**Supplementary Table 2:** Concerns matrix

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | | |  | CONCERNS MATRIX | | | | | | | |
|  |  |  |  | | |  |  | |  |  |  |  |
|  |  | *P* |  | | |  | | **Top 3-5 prioritised uncertainties to address using MEA** | | | | |
| **Priority Legend (*P*):** 0: not evaluated 1: no priority 2: minor priority  3: moderate priority - itself not sufficient to block reimbursement 4: 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 uncertainties 2. Connect uncertainties to real world clinical outcomes, cost per patient, budget impact, cost-effectiveness 3. 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 |  |  |