NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGY

Selumetinib for treating symptomatic and inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in children aged 3 years and over [ID1590]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD)**

2. **Comments on the Evaluation Consultation Document from Astrazeneca UK**

3. **Consultee and commentator comments on the Evaluation Consultation Document** from:
   - Childhood Tumour Trust
   - Nerve Tumours UK

4. **Evidence Review Group critique of company comments on the ECD**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Selumetinib for treating symptomatic and inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in children aged 3 years and over [ID1590]

Highly Specialised Technology Evaluation

Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee	AstraZeneca	[redacted] SPRINT Phase II Stratum I is the most relevant data source for selumetinib in the licensed indication of paediatric patients with neurofibromatosis type 1 (NF1) with symptomatic, inoperable plexiform neurofibroma (PN). The evidence from this clinical trial is supportive of the effectiveness of selumetinib at stabilising and reducing PN volume, compared with best supportive care.[1] However, there are limitations associated with this evidence base; these limitations are inevitable consequences of the ultra-rarity and heterogeneity of NF1 PN. In light of the available evidence, we maintain that the modelling approach in the company submission represents the best approach and only feasible approach. The rationale behind the modelling approaches taken has been further explained within this response, and we have adopted a large extent of the recommendations within this response (where feasible). However, use of some assumptions in the modelling remains inevitable and we acknowledge that this may contribute a degree of uncertainty. [redacted] [redacted] **[Figure 1 received but not reproduced in this table]**	Comment noted.

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			[Figure 2 received but not reproduced in this table] Selumetinib represents a step-change in the management of paediatric patients with symptomatic, inoperable NF1 PN, a patient population where this is a substantial unmet need for an effective treatment. Selumetinib treatment results in durable stabilisations and reductions in PN volume in paediatric patients, preventing or reducing the most rapid stage of PN volume growth.[1] In the following responses, AstraZeneca have sought to implement the committee's feedback wherever feasible. [redacted]	
2	Consultee	AstraZeneca	**The conclusions regarding the clinical evidence are sound, and an accurate interpretation of the evidence** The committee evaluated all evidence from the pivotal SPRINT Phase II Stratum I study, the most relevant data source for selumetinib in NF1 PN.[1] The committee concluded that based on the clinical trial evidence, selumetinib is effective at reducing the volume and size of PN compared with best supportive care (Evaluation Consultation Document [ECD] Report page 4), and that the results from the SPRINT trial are generalisable to the UK population (ECD Report Section 3.10).	Comment noted.
3	Consultee	AstraZeneca	**The development of a patient-level model is unfeasible** The committee stated that they would prefer to see a patient-level model. As discussed during the Committee Meeting, the available evidence package (Phase II Stratum I of the SPRINT clinical study and National Cancer Institute [NCI] Natural History study) does not support the development of a patient-level model. Very few Highly Specialised Technology (HST) appraisals have used patient-level models, likely due to the need to have sufficient quantities of patient-level data available to inform such cost-effectiveness analyses, and the challenge of recruiting patients to studies in ultra-rare conditions. The one HST appraisal identified by AstraZeneca in which a patient-level model was developed had a significantly longer-term evidence base (over 14-years) and larger clinical trial population of 112 patients to draw from.[2] This appraisal also used relatively well-established sub-models in different organs (e.g. pancreas, liver, cardiovascular, kidney, etc) and the well-established surrogate outcome of HBA1c to calculate transition probabilities.[2] While we acknowledge that a patient-level simulation would allow the development of a more detailed model which more closely reflects the heterogeneity of patients with NF1 PN, it would not have been feasible to meet this recommendation with the available data. We explored the feasibility of developing a regression-based patient level model at the stage of early model conceptualisation. However, the heterogeneity of NF1 PN, coupled with the limited sample size for the SPRINT Phase II Stratum I study (n=50),[1] made it unfeasible to establish a quantitative relationship between potential covariates sufficiently informative for decision-making purposes. It is worth emphasising that within the context of an rare condition, and, relative to the total estimated number of children with NF1 PN in the UK and other related studies, the SPRINT Phase II trial achieved	Comment noted. Although it would have preferred a model structure that represents the disease and includes outcomes that clinical and patient experts advised were important, the committee recognised the difficulty of including clinical outcomes in the model due to the heterogeneity of NF1 PN and this would require many

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			a good sample size. Covariates explored included: age, PN location, PN volume and quality of life (please see results included below the heading 'Further characterisation with regression analyses'). In addition, no patient-level health-related quality of life (HRQoL) data and other patient reported outcomes were available from the Natural History study to support such analysis; this also meant that we couldn't establish a quantitative relationship between potential covariates and HRQoL in patients treated with best supportive care (BSC). The very high level of heterogeneity within the NF1 PN patient population also made it difficult to define a series of distinct health states. As multiple individual PN can occur anywhere on the body, combinations of treatment effect modifiers such as PN location, PN size, PN growth rate and age result in all patients having different and unique health states. [redacted].[3] It is also impossible to quantify the individual and combined impacts of each effect modifier on HRQoL, especially with data from 50 patients. For example, subgrouping the analysis by PN location would have reduced the maximum sample size to only [redacted].[1] The heterogeneity of NF1 PN was emphasised during the committee meeting in November 2021, where a patient expert explained that PN affect everyone differently, and can be unpredictable, making living with NF1 PN challenging. We appreciate that a degree of simplification has been necessary in order to develop the current model. However, the modelling approach remains the most robust possible, given the available data and the heterogeneity of NF1 PN. The current modelling approach accounts for the overall improvements in clinical outcomes and quality of life seen at an individual and population level in selumetinib treated patients, alongside stabilisations and reductions in PN volume (see comment #7 for further details). **Patient-level modelling would result in a model associated with a significantly higher level of uncertainty**, due to a larger number of assumptions that would have to be made on the quantitative relationship between each effect modifier and outcome. This would impair the ability of the committee to draw a conclusion on the cost-effectiveness of selumetinib that improves on the existing approach. During the open session of the Evaluation Committee Meeting (10th November 2021), there was lengthy discussion on the cost-effectiveness model during which we presented potential modelling approaches and the advantages and disadvantages of each, discussed our recommended modelling approach and provided an explanation as to why it was not feasible to develop a patient-level model. At that time, no concerns were raised by the Appraisal Committee and indeed, it was stated by the health economic expert on the committee that our model was likely to be conservative given the assumptions that we had made. Unfortunately, as discussed above, a patient-level model remains unfeasible, however we believe we have taken a pragmatic approach in developing the most robust model possible with the evidence	assumptions. It concluded the company revised model structure is suitable for decision making. See FED section 3.9 and 3.11.

