## Supplementary Files to the manuscript

*Real-world data from expanded access programmes in health technology assessments: a review of NICE technology appraisals*

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The code and data from this paper are available at the GitHub repository of the first author: https://github.com/TobiasPolak/





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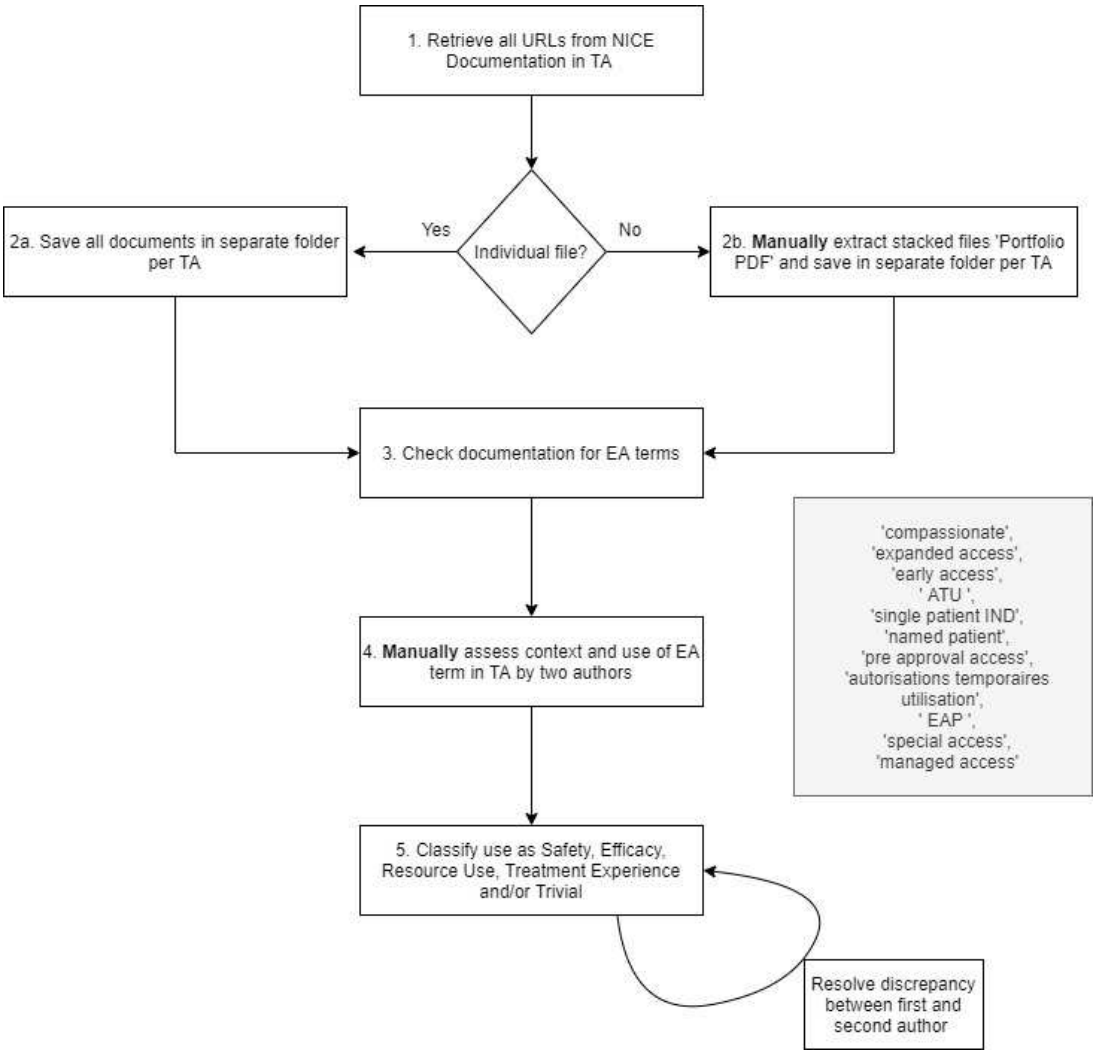
## A. Protocol Workflow



### B. Top 5 Most Referenced Appraisals

**TA391** Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel

In 2016, NICE assessed the cost-effectiveness of anticancer taxane therapy cabazitaxel for the treatment of metastatic prostate cancer that relapsed after it was treated with docetaxel. Sanofi was the submitting Company and the School of Health and Related Research (ScHARR) produced the evidence review group (ERG) report. TA391 is an updated appraisal of TA255.

