**Supplementary Table 2:** Concerns matrix

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| --- | --- | --- | --- |
|   |  |  |  CONCERNS MATRIX |
|   |   |   |   |  |  |   |   |   |   |
|   |   | *P* |  |  | **Top 3-5 prioritised uncertainties to address using MEA** |
| **Priority Legend (*P*):**0: not evaluated1: no priority2: minor priority 3: moderate priority - itself not sufficient to block reimbursement4: major priority - itself blocking reimbursement | **Prioritizing most important uncertainties**  | 0 |  |  |   |
|   |   |   | ↑ |  |  |   | ↑ |   | ↑ |
| **Steps:**  |   | **Real world health outcomes** |  | **Cost per patient** | **Budget impact/ revenue** | **Cost-effectiveness** |
| 1. Identify uncertainties2. Connect uncertainties to real world clinical outcomes, cost per patient, budget impact, cost-effectiveness3. Prioritise using legend | **Narrowing down main uncertainties** | *P* | Main uncertainties | *P* | Main uncertainties | *P* | Main uncertainties | *P* | Main uncertainties |
| 0 |   | 0 |  | 0 |   | 0 |   |
|  |
|  |
|  |
|   |   |   | ↑ |  |  |   | ↑ |   | ↑ |  |
| **UNCERTAINITES** | **Description** | **Expected influence on real world health outcomes** |  | **Expected influence on cost per patient** | **Expected influence on budget impact / revenue** | **Expected influence on cost-effectiveness** |  |
| **Uncertainties related to the size and characteristics of the population** |   | *P* |   | *P* |  | *P* |   | *P* |   |  |
| Incidence and prevalence |   | 0 |   | 0 |  | 0 |   | 0 |   |  |
| Size of the target population |   | 0 |   | 0 |  | 0 |   | 0 |   |  |
| Characteristics of subpopulations and target population, such as age and time since diagnosis |   | 0 |   | 0 |  | 0 |   | 0 |   |  |
| The spectrum and variations of disease manifestations, such as symptom severity |   | 0 |   | 0 |  | 0 |   | 0 |   |  |
| Different genotypes or phenotypes |   | 0 |   | 0 |  | 0 |   | 0 |   |  |
| […] |   | 0 |   | 0 |  | 0 |   | 0 |   |  |
| **Uncertainties related to the natural history of the disease and its current management** |   |   |   |   |  |   |   |   |   |  |
| Absence of evidence on natural course of history of the disease over time, with different prognoses for patients with varying characteristics |   | 0 |   | 0 |  | 0 |   | 0 |   |  |
| Absence of current standards of care |   | 0 |   | 0 |  | 0 |   | 0 |   |  |
| Uncertainty about the relevant comparator |   | 0 |   | 0 |  | 0 |   | 0 |   |  |
| Uncertainty on the relevant endpoints for clinicians and patients to assess and monitor the disease state |   | 0 |   | 0 |  | 0 |   | 0 |   |  |
| […] |   | 0 |   | 0 |  | 0 |   | 0 |   |  |
| **Uncertainties related to the new treatment** |   |   |   |   |  |   |   |   |   |  |
| Uncertainties about the size of the treatment effect |   | 0 |   | 0 |  | 0 |   | 0 |   |  |
| Uncertainty on the optimum posology |   | 0 |   | 0 |  | 0 |   | 0 |   |  |
| Uncertainty on the treatment effect within subgroups |   | 0 |   | 0 |  | 0 |   | 0 |   |  |
| The effect size in the real target population when the trial population is different |   | 0 |   | 0 |  | 0 |   | 0 |   |  |
| The characteristics of patients benefiting more from treatment (and the ability of a biomarker to identify those patients) |   | 0 |   | 0 |  | 0 |   | 0 |   |  |
| The durability of the effect |   | 0 |   | 0 |  | 0 |   | 0 |   |  |
| The possibility to retreat after recurrence |   | 0 |   | 0 |  | 0 |   | 0 |   |  |
| The way in which the new treatment will modify further treatments in the treatment sequence |   | 0 |   | 0 |  | 0 |   | 0 |   |  |
| Uncertainty about adverse events and safety not yet observed in the trials |   | 0 |   | 0 |  | 0 |   | 0 |   |  |
| […] |   | 0 |   | 0 |  | 0 |   | 0 |   |  |