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			package we have available. <u>Further characterisation of results with regression analysis</u> For full transparency, we have provided additional details of the analysis to assess whether quantitative relationships could be established between key variables, specifically: investigating the relationship between Pediatric Quality of Life Inventory™ (PedsQL) total scores and patient characteristics, disease characteristics or tumour size. Regression analyses were performed using the PedsQL total scores collected from SPRINT Phase II Stratum I; self-reported values were used where available, otherwise parent/guardian reported scores were used. As patient and disease characteristics were only captured at baseline, the regressions were run using only baseline quality of life data. *Patient and disease characteristics* The first analysis investigated the effect of NF1 PN disease duration and age on patient quality of life. It is logical that the longer a patient has had a given disease, the greater they are likely to have suffered from the effects of the disease; a patient cannot have had a disease for longer than they have been alive. In particular, once PN-related morbidities develop, they are extremely unlikely to resolve spontaneously.[4] As duration of disease is correlated with patient age, age was included as an explanatory variable, to accurately estimate the effect of the two different variables. **The regression showed insignificant coefficients, providing no evidence to suggest PedsQL score is predicted by age or disease duration** ([Figure **3 received but not reproduced in this table]**). This result is unexpected, based on the natural history of NF1 PN. The inability to identify a significant relationship is likely due to the small dataset and heterogenous patient population, inevitable consequences of the rarity and complexity of NF1 PN. With a larger dataset it may be that a relationship would have been found between quality of life and age or disease duration. **[Figure 3 received but not reproduced in this table]** The second analysis examined body surface area (BSA) and weight. Patient BSA is related to age, height, and weight, and thus may act as a good proxy for all these factors without using excessive statistical power by requiring three coefficients to be included. The regression analysis for BSA (**Error! Reference source not found.**), however, indicates that **there is limited support for the hypothesis that PedsQL is linked to BSA**. In addition to a lack of significance, the interquartile range of BSA is only 0.5, meaning that any practical impact of PedsQL is half of the observed coefficient. Again, this	

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			finding is likely due to the inevitable limitations of data collected in rare and heterogenous patient population. **[Figure 4 received but not reproduced in this table]** In order to confirm the results of the analysis for BSA, a regression analysis was performed looking at the impact of weight on PedsQL, in light of evidence suggesting weight may be an important factor in patient reported outcomes for patients with NF1 PN. However, the results of the regression ([Figure 5 received but not reproduced in this table]) indicate that weight is also a poor predictor of PedsQL score, when taken in isolation. **[Figure 5 received but not reproduced in this table]** In the SPRINT study, patients were classified according to whether their disease had progressed (≥20% increase in neurofibroma volume) in the 15-month period prior to enrolment in the study.[1] A regression analysis was conducted to evaluate whether progression status at baseline is a predictor of PedsQL score ([Figure **6 received but not reproduced in this table]**). The coefficient associated with this was not significant; based on the available data, **progression status at baseline does not appear to predict patient PedsQL scores**. This was unexpected, as it was observed that patients who were classified as having 'progressed' at baseline had lower PedsQL scores. The inability to draw a significant correlation is likely due to the inevitable limitations of the available data, in particular the rarity of the NF1 PN and subsequent small sample size. **[Figure 6 received but not reproduced in this table]** *Tumour location* Tumour location was evaluated at baseline in the SPRINT study and has been suggested to be prognostic of patient quality of life. The regression analysis of PN location was first performed using PN locations as coded in SPRINT Phase II Stratum I ([Figure 7 received but not reproduced in this table]). No reference group was used (the intercept was supressed) as it was not clear which group should constitute the intercept. The results were therefore difficult to interpret, due to both the small and highly variable sample size (ranging from [redacted]), and to the uncertainty over which group should be used as the intercept relative to which all other coefficients would be estimated. **[Figure 7 received but not reproduced in this table]**	

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			PN locations were therefore reassigned to one of four categories, classifying PN as to whether there was involvement on the trunk, head, neck or extremity. This then allowed an intercept to be used in the equation and four coefficients to be estimated, by increasing the power for detecting a difference in each PN location (with patients potentially having more than one PN location depending on the extent of their PN; [Figure 8 received but not reproduced in this table]). **[Figure 8 received but not reproduced in this table]** In the recoded approach, the location of the PN and involvement of the trunk, head, neck or extremity does not predict PedsQL score. This is likely due to the extremely heterogenous nature of PN and the complex interplay of precise PN location and volume in determining the extent and severity of PN-associated morbidities. Overall, of the different patient and disease characteristics evaluated at baseline in the SPRINT Phase II Stratum I and considered within these regression analyses, none can be linked to PedsQL total score. *Tumour volume* Regression analysis was also used to estimate the relationship between PedsQL scores and target tumour volume. Both PN volume measured by investigator (primary data) and measured by independent review (secondary data) were analysed (see SPRINT Clinical Study Report for further details).[5] For data from the central, independent review, where two values were available on the same date for a patient (Radiographer 1 and Radiographer 2 in the data), the mean of the values was taken. Using either volume measurement, PN volume does appear to be linked to PedsQL score (**Error! Reference source not found.** and [Figure **10 received but not reproduced in this table]**). However, the coefficients were small and the heterogeneity in tumour volume in this patient population should be noted. **[Figure 9 received but not reproduced in this table]** **[Figure 10 received but not reproduced in this table]** Given the heterogeneity in PN volume (and also body size between patients), a 'normalised PN volume' was constructed, in which PN volume was divided by the body weight of patients, to account for differences in both PN size and patient size. As only baseline weight was available in the raw data, this was used, but is not expected to vary substantially over the (relatively short) trial period. For consistency, total tumour volume measured by independent review was taken. In the regression analysis, the coefficient was found to be at a reasonable level ([Figure **11 received but not reproduced**	

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			in this table]). **[Figure 11 received but not reproduced in this table]** Though a reduction in PN size, both in absolute and normalised terms, appears to lead to an increase in PedsQL total score, the small coefficients associated with tumour size mean that changes in volume have a weak correlation with the PedsQL total score. As explained in the comment #7 of this response document, this weak relationship between tumour volume and PedsQL is *not* because the volume reduction does not improve HRQoL. Patients who experienced volume reduction also experienced HRQoL improvement in SPRINT Phase II Stratum I, and this effect was not observed in the Natural History study.[1] The weak relationship seen here is because **absolute** volume reduction is not directly linked to degree of HRQoL improvement; there is a complex interplay of many factors, and a high degree of heterogeneity within the NF1 PN patient population. *Summary* In conclusion, correlations between PedsQL total score and treatment effect modifiers could not be established or were weak in the regression analyses. This is likely due to the extremely heterogenous nature of PN and the complex interplay of precise PN location and volume in determining the extent and severity of PN-associated morbidities. This lack of correlation makes a development of a patient-level modelling challenging. Even if there were correlations, because of the challenges on mapping PedsQL to utility score (see comment #8 for further details), it would not be possible to assign corresponding utility score to each health state in a patient-level model. Therefore, the modelling approach in the company submission represents the best approach given the available evidence package.	
4	Consultee	AstraZeneca	**Addition of a progression-free state for the best supportive care arm** It was suggested that a progression-free state should be added to the BSC arm (see ECD Report recommendation 1.2 and Section 3.11). However, addition of a progression-free state for the best supportive care arm would imply that patients receiving best-supportive care experience the same rate of PN growth (or PN volume reduction) and quality of life as selumetinib treated patients in a progression-free state. This would be neither accurate nor appropriate. However, we have implemented a progression-free survival (PFS) state in the model for the BSC arm as per the Committee's request. <u>Equivalent experience of PN growth</u> In the Gross et al. 2018 analysis of the NCI Natural History study, no patients aged ≤18 years experienced a reduction in tumour volume from baseline; across the study, a median growth rate of 15.9% per year was observed (lower quartile 10.1%, upper quartile 28.0%).[4] Whilst the PN growth rate experienced by individual patients varies, with some growing rapidly and others more slowly, the trend is for growth over of time.	Comment noted. The committee welcomed the addition of a progression-free state to the best supportive care arm. It concluded utility values for health-states defined by the presence or absence of disease progression,