In this appraisal, the company did not collect data on health-related quality of life in the main trial that investigated the use of cabazitaxel, so it took utility values from the expanded access programme in the United Kingdom. The ERG found several issues with data from this program: the open-label nature, generalizability (patients were **potentially more fit** than in the trial), the analysis was performed at interim and had not yet been subject to peer review.

The Committee partly shared the vision of the ERG: '*the Committee was concerned about the uncertainty around the utility value and whether the utility value as calculated from the early access programme could be applicable to the wider population with hormone-refractory metastatic prostate cancer refractory to docetaxel treatment'*. On the other hand, the committee also appreciated the efforts of the company: '*The committee acknowledged the limitations of using data from the UK early access programme but, in the absence of more robust evidence on health-related quality of life, it concluded that the company had used the best available data to estimate utility values'.*

The initial Final Appraisal Determination did not recommend the use of cabazitaxel, leading the company to appeal to the Appeal Panel, focusing in part on the interpretation of the EAP trial. ("the context of the EAP trial was misinterpreted, data from the EAP trial were incorrectly interpreted, and the nature of interim data was misunderstood by the committee"). The Appeal Panel '*understood both sides' positions and regarded them both as reasonable*' and as such dismissed all the grounds of appeal. After a new confidential discount to the price of cabazitaxel was arranged, its use has been recommended within the NHS.

**TA667** Caplacizumab with plasma exchange and immunosuppression for treating acute acquired thrombotic thrombocytopenic purpura

In 2020, NICE assessed the cost-effectiveness of the humanized antibody caplacizumab, used together with plasma exchange and immunosuppression for the treatment of acute acquired thrombotic thrombocytopenic (TTP) purpura. Caplacizumab inhibits the interaction between Von-Willebrand-factor and thrombocytes, thereby reducing the aggregation of thrombocytes which is typical for TTP. Sanofi was the submitting Company and the Peninsula Technology Assessment Group (PenTAG) produced the evidence review group (ERG) report.

In the main trial for caplacizumab (HERCULES, N=145), no patient died while on treatment with caplacizumab (0%). Due to the unreliability of mortality data from the trial (clinicians noted that mortality was unlikely to be 0%), data from the compassionate use programme was brought in. At the first data lock, 8 out of 187 (4.2%) of the patients perished, and 9/239 (3.8%) at second data lock.

The limited information available rendered the interpretation of these data difficult. Mortality from the compassionate use programme was based on deaths reported via Adverse Event Reporting. No baseline characteristics were available to compare patients among data sources: *The monitoring programme for caplacizumab was a compassionate use programme rather than a data collection programme. As such, the only information available includes where the patient was from, whether caplacizumab was received and whether the patient died, (…). Therefore, an assessment of the similarity between mortality sources using patient characteristics could not be conducted* .

Therefore, the ERG '*notes potential ambiguities and sources of bias in the compassionate use program (…) including unknown follow-up periods, unclear recruitment process, and that it draws from an international population'*.

The company interjected that '*the compassionate use programme estimates selected to represent caplacizumab in the comparison are, if anything, too high*' – as *'clinicians agreed that treatment with caplacizumab is started later in the compassionate use programme that it would be if it was made available through routine funding (as requests are individual and caplacizumab is not available on site). Mortality data based on this programme should therefore be considered as the maximum mortality expected with caplacizumab.'*

The committee agreed that it was impossible to '*estimate reliably the extent of the benefit using the randomised trial data*' and recognized the need for use of data on deaths from the global compassionate use scheme. It noted that the absolute rate of death for people treated with caplacizumab under the compassionate use scheme was likely to be valid, but that the relative benefit ascribed to caplacizumab from observational data '*was very likely to be confounded'*.

Furthermore, the committee noted that *'Some potential cost savings associated with caplacizumab may not be included in the company's model'* as '*The company stated that, based on its observations from the compassionate use scheme for caplacizumab, in NHS clinical practice, people would have it for a shorter duration than in the trials. The committee in general prefers not to disassociate estimates of cost and effectiveness from a trial. However, it appreciated that many assumptions about caplacizumab's effectiveness in this model were not taken from the main trial. It also thought that some potential cost savings associated with caplacizumab may not have been included in the company's model.'*

Despite the remaining uncertainty, *'(…) the assumptions in the economic modelling are plausible. Also, there are potential benefits with caplacizumab that are not included in the cost-effectiveness estimates. Overall, the estimates are within the range normally considered a costeffective use of NHS resources. So, caplacizumab is recommended for treating acute acquired TTP'*.

