**Appendix**

**Table 1.** Definitions of uncertainties and SVJs collected from HTA reports

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| **CLINICAL UNCERTAINTIES** | |
| **Clinical benefit** | 1) Clinical trial demonstrated a modest or low clinical benefit  2) Different studies demonstrated different clinical benefit of the treatment  3) Clinical benefit achieved only in a subpopulation 4) Clinical benefit is not statistically significant compared to that of the comparator  5) Concerns around the real magnitude of the clinical benefit including; long-term effect of the medicines, assumptions on retreatment rates or assumption on the discontinuation of treatment or on a return to a rate of progression equivalent to the natural history of the disease or on the choice of data. |
| **Clinical evidence** | 1) Lack of comparative clinical data 2) Lack of long-term evidence 3) Lack of safety data |
| **Study design** | 1) Limitation(s) in the clinical trial design leading to confounding factors in the clinical benefit  2) Blinding used in the study is unsuitable 3) Small sample/study population size  4) Use of surrogate instead of clinical endpoints |
| **Clinical comparator** | 1) Clinical trial comparator not marketed or not used in routine clinical practice of the study country  2) Clinical trial comparator is not the standard of care in the study country 3) Clinical trial comparator is a placebo (placebo-controlled trial) |
| **Generalizability of trial population** | 1) The trial population is not generalizable to the population of the study country due to ethnicity/ baseline characteristics and prevalence 2) The trial population is underrepresented in the population of the indication under review 3) Only a subgroup of the trial population is considered suitable for the indication under review |
| **Relevance to clinical practice** | 1) Product not used in routine clinical practice of the study country 2) Differences in the administration/dose compared to standard of care 3) Treatment criteria (e.g. baseline of the patients for treatment initiation) differ between the study and clinical practice 4) Product has limited use in the study country |
| **ECONOMIC UNCERTAINTIES** | |
| **Modelling** | 1) Inappropriate use of curves  2) Inappropriate extrapolation method used 3) Misrepresentation of the population or of a specific subgroup under review  4) Computational errors |
| **Model type** | 1) The use of a certain model is not suitable for the analysis |
| **Economic comparator** | 1) Comparator used in the model is not marketed, and/or is not the standard of care in the study country, and/or is not used in the clinical practice of the study country |
| **Cost** | 1) All or some costs included in the model are too low or too high 2) Model does not include specific cost that would lead to over/under- estimation of the cost-effectiveness such as administration cost or wastage |
| **Utilities** | 1) Utility values used in the model are not suitable leading to over-estimation or under-estimation of the ICER 2) Utility source is not suitable/ or the measured was not appropriate |
| **Cost-effectiveness** | 1) ICER over threshold 2) ICER too high even after testing with sensitivity analysis or re-evaluation carried out by manufacturer/HTA body/ external reviewers |
| **SOCIAL VALUE JUDGEMENTS** | |
| **Rarity** | Rarity of the disease and/or orphan status of the respective treatment |
| **Severity** | Disease severity and its impact on the patients and the caregivers |
| **Unmet need** | Unmet need for new treatments in the indication under review |
| **Short life expectancy** | Targeted disease has a poor prognosis with a short life expectancy |
| **Innovation** | Treatment offers a therapeutic advancement or an innovative mechanism of action compared to currently available treatments for the therapeutic indication in question |
| **Administration advantage** | Treatment offers enhanced route and frequency of administration compared to currently available treatments for the therapeutic indication in question |
| **Impact on society** | Treatment offers significant improvement on the organization of care and subsequently on the wider society |
| **Impact on QoL** | Treatment offers significant improvement on HRQoL |
| **Emotional burden** | Treatment offers significant improvement on the emotional burden created by the disease to patients or families |
| **Functional burden** | Treatment offers significant impact on the ability of the patients and their families/caregivers to work and carry out daily activities |
| **Safety profile** | Treatment has a favourable safety profile compared to currently available treatments for the therapeutic indication in question and/or the safety profile of current treatments is heavily affecting patients such that they would prefer to be able to have access to more treatment options with a different safety profile |
| **Special considerations** | Set of considerations explicitly considered in the HTA country that are consistently used to shape decisions (e.g. Human dignity principle in Sweden or the end of life criteria in England and Scotland) |