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			In addition, patients treated with best supportive care experience persistent PN growth, even if this growth rate does not meet the formal definition of 'progressive disease' as used in the SPRINT Phase II Stratum I study (a ≥20% increase in PN volume).[1, 4] In total, eight PN in the Gross et al. 2018 analysis of the Natural History study had a <20% relative volume difference between baseline and maximum assessment (volumetric assessment at which the PN was at its maximum volume). However, median growth in these eight PN was 14.2% (5.7% per year), demonstrating that despite being classified as 'stable', these PN were still undergoing growth.[1] As such, the experience of all patients treated with BSC is equivalent – patients experience continuous PN growth at varying rates. **It would therefore be inaccurate to model different patient experiences for those treated with BSC in progression or progression free health states; it is appropriate to assign the same utility to all patients in the BSC arm.** <u>Equivalent experience of PN-associated morbidity, and therefore quality of life</u> The addition of a PFS state for the BSC arm would imply that BSC-treated patients with progressive disease and those in the PFS state experienced a different quality of life. However, this is not supported by the evidence for the experience of patients within the Natural History study. As previously described, patients in the Natural History study experienced a variety of PN growth rates. However, all PN included in the Gross et al. 2018 analysis which had associated morbidity present at baseline still had a morbidity present at maximum assessment. Furthermore, 30/57 PN had an increase in the number of associated morbidities between baseline and maximum assessment and morbidities increased in severity ([Figure **12 received but not reproduced in this table]**). In particular, 27 PN required an increased in the number of pain medications required over the same period; an increase in the number of PN requiring opioid and neuropathic painkillers was also observed.[4] **[Figure 12 received but not reproduced in this table]** The Natural History study demonstrates that in the absence of disease-modifying treatment, patients are extremely unlikely to experience an improvement in their existing PN-associated morbidities, regardless of PN growth rate.[4] Furthermore, the Natural History study demonstrates that PN-associated morbidities have a considerable negative impact on patients' HRQoL.[6-8] As emphasised by patient experts at the committee meeting, it is clinical outcomes such as improvements in pain, motor function, airway function, visual function and physical functioning, that are of greatest importance to individuals with PN and their carers. It is therefore reflective of the natural history of NF1 PN to model a constant utility for progressive disease for patients treated with BSC.	should be consistent between the selumetinib and best supportive care arms See FED section 3.12

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			Application of the committee recommendation in the model Whilst the company do not agree with using different utility scores in the BSC arm by progression state, due to the reasons outlined above, we have implemented the recommendation from the committee, in order to test the impact of using PFS in BSC arm. To facilitate the committee's request to incorporate progression in the BSC arm, patients in the BSC-treated arm are assumed to enter in a stable (non-progressive state). However, as patients in the BSC arm do not experience the PN volume reduction or symptom improvement seen with selumetinib treatment,[1] they could not experience equivalent utility to patients with PFS in the selumetinib arm (a utility score of [redacted]). We have therefore applied a utility score of [redacted], which is the midpoint between the baseline utility ([redacted]) and the utility score of selumetinib-treated patients in the progression-free state ([redacted]). The updated model therefore takes a conservative approach, which favours the BSC arm and does not reflect the experience of patients in the SPRINT Phase II Stratum I.[1] The modelling assumes that patients in the BSC arm in the progression-free state have higher utility scores than baseline, however these patients would not have experienced any tumour reduction or symptom improvement from baseline. Parametric survival analyses of time-to-progression data for the age-matched natural history cohort were conducted in line with the recommendations in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14.[9] Of the parametric distributions explored, the lognormal distribution had the best fit (as determined using goodness-of-fit statistics). Within the updated model, PFS follows this lognormal curve until patients reach the age of 18, after which point a lower progression rate is applied, representing the stabilisation of PN growth seen in adulthood (see comment #4 for further details). The results from this revised modelling approach are shown in [Figure **13 received but not reproduced in this table**]. [redacted]. **[Figure 13 received but not reproduced in this table]**	
5	Consultee	AstraZeneca	**Only a very small proportion of adults with NF1 PN experience progression, and therefore including progression within the model after the age of 18 would not reflect the natural history of the disease** The committee recommended that the model should allow progression to happen after the age of 18 years (see ECD Report Section 3.12). In the Akshintala et al. 2020 analysis of the Natural History study, the median PN growth rate observed in patients aged ≥18 years was 0.7% per year; this is in significant contrast with a median tumour growth rate of 14.6% per year observed in patients aged <18 years, and substantially lower than a ≥20% increase used to define progressive disease. These data demonstrate	Comment noted. The committee recognised that there would be progression after the age of 18 but noted some uncertainty in the assumption of

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			that in adult patients, PN growth rates are generally very close to zero.[10] Indeed, the slowing and stabilisation of PN growth into adulthood was emphasised by clinical experts during the committee meeting. Whilst there might be some outliers, published data suggests that adults have an exceptionally low likelihood of progression. However, to acknowledge the small potential of progression after the age of 18, we have revised the model to allow patients to experience progression after the age of 18. To reflect the slow growth rate of PN after the age of 18, we have applied an annual progression rate of [redacted] for both the selumetinib arm and BSC arm after the age of 18. In the paediatric Natural History age matched cohort, 85% of patients experienced tumour progression over three years;[1] this equates to a rate of progression of 28.3%/year. As paediatric patients experience a tumour growth rate that is ~21 times higher than adult patients (14.6%/year versus 0.7%/year),[10] we used the simple calculation of [redacted] to derive a progression rate of [redacted] for patients aged >18 years. Tumour growth rate is even lower in older adult patients (in line with general increase in height); we have therefore assumed that any further PN progression would stop by the age of 24, in both the selumetinib and BSC arms. Clinical experts who had previously been consulted for the selumetinib appraisal were contacted again to give their input on assumptions around tumour progression after the age of 18. The assumptions were presented as follows: ***Assumptions on tumour progression after the age of 18.*** *In a study analysing the Natural History study, the median PN growth rate observed in patients aged ≥18 years was 0.7% per year; this is in significant contrast with a median tumour growth rate of 14.6% per year observed in patients aged <18 years. Considering the slow PN growth rate in adulthood, we can arbitrarily assume that an additional [redacted] of adult NF1 PN patients experience PN progression (>20% PN growth from baseline) every year until age of 24. This would mean that among adult patients who haven't had PN progression at the age of 18, about [redacted] of them will eventually experience PN progression after age of 18.* - *Would this be a reasonable assumption?* Of the four clinical experts contacted, two responded and agreed that these assumptions are appropriate. In acknowledgement of the potential for remaining uncertainties, we have used more conservative parameters ([redacted] as a progression rate for patients aged >18 years) in the model. The results from this revised modelling approach are shown in [Figure **14 received but not reproduced in this table]**. Including progression after the age of 18 has minimal impact on the overall ICER [redacted]); it can therefore be concluded that this is not a key area of uncertainty within the modelling. **[Figure 14 received but not reproduced in this table]**	stopping exactly at the age of 24. See FED section 3.13