**TA588** Nusinersen for treating spinal muscular atrophy

In 2018-2019, NICE assessed the cost-effectiveness of the antisense oligonucleotide nusinersen, used in the treatment of spinal muscular atrophy. Nusinersen promotes the formation of the functional SMN protein, through modulation of intron splicing, essential for normal function of motor neurons. Sanofi was the submitting Company and the Peninsula Technology Assessment Group (PenTAG) produced the evidence review group (ERG) report.

NICE initially did not recommend the use of nusinersen for treating SMA as it was not deemed a cost-effective use of NHS resources. NICE consulted with the public and professionals and noted that '*Following consultation, the committee heard that there was real-world evidence that would be relevant for the committee's decision making that had not been considered by the company.'*

Although the Company briefly touches upon data from the early access programme (EAP) in UK and Ireland (63 patients, of which 25 males and 38 females) and additionally points at the publication of a second European EAP conducted in other European countries (N=36, Gargaun et al.), the Spinal Muscular Atrophy Support UK and The SMA Trust points to several other studies in the consultation period: '*We note that the real-world studies only review outcomes for children with SMA Type 1 for the first six months of treatment but consider 'real world' evidence critical to decision making. They all assist with confirming the certainty of evidence of effectiveness (see below). In particular we refer to: Reviews of the Expanded Access Programme:*

- *Europe - 33 children aged from 8.3 to 113.1 months - December 2016 - May 2017. Aragon-Gawinska, K et al. (2018)*
- *Australia – 16 patients aged 2.5 months to 35.7 years November 2016 – September 2017 Farrar, M et al. (2018)*
- *England - Great Ormond Street Hospital – 21 patients aged 8.3 – 113.1 months March – October 2017 Tillmann, A et al. (2018)*
- *Germany – 61 patients aged 1 – 93 months in seven neuromuscular centres November 2016 – June 2017 Pechmann, A et al. (2018)*
- *Italy – 104 patients – aged 3 months – 19 years 9 months - first six months of EAP Pane, Pane M et al. (2018)*
- *Hoy, S (2018)'*

The committee responded: '*The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.*

The company stated that they did not consider these data '*because the results were consistent with the clinical data that it had presented and, in comparison, the data were immature, would be from non-UK sources and would only include SMA type 1'.* The committee stated '*that it would have liked the company to identify supportive real world evidence, given the clinical uncertainties identified.'* - but also acknowledged that the company already included several types of data.

In the end, Nusinersen became available through a managed access agreement *', including the collection of more data to address the uncertainties. '*

**HST7** Strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency

In 2018, NICE assessed the cost-effectiveness of strimvelis, used to treat severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID). Patients with ADA-SCID have a dysfunctional gene, needed for the production of the enzyme adenosine deaminase (ADA), leading to defective lymphocytes and thereby severe immunodeficiency. Strimvelis consists of genetically modified bone marrow cells of the patient, reactivating ADA production. Strimvelis is used in patients who are ineligible for allogeneic bone-marrow transplantation. Since strimvelis is a gene therapy product, its cost-effectiveness is evaluated through a 'highly specialised technology guidance' (HST). GlaxoSmithKline was the submitting company, and the Centre for Reviews and Dissemination and Centre for Health Economics in York prepared the Evidence Review Group (ERG) report.

The submission of data for the gene therapy Strimvelis comprised a mix of evidence sources: '*The safety and efficacy of Strimvelis have been evaluated in a programme comprising 2 pilot studies, 1 pivotal study, a compassionate use programme (CUP), and a long-term follow-up (LTFU) study.'*

The company preferred to report the results of the clinical trials together, as an '*integrated population', with results from the Named Patient Programme (NPP) presented alongside as supportive evidence. The company stated that it did not include the NPP data in the integrated population because the population of the NPP was substantially different to the population in the other trials, and that it could not access all the patient-level data because the NPP was a clinician-initiated process.*

