impact on the benefit-risk assessment** and subsequent marketing authorisation decision **is important for stakeholders** (patients, healthcare professionals, Health Technology Assessment bodies/payers) to understand the rationale behind the decision and subsequently **make informed decisions**. This study provides a basis for a classification of regulatory uncertainties and coping strategies.

Objectives

To develop **a classification of regulatory uncertainties and coping strategies** that enables exploring:

- Relationships between uncertainties and coping strategies and potential **differences according to variables** relating to the type of drug and its regulatory pathway
- Uncertainties where **patient preference studies** could help address the uncertainty

Methods

- Extraction and analysis of uncertainties and coping strategies from European Assessment Reports (**EPARs**, figure 1), the summary of the Risk Management Plan (RMP) and Summary of Product Characteristics (SmPC) of oncology products with positive opinion between 2011-2017
- Parallel classification of uncertainties

Results

- 276 uncertainties were extracted from 64 oncology products
- The final classification consisted of the following categories (table 1):
  - **Uncertainties:**
    - **Type: what do regulators think is causing the uncertainty?**
    - **Issue: what are regulators uncertain about?**
  - **Coping strategies: how do regulators manage the uncertainty?**
- On average, 4.3 ± 2.3 (mean ± standard deviation) uncertainties were identified and extracted per product
- Univariate and multivariable regression models revealed that **the number of uncertainties per product** was:
  - Significantly (p=0.01) **lower for products with a Randomised Controlled Trial (RCT)** (3.9±2.1) versus without RCTs (5.5±2.6)
  - Not significantly correlated with other covariates: scientific advice or protocol assistance on the clinical development plan yes/no, orphan product yes/no, accelerated procedure yes/no, haematological cancer yes/no, conditional or exceptional marketing authorisation yes/no
- Regulators attributed the majority of uncertainties to **insufficient (65%) or unreliable (21%) data**
- Regulators **accepted the majority of uncertainties** (66%, diagram second column) **with request for more data** post-approval (66%, diagram first column)
- The coping strategy **"ask data"** was:
  - Significantly **more applied** for uncertainties associated with products **without RCT design** (RCT 59% vs no RCT 78%)
  - Significantly **more applied** for uncertainties associated with products that were given a **conditional or exceptional marketing authorisation** (regular 61% vs conditional or exceptional 76%)
  - Not significantly correlated with the other co-variates: scientific advice or protocol assistance on the clinical development plan yes/no, orphan product yes/no, accelerated procedure yes/no, haematological cancer yes/no

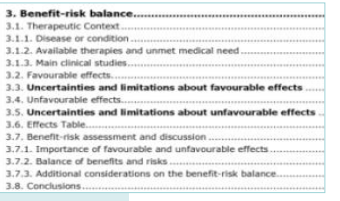

Figure 1: *EPAR table of contents introduced since 2011 that includes specific sections for describing uncertainties in the benefit-risk balance section*

Classification of uncertainties and coping strategies

Category and sub-category	n (%) total	n (%) advice	n (%) RCT	n (%) orphan	n (%) accelerated	n (%) haematological	n (%) conditional/ exceptional	Example from EPAR or SmPC
1. Uncertainties	276 (100%)	205 (74%)	182 (66%)	114 (41%)	72 (26%)	84 (30%)	88 (32%)	
Type: *uncertainty caused by…*								
Unreliable data	59 (21%)	48 (23%)	35 (19%)	38 (33%)	18 (25%)	25 (30%)	28 (32%)	Investigator bias
Lack of understanding of the data	15 (5%)	11 (5%)	13 (7%)	2 (2%)	3 (4%)	2 (2%)	3 (3%)	New animal model
Insufficient data	179 (65%)	133 (65%)	117 (64%)	62 (54%)	40 (56%)	48 (57%)	50 (57%)	Limited QTc data
Conflicting data	23 (8%)	13 (6%)	17 (9%)	12 (11%)	11 (15%)	9 (11%)	7 (8%)	QT increase only in one of the two studies
Issue: *uncertainty about the…*								
Effect size or type	131 (47%)	106 (52%)	80 (44%)	70 (61%)	41 (57%)	53 (63%)	53 (60%)	Magnitude of response difficult to interpret
Subpopulation	85 (31%)	58 (28%)	61 (34%)	21 (18%)	18 (25%)	15 (18%)	18 (20%)	Uncertain efficacy in patients with poor performance status
Long term effect	29 (11%)	22 (11%)	17 (9%)	12 (11%)	5 (7%)	9 (11%)	9 (10%)	Unknown how many required cycles for durable response
Benefit-risk balance	19 (7%)	14 (7%)	15 (8%)	9 (8%)	6 (8%)	5 (6%)	6 (7%)	Need to study optimal dose to maximise the benefit-risk
Other	12 (4%)	5 (2%)	9 (5%)	2 (2%)	2 (3%)	2 (2%)	2 (2%)	Further investigation needed to envisage effective RMM
2. Coping strategy								
Ask data*	181 (66%)	133 (65%)	107 (59%)	73 (64%)	41 (57%)	58 (69%)	67 (76%)	Post-authorisation study characterising safety
Manage impact via SmPC or RMM**	60 (22%)	46 (22%)	42 (23%)	23 (20%)	18 (25%)	16 (19%)	15 (17%)	Monitoring during first eight weeks of therapy
Apply reasoning**	33 (12%)	27 (13%)	22 (12%)	14 (12%)	10 (14%)	11 (13%)	11 (13%)	The safety profile was considered current knowledge
Accept the uncertainty**	183 (66%)	132 (64%)	118 (65%)	77 (68%)	44 (61%)	57 (68%)	62 (70%)	Small safety database acceptable despite limitations