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6	Consultee	AstraZeneca	**Only a very small proportion of adults with NF1 PN experience progression, and therefore it is expected that very few patients would continue treatment beyond the age of 18** The committee requested that the possibility for selumetinib treatment to continue beyond the age of 18 years be included within the model (see ECD Report Recommendation 1.2 and Section 3.12). The marketing authorisation for selumetinib states that the treatment is indicated for paediatric patients aged 3 years and above, and that there are limited data in patients older than 18 years, therefore continued treatment in adulthood should be based on benefits and risks to the individual patient.[11] The authorisation also states that commencing treatment in adulthood is not appropriate; where there is continued benefit of selumetinib treatment beyond the age of 18 years, selumetinib treatment could be continued.[11] However, as discussed in comment #4, the number of adults with NF1 PN who experience progression beyond the age of 18 years is negligible. For this reason, it is expected that most, if not all patients would discontinue treatment when they reach adulthood. Nonetheless, we have revised the model to incorporate patients who may continue to experience disease progression after the age of 18 (please see comment #4 for details). As a large portion of patients would discontinue when they reach adulthood, we have assumed that [redacted] of patients would stop treatment when they reach adulthood, and the remaining [redacted] would continue treatment based on the Weibull curve for time-to-discontinuation. Clinical experts who had previously been consulted for the selumetinib appraisal were contacted again to give their input on this assumption; the assumption was presented as follows: ***Treatment discontinuation after age of 18.*** *Among patients who started selumetinib treatment at the age of 10 and continued until age of 18, our modelling assumed [redacted] would stop the treatment when they reach adulthood; the remaining [redacted] would continue treatment into adulthood.* - *Would this be a reasonable assumption?* Of the four clinical experts contacted, two responded and agreed that this assumption was appropriate. In light of the potential uncertainty surrounding this assumption, we have used more conservative parameters ([redacted] instead of [redacted] stopping treatment when they reach adulthood) in the model. The results from this revised modelling approach are shown in [Figure **15 received but not reproduced in this table]**. Whilst inclusion of treatment continuation after 18 does [redacted], selumetinib remains cost-effective in this scenario. **[Figure 15 received but not reproduced in this table]**	Comment noted. The committee concluded that the percentage of people continuing selumetinib treatment beyond the age of 18 provided by the company was reasonable. See FED section 3.14
7	Consultee	AstraZeneca	**Accounting for age or PN location within the model would not be feasible due to a lack of correlations**	Comment noted. The committee recognised the

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			The committee recommended development of a patient level simulation model which accounts for the age and location of PN (see ECD Report Recommendation 1.2 and Section 3.11). As discussed in comment #2, in order to determine how age or PN location could be accounted for in the model, univariable regression analyses were carried out to investigate the relationship between PedsQL total scores, age and duration of disease, and PN location. These analyses used the PedsQL total scores collected from SPRINT Phase II Stratum I; self-reported values were used where available, otherwise parent/guardian reported scores were used. As age and duration of disease and PN location were only captured at baseline, the regressions were run using only baseline PedsQL scores. Age The first analysis investigated the effect of NF1 PN disease duration and age on patient quality of life. It follows logically that the longer a patient has had a given disease, the greater they are likely to have suffered from the effects of the disease; a patient cannot have had a disease for longer than they have been alive. As duration of disease is correlated with patient age, age was included as an explanatory variable, so as to accurately estimate the effect of the two different variables. The regression showed insignificant coefficients, providing no evidence to suggest PedsQL score is predicted by age or disease duration ([Figure **16 received but not reproduced in this table]**). As previously mentioned, this result is unexpected, based on the natural history of NF1 PN. The inability to identify a significant relationship is likely due to the small dataset and heterogenous patient population, inevitable consequences of the rarity and complexity of NF1 PN. With a larger dataset it may be that a relationship would have been found between quality of life and age or disease duration. **[Figure 16 received but not reproduced in this table]** PN location The analysis of PN location was first performed using PN locations as coded in SPRINT Phase II Stratum I ([Figure **17 received but not reproduced in this table]**). No reference group was used (the intercept was supressed) as it was not clear which group should constitute the intercept. The effect of not including an intercept is that the regression line passes through the origin, which tends to have the effect of misleading the results and removing the predictability of the analysis, which giving the model the appearance of significance. The results were therefore difficult to interpret, due to both the small and highly variable sample size ([redacted], and to the uncertainty over which group should be used as the intercept relative to which all other coefficients	difficulty of including clinical outcomes in the model due to the heterogeneity of NF1 PN and this would require many assumptions. It concluded the company revised model structure is suitable for decision making. See FED section 3.9 and 3.11.

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			would be estimated. **[Figure 17 received but not reproduced in this table]** PN locations were therefore reassigned to one of four categories, classifying PN as to whether there was involvement on the trunk, head, neck or extremity. This then allowed an intercept to be used in the equation and four coefficients to be estimated, by increasing the power for detecting a difference in each PN location (with patients potentially having more than one PN location depending on the extent of their PN; [Figure **18 received but not reproduced in this table]**). **[Figure 18 received but not reproduced in this table]** In the recoded approach, the location of the PN and involvement of the trunk, head, neck or extremity does not predict PedsQL score. In conclusion, the analyses presented here demonstrate that quality of life, as measured by PedsQL, cannot be predicted either by age and duration of disease, or PN location, making it unfeasible to account for these variables within a patient level simulation model. This is likely due to the extremely heterogenous nature of PN and the complex interplay of precise PN location and volume in determining the extent and severity of PN-associated morbidities.	
8	Consultee	AstraZeneca	**Accounting for clinical outcomes (e.g. pain) within the model would require a large number of assumptions. The current modelling approach, whilst simplified, reflects the efficacy of selumetinib through the most robust methods** The committee requested that the cost-effectiveness model reflects clinical outcomes that are important to people with PN, carers and clinicians, such as pain, which were felt to be more important than PN volume reduction (see ECD Report Recommendation 1.2 and page 4). During model conceptualisation, the possibility of employing a modelling methodology that would incorporate clinical outcome measures was explored. However, a number of challenges were encountered in relation to the available data: – Very few patients had each type of morbidity at baseline within the SPRINT Phase II Stratum I. For example, clinical and patient experts explained that pain is a particularly important outcome, but only 52% of patients had pain at baseline (only 26 patients).[1] The very small data sets would have contributed a large degree of uncertainty to the modelling approach. To note, within the context of a rare condition, and, relative to the total estimated number of children with NF1 PN in the UK and other related studies, the SPRINT Phase II trial achieved a good sample size. The small data set is therefore an inevitable feature of a	Comment noted. The committee recognised the difficulty of including clinical outcomes in the model due to the heterogeneity of NF1 PN and this would require many assumptions. It concluded the company revised model structure is suitable for decision making. See FED section