The ERG critiqued this decision: '*However, the ERG did not consider it appropriate that data from the Named Patient Population were excluded from the narrative synthesis of clinical effectiveness evidence. This is particularly important given the small sample size of the Strimvelis Integrated Population (n=18) and therefore the need to consider all available data when evaluating the effectiveness of this treatment.'*

Indeed, the Company even requested (to no avail) the ERG to remove the wording 'NPP study', as '*Noting the NPP as a study wrongly indicates that the NPP is part of the Strimvelis clinical programme and therefore at the same level in terms of availability and quality of evidence.*

NICE however specifically requested more information on these patients. '*A3. Please provide a narrative summary of the data (e.g. in terms of overall survival, intervention-free survival, adverse events etc.) available from the named patient programme using the same format as in the main clinical effectiveness section on the Strimvelis Integrated Population.'*

As the named-patient program was investigator-initiated, access to data was limited: 'A3. *Table 1 contains the requested information, as available, for patients in the NPP. Data on the proportion of patients with viral infection at baseline are not available. As the ERG has noted, the NPP is not run by GSK, which limits access to data and as such it is difficult to speculate on wider applicability of these immature and incomplete data. The programme is ongoing and data are not scheduled for formal analysis until all patients have reached 3 years of follow-up'.*

Strimvelis is recommended as a treatment option for treating adenosine deaminase deficiency–severe combined immunodeficiency (ADA–SCID) when no suitable human leukocyte antigen-matched related stem cell donor is available.

**TA604** Idelalisib for treating refractory follicular lymphoma

In 2019, NICE assessed cost-effectiveness of idelalisib, used as monotherapy for refractory follicular lymphoma, a malignancy of B-lymphocytes. Idelalisib is a kinase inhibitor, reducing the activity of phosphoinositide 3-kinase p110δ (PI3Kδ), which is an enzyme involved in growth, proliferation, differentiation and survival of blood cells. PI3Kδ is known to be overactive in B-cell malignancies, and is therefore used as therapeutic target in follicular lymphoma. Gilead was the submitting company, and Kleijnen Systematic Reviews produced the Evidence Review Group (ERG) report.

The single-arm main trial (DELTA) was supplemented with data from the Compassionate Use Program: *The company supplemented the DELTA study with another source of evidence for idelalisib: the Compassionate Use Programme (CUP). This provided retrospective observational data from patients with follicular lymphoma having compassionate treatment in the UK and Ireland. The company took a subset of 79 patients with relapsed or refractory follicular lymphoma that had been treated with idelalisib. In these patients, median progression-free survival was 7.1 months, and median overall survival was not reached.*

The Committee decided that **neither** data set was '*adequate enough for using to determine how well patients on idelalisib fared compared with people who had not taken idelalisib.'* Despite the absence of controlled trials, the committee discussed the evidence presented to determine which set (trial or CUP) was most generalizable to the use of idelalisib clinical practice. Evidence was ambivalent:

- *The committee noted the difference in Eastern Cooperative Oncology Group (ECOG) performance status and Follicular Lymphoma International Prognostic Index (FLIPI) I and II scores between DELTA and the CUP. Notably, 8% of patients in DELTA had an ECOG score of 2 to 4 compared with 25% of patients in the CUP, reflecting poorer performance among patients in the CUP. The clinical experts stated that the ECOG performance status in CUP more closely reflected clinical practice than that in DELTA.*
- *The clinical experts noted that the time since completing the last therapy was shorter in DELTA than in the CUP, suggesting that patients in DELTA had a poorer prognosis*

Resulting in the ambivalent conclusion that *'the populations in DELTA and the CUP were different. (…) Also, patient and disease characteristics at baseline differed, with some suggesting a more favourable prognosis in DELTA than in the CUP, and others suggesting the opposite.' Even help from clinical experts could not resolve the issue, as 'the clinical experts suggested that the CUP cohort was more likely to reflect the intended UK treatment population because it was a 'real-world' study with patients from Britain and Ireland. However, the clinical experts acknowledged that such studies lack the methodological rigour typical of a clinical trial.'* In the end, '*The committee concluded that it was unclear whether the DELTA population or the CUP cohort more closely reflected clinical practice and took both into account for decision making.'*

Idelalisib was not recommended in the Final Appraisal Determination. '*There are a wide range of cost-effectiveness estimates but, because the evidence is weak, idelalisib is not considered to represent a cost-effective use of NHS resources. Therefore, idelalisib cannot be recommended for routine use in the NHS.'*