Table 1: Classification applied to 276 uncertainties extracted from 64 approved oncology products. *Advice = % of uncertainties related to a product for which scientific advice or protocol assistance was given on the clinical development plan; RCT= % of uncertainties related to a product for which an RCT was performed; orphan = % of uncertainties related to an orphan product; accelerated= % of uncertainties related to a product approved via an accelerated procedure; haematological = % of uncertainties related to products for haematological cancers; conditional/exceptional= % of uncertainties related to products that received a conditional or exceptional marketing authorisation. *The percentage of uncertainties for which new data was asked (diagram, column 2). **The sum of the three last coping strategies gives 100% (diagram, column 3); each of the last three categories includes uncertainties both with and without asking for new data in addition. Abbreviations: RMM= risk minimisation measure; QTc= corrected QT.*

Examples of uncertainties related to patient preferences

Uncertainty from EPAR	Type	Issue	A patient preference study could …
Unknown whether response rate translates into clinical benefit	Lack of understanding	Effect size or type	Quantify the value of response rate as endpoint according to patients and the minimal amount of response rate patients require in return for the toxicities of the drug
Results suggested better efficacy for higher dose, but also a higher toxicity	Insufficient data	Benefit-risk balance	Calculate the proportion of patients who are willing to accept the risks in turn for the benefits of the drug for a given dose
The clinical implication of a positive non-clinical phototoxicity assay is undetermined	Lack of understanding	Effect size or type	Quantify the importance of photosensitisation to patients and the maximal amount of phototoxicity patients are willing to accept in return for the benefit of the drug

Table 2: Examples of identified uncertainties where patient preference studies could potentially help address the uncertainty

Diagram showing the association between the uncertainty type and coping strategy

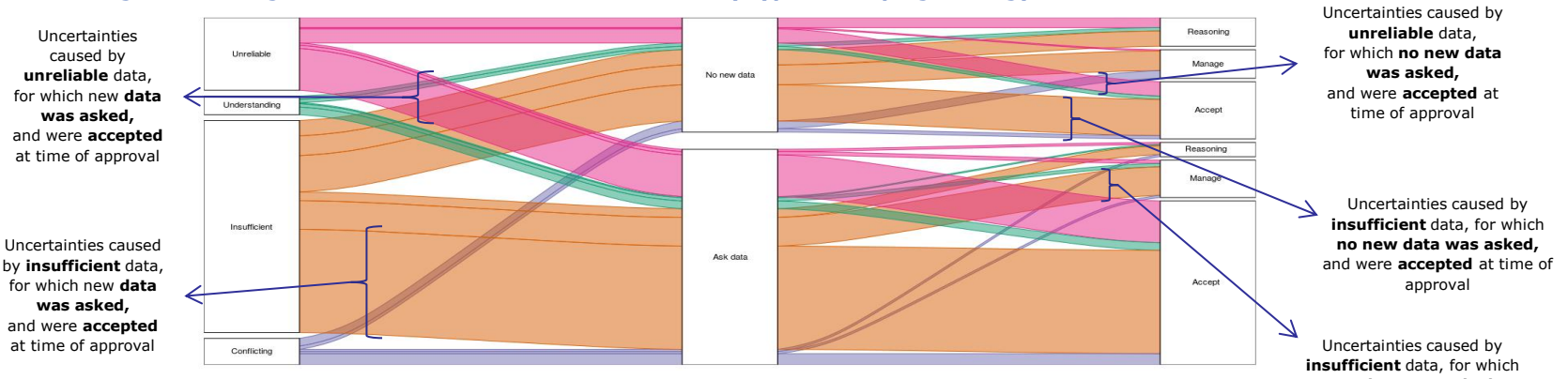

Figure 2: *Uncertainties are clustered in streams that each represent a group of uncertainties with a similar type (column 1, indicated by different colours) and coping strategy (column 2 and 3). The height of stream and block of represents the proportion of uncertainties categorised into each of the sub-categories. Following the streams from left to right allows identifying for each stream of similar uncertainties their type and coping strategy. Colours indicate the different types of each stream of uncertainties: unreliable data= pink; lack of understanding= green; insufficient data= orange; conflicting data= purple.*

Conclusions

- This study developed a **classification of regulatory uncertainties and coping strategies,** provides insights into the **main types (insufficient or unreliable data) and coping strategies (accept uncertainty while asking more data)** as well as main variables associated with a lower number of uncertainties per product **(RCT design)** and increased use of the coping strategy "ask data" post-approval **(no RCT design, conditional or exceptional approval)**
- The comprehensiveness and clarity of the **classification should be further validated** e.g. by investigating inter-rater agreement between different individuals performing the categorisation
- The **applicability of the classification should be further investigated** by applying it to additional uncertainties (e.g. to products in other therapeutic areas or from 2017 onwards) as well as by prospectively applying it from the start of the benefit-risk assessment (e.g. to the list of questions posed by regulators at day 120 and list of outstanding issues at day 180 of the marketing authorisation) and following-up during the marketing of the drug
- The further development and application of this **classification has the potential of strengthening the management, quantification and communication of uncertainties**, especially of those that are attributed to insufficient or unreliable data and accepted without request for new data

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