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			rare disease study – In addition, patients with NF1 PN will often experience multiple PN-associated morbidities, as a result of having PN in multiple locations.[4, 12-14] Indeed, patients in SPRINT Phase II Stratum I had a median of three morbidities at baseline (range 1–5).[1] Similarly, across the 57 patients of the Natural History study many of the observed PN were associated with multiple morbidities; more specifically, 23% of PN were associated with two morbidities and 10% of PN were associated with three or four morbidities at baseline.[4] As such, it is not feasible to correlate changes in patient quality of life with specific morbidities. It is even more challenging if other effect modifiers were also considered at the same time, such as PN size, location, growth rate and age, because of the very high heterogeneity of NF1 PN and the small sample size Clinical experts commented that reducing the volume of PN by 20% may not result in a clinically meaningful improvement for some individuals with PN. Given the heterogeneity of the size and location of PN, as well as the heterogeneity of associated morbidities, it could be difficult to define a quantitative relationship between change in PN volume and each clinical outcome assessment at a population level. However, when taking a patient-level view, a quantitative relationship may still not be feasible but tumour volume reduction can be linked to improvements in HRQoL or clinical outcome measures such as pain. The relationship between tumour volume reduction from baseline and patient-reported outcomes was evaluated in SPRINT Phase II Stratum I with a post-baseline scan. Scatter plots presenting the correlation between PedsQL total scores and tumour volume change, and between Numerical Rating Scale-11 (NRS-11) pain scores and tumour volume changes, show that in most cases volume reduction is linked to improvements in HRQoL or pain ([Figure **19 received but not reproduced in this table]** , [Figure **20 received but not reproduced in this table]** and **Error! Reference source not found.**). Whilst some patients treated with selumetinib experience symptom improvement without volume reduction, and absolute amounts of volume reduction cannot be correlated to the degree of symptom improvement, overall there is a trend for improved quality of life and pain outcomes with reduced tumour volume in each patient. It should be noted that in the Gross et al. 2018 analysis of the Natural History study, no spontaneous reductions in PN volume were observed in children aged <18 years and no improvements in PN-associated morbidities occurred. The Natural History study demonstrates that, in the absence of disease-modifying treatments, symptom improvements are extremely unlikely to occur.[4] It can therefore be concluded that the improvements in PedsQL scores observed in SPRINT Phase II Stratum I are due to treatment with selumetinib. **[Figure 19 received but not reproduced in this table]**	3.9 and 3.11.

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			[Figure 20 received but not reproduced in this table] **[Figure 21 received but not reproduced in this table]** As stated above, PN volume change at an individual patient level is related to improvements in important symptoms such as pain and HRQoL. While the degree of volume reduction may not be directly corelated with the degree of pain and HRQoL improvement, we do know from the SPRINT Phase II Stratum I results that the volume reduction results in positive clinical outcomes in most patients. Therefore, we chose to include disease progression (representing change in PN volume) as a main driver of the model, as the most feasible and evidence-based approach.	
9	Consultee	AstraZeneca	**The mapping of PedsQL data from SPRINT to Child Health Utility 9D (CHU9D) would not appropriately reflect patient utility scores** The committee concluded it would have preferred to see an attempt at mapping and use of direct utility data from the trial included in the analysis or at the very least use the mapped values to validate the time trade off values (see ECD Report page 18). The committee acknowledged the challenges in mapping to EuroQol Five Dimensions (EQ-5D), but proposed that other mapping algorithms were available and the PedsQL data from SPRINT could have been mapped to the CHU9D. Similar to the previously discussed issues of mapping the PedsQL to EQ-5D, to our knowledge there are only a limited number of validated algorithms for the mapping of PedsQL to the CHU9D: Lambe *et al*., Mpundu-Kaambwa *et al*. and Sweeney *et al*.[15-17] Furthermore, the different studies raised similar limitations regarding the development and/or validation of such algorithms, such as the poor performance for certain age groups or for patients with a severe disease and low quality of life. For example, whilst a study by Lambe *et al*. for estimating CHU9D index scores from PedsQL data was based on a UK cohort of children with health issues (cortico-sensitive nephrotic syndrome) and could therefore be theoretically considered suitable in this case, the age range of included patients was comparatively narrow with 5–12 years and a considerable number of children had (near) perfect health; Lambe *et al*. therefore concluded for the resulting mapping algorithm that "caution should be exercised when using this with children younger than five years, older adolescents (>13 years) or patient groups with particularly poor quality of life".[15] Correspondingly, when we applied the Lambe *et al.* algorithm to baseline PedsQL data obtained from the SPRINT study population (3–18 years of age), the resulting utility overall value for patients with NF1 PN was unrealistically high, with a median score of [redacted]; [Figure **22 received but not reproduced in this table]**). Other available mapping algorithms by Mpundu-Kaambwa *et al.* and Sweeney *et al.* were also limited to comparatively narrow age bands, in terms of the included patient populations (e.g. 10–12 years or 15–	Comment noted. The committee would have preferred to see direct utility data from the trial included in the analysis. It recognised that there remains considerable uncertainty relating to the utility values estimated from the time trade off interviews but concluded in the absence of any plausible mapped utilities they would have to use them for decision making. See FED section 3.17

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			17 years of age) and based on Australian general population cohorts.[16, 17] In this context, it should also be noted that it was already acknowledged during the committee meeting that it is difficult to extrapolate from healthy individuals to patients with NF1 PN when mapping utility values. In addition, another study by Mpundu-Kaambwa *et al*. aimed to assess the validity and generalisability of five mapping algorithms (for predicting CHU9D utilities from PedsQL scores), with the finding that all algorithms performed worse amongst children with disabilities/health conditions (relative to children without disabilities/health conditions).[19] Similarly, when developing their mapping algorithm as well as validating existing algorithms by Lambe *et al.* and Mpundu-Kaambwa *et al.*, Sweeney *et al.* clearly stated that "This work again confirms that mapping algorithms generally perform poorly in children with relatively poor HRQoL; as such, the use of any of these mapping algorithms will underestimate any actually experienced HRQoL gains and this bias increases with disease severity".[17] In line with this, when we also applied the two additional mapping algorithms available from Mpundu-Kaambwa *et al.* and Sweeney *et al.*, resulting median utility scores were also unrealistically high ([Figure **22 received but not reproduced in this table]**), and are thus not considered reflective of the actual HRQoL experienced by patients with NF1 PN. **[Figure 22 received but not reproduced in this table]** In consequence, and as demonstrated by the application of existing mapping algorithms, the mapping of PedsQL data obtained from the SPRINT study population (3–18 years of age)[1] into CHUD9 would not appropriately reflect patient utility scores or take into account the full evidence available from the SPRINT PedsQL data. We therefore maintain that the utility scores from the performed vignette study should be considered a more appropriate option for the application of quality of life data in the economic analysis. We further believe that this approach is also in line with precedence from previous NICE appraisals of orphan drugs that faced similar challenges regarding the collection of suitable utility data: – For the appraisal of nusinersen in spinal muscular atrophy (TA588), the committee noted that "identifying robust utility values in babies and young children is exceptionally challenging"; correspondingly, the final economic analysis was based on patient utilities mainly generated by the company from their clinical advisers, which was also considered the most appropriate approach by the Evidence Review Group (ERG) given the issues with and limited face validity of existing preference-based utility estimates[20] – The appraisal of asfotase alfa in paediatric-onset hypophosphatasia (HST6) included utility values estimated by nine clinical experts as part of a vignette study; whilst some methodological limitations were flagged by the ERG, the provided utility values were	

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			considered overall reasonable estimates[21] – Similarly, the appraisal of burosumab in X-linked hypophosphataemia (HST8) included utility values obtained from a dedicated vignette study, with the committee concluding that "the utility values were uncertain but, in the absence of an alternative, were acceptable for decision-making"[22] – For the appraisal of cerliponase alfa in neuronal ceroid lipofuscinosis (HST12), the committee discussed that it would generally prefer to include values directly collected in trials; however, it acknowledged that the available PedsQL data from the relevant trials may not be realistic and considered EQ-5D values from the company-provided vignette study instead[23]	
10	Consultee	AstraZeneca	**Five years of utility waning after discontinuation can be considered to appropriately reflect selumetinib treatment benefits, however the base case analysis has been adjusted to three years of waning and a scenario based on waning over one year has been provided** The committee concluded that a waning of utility one year after progression was reasonable (see ECD Report Section 3.19). When considering the most likely decline in patients' quality of life following treatment discontinuation, it is important to also account for the preventative nature of treatment with selumetinib. Whilst untreated patients with NF1 PN experience continuous PN growth, the majority of patients treated with selumetinib instead experience a degree of tumour reduction ([Figure **23 received but not reproduced in this table]**). As such, the difference in tumour volume when compared to untreated patients is expected to steadily increase for the entire period a patient is on treatment with selumetinib; more importantly, this difference would also be reflected in the associated patient burden. **[Figure 23 received but not reproduced in this table]** For example, propensity score analyses demonstrated a mean difference in annual PN growth rate between untreated patients from the Natural History Study and treated patients from SPRINT Phase II Stratum I of [redacted]% to [redacted]% ([Figure **24 received but not reproduced in this table]**); correspondingly, patients being on treatment for three years can be expected to have a target tumour volume less than half of what would be expected for an untreated patient.	Comment noted. The committee preferred a more rapid decline in utility that matches the time to obtain on-treatment utility after starting selumetinib. See FED section 3.20

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			[Figure 24 received but not reproduced in this table] Therefore, even if a patient should experience tumour growth again following discontinuation of selumetinib their PN would, at this point, be substantially smaller and pose less of a burden than if they had not been treated to begin with; this residual benefit on the patient's quality of life can also be expected to persist in the long term, as PN volume and associated burden continue to be comparatively smaller in discontinued patients than in untreated patients of the same age. However, to acknowledge the committee's recommendation, we have adjusted the model base case to apply a reduced duration of utility waning of 3 years ([Figure **25 received but not reproduced in this table]**); in addition, we present below the results of a scenario based on decreasing the duration of utility waning even further to a minimum of 1 year ([Figure **26 received but not reproduced in this table]**). [redacted] **[Figure 25 received but not reproduced in this table]** **[Figure 26 received but not reproduced in this table]**	
11	Consultee	AstraZeneca	**Estimating caregiver utility dependent on PN location and morbidity is not feasible** Estimating caregiver quality of life based on a respective patient's PN location and associated morbidity faces similar challenges as the estimation of patient quality of life by PN location or morbidity (see comment #7 and ECD Report Section 3.15). Although all patients in SPRINT Phase II Stratum I had PN-related symptoms at baseline, per the eligibility criteria, there was considerable heterogeneity in the types of symptoms observed and related severity reported. More importantly, patients in SPRINT Phase II Stratum I had an average of three (range, 1–5) different target PN morbidities.[1] Similarly, across the 57 patients of the Natural History Study many of the observed PN were associated with multiple morbidities; more specifically, 23% of PN were associated with two morbidities and 10% of PN were associated with three or four morbidities at baseline.[4] Therefore, it is unfeasible to derive (and subsequently model) the specific impact of single locations/morbidities and, in particular, account for the likely interplay of different combinations of morbidities. As such, and based on the available evidence regarding a general relationship between target PN	Comment noted. The committee would have preferred to see disutility values dependent on PN location and the associated morbidity. See FED section 3.18.

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			volume reduction and improvements in some aspects of quality of life, we considered it more practical and appropriate to apply broader utility estimates for treated/untreated patients with unspecified PN locations. In consequence, caregiver utility should be equally applied independent of specific PN locations/morbidities.	
12	Consultee	AstraZeneca	**The model has been revised and caregiver disutility has now been applied in both the selumetinib and BSC arm** The committee reiterated the stated ERG preference of using a utility decrement for parents and carers (0.07) based on previous NICE HST reviews; it further stated that, in consideration of carers of children with activity limitations, the carer disutility as submitted for selumetinib ([redacted]) was too high. The committee also advised that the carer disutility should be applied to the selumetinib arm too. However, patients and carers dealing with NF1 PN face more challenges than just activity limitations, due to the heterogeneous and pervasive nature of the disease; this was confirmed by the patient group representatives present at the committee meeting. For example, NF1 PN has a significant negative impact on patients' emotional and social wellbeing;[24] patients with NF1 PN may experience [redacted] XXXXXX. In addition, caregivers have reported [redacted] and the emotional impact of NF1 PN, particularly anxiety which results from uncertainty surrounding PN growth and PN-associated morbidities.[24, 25] As such, it is highly probable that the utility decrement for parents and carers suggested by ERG (0.07) does not fully reflect the burden for parents and carers of patients with NF1 PN; we therefore still maintain that a carer disutility of [redacted] appropriately reflects the carer burden presented by uncontrolled NF1 PN treated with BSC only. We acknowledge the committee's preference to also include caregiver disutility in the selumetinib arm; however, this should also reflect the impact of effective disease control with selumetinib when compared to BSC, by applying a correspondingly lower disutility value. As such, we have included a caregiver disutility value of [redacted] in the selumetinib arm, which represents a reasonable point between the disutility still applied in the BSC arm ([redacted]) and the ERG preferred value based on NICE HST precedence (0.07). In consequence, the absolute difference in carer disutility between the two treatment arms, reflecting the impact of disease control with selumetinib on caregiver QoL, would therefore be reduced to [redacted] (compared to the previously modelled difference of [redacted]). We have revised the model accordingly, applying a disutility of [redacted] to the carers of BSC-treated patients and a disutility of [redacted] to the carers of selumetinib-treated patients (**Error! Reference source not found.**). [redacted]	Comment noted. The committee noted it had not been presented with supportive evidence for the company's carer disutility value. It also recalled that this value is unjustifiably higher than carer disutility values used in previous NICE appraisals. See FED section 3.18

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			[redacted] **[Figure 27 received but not reproduced in this table]**	
13	Consultee	AstraZeneca	**Caregiver utility scores should be applied to more than one carer (see ECD Report Section 3.18)** Patient and caregiver expert feedback provided during the first committee meeting supports the assumption that care for a patient with NF1 PN is likely to place a burden on the entire family, and not just one single family member who may provide the majority of physical caregiving. In addition, in the patient expert statements submitted to NICE in November 2021 (prior to the first committee meeting), it was emphasised that the impact of NF1 PN is on the whole family, which can include a patient's parents and siblings.[27] As such we maintain that the originally submitted approach for estimating parent/carer burden (applying it to 1.4 people, based on the average UK household size being 2.4 people and one person being the patient) still provides the most appropriate estimate and may potentially be a conservative assumption.	Comment noted. The committee concluded there was not enough evidence to assume the carer disutility applies to more than 1 carer. See FED section 3.19.
14	Consultee	AstraZeneca	**Full resource use costings have been applied conservatively** The committee concluded that it would like to see analyses with full resource use included for both arms of the model (see ECD Report Section 3.13). Based on the committee's recommendation, additional cost items have been included within the model, with most of these being additional monitoring costs for selumetinib treated patients. NF1 PN patients require regular monitoring to check their disease status and patients treated with selumetinib would also need additional monitoring before starting and during treatment. We have collected information on the frequency of additional monitoring items, by treatment status and year, from a clinical expert and calculated the corresponding cost ([Figure 28 received but not reproduced in this table] **[Figure 29 received but not reproduced in this table]** and **Error! Reference source not found.**). **[Figure 28 received but not reproduced in this table]** **[Figure 29 received but not reproduced in this table]** We did not assume potential cost savings from symptom improvement due to treatment with selumetinib, even if this could be expected. This is because we did not have enough quantitative data to support this. As such, this can still be considered a very conservative approach.	Comment noted. The committee recognised the uncertainty in the estimates but concluded the resource use costs associated with selumetinib treatment compared with best supportive care provided in the company revised model were suitable for decision making. See FED section 3.15

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			The results from this revised modelling approach are shown in [Figure 30 received but not reproduced in this table]. [redacted] **[Figure 30 received but not reproduced in this table]**	
15	Consultee	AstraZeneca	**Addition of two magnetic resonance imaging (MRI) scans per year** The committee requested that two additional MRIs are included within the selumetinib arm of the model (see ECD Report section 3.14). During the first committee meeting, clinical experts confirmed that patients who receive selumetinib will most likely receive two MRIs per year while patients treated with BSC will receive only one MRI; this would effectively result in one additional MRI per year for selumetinib-treated patients. Committee members also noted that the use of two additional MRI in the company submission base case was a conservative approach. However, in the evaluation consultation document it is stated that the clinical expert consulted during the committee meeting envisaged that "in NHS clinical practice, two 'additional' MRI scans per year would be the most needed by people having selumetinib unless any acute changes happened." Therefore, the committee concluded the company assumption of two additional MRI scans per year was reasonable. As we already used two additional MRIs in the model base case analysis, there was no need to update the model based on this recommendation. However, we would like to emphasise that two additional MRIs (therefore total of three MRIs per year) can be considered a conservative assumption.	Comment noted. The committee concluded that the company assumption of 2 additional MRI scans per year was reasonable. See FED section 3.16.
16	Consultee	AstraZeneca	**Summary of the impact of performed model revisions** The impact of each of the revisions described above on the cost-effectiveness model results is summarised in [Figure 31 received but not reproduced in this table]. The accumulated impact of all model revisions is further summarised in **Error! Reference source not found.**, resulting in a final revised ICER of £[redacted]. Therefore, with the model revised as far as possible/feasible in light of the committee's recommendations, selumetinib remains a cost-effective treatment for the NHS. **[Figure 31 received but not reproduced in this table]** **[Figure 32 received but not reproduced in this table]**	Comment noted . The committee preferred the assumptions used by the ERG in their revised base case. Some of these assumptions were the same as the company's. Some of the

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				assumptions differed from the company's in relation to: • inclusion of a progression-free state in the best supportive care arm, with the same utility as those applied to the progression-free state in the selumetinib arm • a carer disutility value of 0.07 applied to carers of people in the best supportive care arm and a carer disutility value of 0.035 applied to carers of people in the

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				selumetinib arm • carer disutility values applied to 1 carer • linear decline in utility over 1 year after progression in the selumetinib arm See FED section 3.22.
17	Consultee	The Neurofibromatosis Association	Surgery has been the main treatment till MEK inhibitors became available (i.e. selumetnib and related drugs). Many plexiforms cannot be entirely removed by surgery, but surgery can improve function and quality of life. a) What is the definition of inoperable? b) Is there a plan to use selumetinib in conjunction with surgery, either before or after, to improve outcome?	Comment noted. Inoperable is defined as PN which cannot be completely resected without risk of substantial morbidity because of encasement of, or close proximity to, vital structures, invasiveness, or high vascularity. See FED section 3.5. Technology appraisals only appraise within the products marketing

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				authorisation, therefore cannot comment further on the use of selumetinib.
18	Consultee	The Neurofibromatosis Association	We believe that the decision making about who should receive selumetinib, should be undertaken by the national neurofibromatosis teams at Guy's Hospital, London and St. Mary's Hospital, Manchester, where there is already a joint, established MDT in combination with Great Ormond St. Hospital. This would tap into existing experience and expertise and avoid over or under treatment.	Comment noted. The committee recognised that children with PN associated with NF1 are managed within 2 nationally commissioned services in Manchester and London. See FED section 3.5 and 3.6
19	Consultee	The Neurofibromatosis Association	We think that treatment could be carried out in conjunction with local centres as this avoids unnecessary disruption to schooling, parents' employment and family life.	Comment noted
20	Consultee	The Neurofibromatosis Association	We believe that the measures that look at effectiveness of treatment should be robust and weight should be given to patient perceived quality of life.	Comment noted. The reference case stipulates that the perspective on outcomes should be all direct health effects whether for patients or, where relevant, other individuals (principally carers). The perspective adopted on cost

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				should be that of the NHS and PSS. If the inclusion of a wider set of costs or outcomes is expected to influence the results significantly, such analysis should be presented in addition to the reference case analysis; see section 5.1.7–5.1.10 of the Guide to the methods of technology appraisal.
21	Consultee	The Neurofibromatosis Association	We do not know how long the drug should be given for and whether there will be a need for ongoing treatment in adult clinics.	Comment noted. The committee concluded that the percentage of people continuing selumetinib treatment beyond the age of 18 provided by the company was reasonable. See FED section 3.14
22	Consultee	Childhood Tumour Trust	1Selumenitib could possibly help more children than initially indicated. a. There is no national database recording numbers with NF and plexiform tumours. b. There is also no indication of what criteria a child has to meet to be eligible for the drug so it is	Comment noted. The marketing authorisation for selumetinib

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			impossible to clearly indicate numbers	includes treating symptomatic and inoperable plexiform neurofibromas (PN) associated with type 1 neurofibromatosis (NF1) in children aged 3 and over.
23		Childhood Tumour Trust	Clear criteria must be in place for indicating who can receive the drug. a. The use of the wording “inoperable tumour” as a criteria is misleading as most plexiform tumours are inoperable by nature, but not all of these tumours will meet the criteria for this treatment- the phrase needs to be expanded upon. In explanation I (CB) have a facial plexiform that has had multiple surgeries it is now classed as inoperable, my child has a plexiform that cannot be removed as the bulk of the tumour is inoperable though a small part can be surgically removed, he has two other plexiform tumours which are inoperable around major vessels in his neck, does this mean we would be candidates for treatment with the drug or do we need to meet further criteria? b. Symptomatic is also misleading as this could cover a myriad of things or not as the case may be. How does someone never experiencing a plexiform gauge the pain level of someone who has one?	Comment noted. Inoperable is defined as PN which cannot be completely resected without risk of substantial morbidity because of encasement of, or close proximity to, vital structures, invasiveness, or high vascularity. See FED section 3.5
24	Consultee	Childhood Tumour Trust	Clear criteria should be published, and a guide made available to explain this to the lay person (children and families or carers). i. It is important that there is good communication between the Highly Specialised centres and the NF community via all patient groups so that expectations can be managed well, as many will see this as a wonder drug and feel it would help them or their child and that correct information is given. ii. Many children are not seen by an NF specialist, and many are not in the system (undiagnosed children/families). These guidelines should enable anyone who feels they meet the criteria to request, through their primary care practitioner, an appointment at one of the Highly Specialised centres, or outreach hospitals to	Comment noted. The committee noted that NF1 PN is currently managed in 2 specialist centres in England. Selumetinib would be started at the specialist

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			discuss possible use of the drug. There then should be a clear referral pathway to the relevant treatment centre.	centres, with the potential for treatment to continue in conjunction with local healthcare providers if safe and useful. See FED section 3.25
25	Consultee	Childhood Tumour Trust	Is there a support pathway (counselling/psychological support) and a care pathway in place for those who don't meet criteria/ have to stop the drug due to toxicity/ the drug doesn't work for or stops working? NF has a huge psychological impact upon a person, even more so if they have a debilitating or disfiguring and painful plexiform tumour, to be told that a drug could help them and for this then to fail will have a huge impact upon the child/Young person and their families and carers. They will need support throughout the whole process to manage expectations and deal with any fallout from treatment/lack of treatment.	Comment noted
26	Consultee	Childhood Tumour Trust	It is important to note that although Selumetinib can have an impact in the short term on quality of life due to additional tests and hospital visits the long-term overall outcome should improve quality of life for those with plexiform tumours.	Comment noted..
27	Consultee	Childhood Tumour Trust	The committee mentions comparing the use of Selumetinib with BEST SUPPORTIVE CARE. It is important to note current practices aren't necessarily best supportive care and costs to provide this could be in excess of current recommendations.	Comment noted. The committee concluded the resource use costs associated with selumetinib and best supportive care provided in the company revised model were suitable for decision making. See FED section 3.15.
28	Consultee	Childhood Tumour Trust	Can AZ clarify what is best supportive care and Is best supportive care receiving annually MRI's for a known plexiform and being under a highly	Comment noted. The committee concluded that the assumption

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			specialised centre? As this is certainly not the case for everyone. As parents of children with inoperable Plexiform Tumours we can clearly state our children do not receive yearly MRIs of their plexiform tumours, I (CB) can also clarify as a person with an inoperable plexiform tumour at no time during childhood or as a adult did I or do I have yearly MRI scans. My (CB) son is under one of the Highly Specialised centres and does not get annual scans, my daughter (CB) daughter and I are seen locally. The costs of ongoing holistic care of a patient with NF and an inoperable plexiform tumour overtime could be greater than that of a patient treated successfully with Selumetinib. If a tumour is successfully treated then there would be reduced psychological burden, reduced need for pain relief and pain management, reduced need for therapies specifically associated with loss of function due to the plexiform tumour, reduced impact on schooling (less time off school for medical care), hopefully reducing the need for limb amputation due to plexiform tumours. A knock on impact of the regular MRI's would mean any other plexi forms would be identified early and the drug would also work on these tumours as some children will have multiple plexiform neurofibromas.	of 2 additional MRI scans per year for people receiving selumetinib was reasonable. See FED section 3.16
29	Consultee	Childhood Tumour Trust	MRI scans – General anaesthetic is generally avoided post 6 years of age and in some cases a sedative can be used instead of a GA. Not needing a general anaesthetic will significantly reduce costs of the MRI scans The number of children they are talking about treating currently is a tiny amount in comparison to the general population of people with NF, therefore comparatively the cost is small as they all have to be over the age of 3.	Comment noted The committee concluded that the assumption of 2 additional MRI scans per year for people treated with selumetinib was reasonable. See FED section 3.16
30	Consultee	Childhood Tumour Trust	We feel Black and Ethnic Minorities are significantly under represented NF does not discriminate race, ethnicity, gender, religion yet we find that we see lower numbers of children and younger people from the Black and Ethnic Minority Communities, this could because NF can be harder to pick up or maybe due to the use of the term coffee coloured marks (café au lait) as in people with black skin the marks are not coffee coloured, so it could be people are not picked up at the routine screening appointments. Religion can also have an impact as can cultural values and beliefs. Some children will not be taken to the doctors/hospital and some will not agree with certain treatments. Whilst the committee cannot ensure that these people are reached we can ensure clear guidelines are available to be distributed by the nhs and charities to give these children and young people an opportunity to have equal care.	Comment noted. The NHS aims to provide free, necessary and appropriate treatment to the whole UK population. Legislation on human rights,

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			A 20 year old had to have her leg amputated due to an MPNST. (Cancerous Plexiform Tumour) Although she was known to have NF1 from the age of 7, it took 18 months of her mother fighting to get the 'large red and painful lump' looked at. The cancer has now spread to her lungs and no more treatment is available. We don't know if the Selumetinib may have helped this young girl, but the point is she would never have had the opportunity, as by the time she had reached the Highly specialised centres it was too late. It needs to be very specific who meets the criteria. We need detailed criteria that is clear and easy to follow. Parents/Young people/carers and practitioners need to be able to easily see who is eligible and how to move forward. Criteria cannot just say inoperable plexiform tumours unless the intention is to offer the treatment to everyone in the age range with an inoperable plexiform tumour. Inoperable could also be open to interpretation - does it mean totally inoperable as in no surgery is viable or does it include those that could be de-bulked but cannot he fully removed - those that grow back post-surgery - most plexiforms will continue to grow after de-bulking.	discrimination and equality requires that patients are not denied access, or have different or restricted access, to NHS care because of their race, disability, age, sex/gender, sexual orientation, religion, beliefs, or socioeconomic or other status (Social Value Judgements; 'Principles for the development of NICE guidance', principle 6).

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Selumetinib for treating symptomatic and inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in children aged 3 years and over [ID1590]

Consultation on the evaluation consultation document – deadline for comments 5pm on 05 January 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Evaluation Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	AstraZeneca UK Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	**Primary (new) contact**: Hazel Dawson (hazel.dawson@alexion.com) **Secondary contact**: Janek Hendrich (janek.hendrich@astrazeneca.com)

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Selumetinib for treating symptomatic and inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in children aged 3 years and over [ID1590]

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Comments

Insert each comment in a new row.
Do not paste other tables into this table, because your comments could get lost – type directly into this table.

Introduction

0 **Revised Patient Access Scheme (PAS) price**

SPRINT Phase II Stratum I is the most relevant data source for selumetinib in the licensed indication of paediatric patients with neurofibromatosis type 1 (NF1) with symptomatic, inoperable plexiform neurofibroma (PN). The evidence from this clinical trial is supportive of the effectiveness of selumetinib at stabilising and reducing PN volume, compared with best supportive care.[1] However, there are limitations associated with this evidence base; these limitations are inevitable consequences of the ultra-rarity and heterogeneity of NF1 PN.

In light of the available evidence, we maintain that the modelling approach in the company submission represents the best approach and only feasible approach. The rationale behind the modelling approaches taken has been further explained within this response, and we have adopted a large extent of the recommendations within this response (where feasible). However, use of some assumptions in the modelling remains inevitable and we acknowledge that this may contribute a degree of uncertainty.

[redacted]

[redacted]

Figure 1. Cost-effectiveness model results, based on original model and original PAS price for selumetinib

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
BSC	xxxxx	xxxx	xxxx	-	-	-	-
Selumetinib	xxxxx	xxxx	xxxx	xxxx	xxxx	xxxx	£93,169

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life-years gained; PAS: patient access scheme; QALY: quality adjusted life year.

Figure 2. Cost-effectiveness model results, based on original model and revised PAS price for selumetinib

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Selumetinib for treating symptomatic and inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in children aged 3 years and over [ID1590]

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	<table><tr><th>Technologies</th><th>Total costs (£)</th><th>Total LYG</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER (£) incremental (QALYs)</th></tr><tr><td>BSC</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>-</td><td>-</td><td>-</td></tr><tr><td>Selumetinib</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£70,471</td></tr></table> **Abbreviations:** BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life-years gained; PAS: patient access scheme; QALY: quality adjusted life year. Selumetinib represents a step-change in the management of paediatric patients with symptomatic, inoperable NF1 PN, a patient population where this is a substantial unmet need for an effective treatment. Selumetinib treatment results in durable stabilisations and reductions in PN volume in paediatric patients, preventing or reducing the most rapid stage of PN volume growth.[1] In the following responses, AstraZeneca have sought to implement the committee's feedback wherever feasible. [redacted]
Clinical Evidence *(see ECD Report Section 3.10)*	
1	**The conclusions regarding the clinical evidence are sound, and an accurate interpretation of the evidence** The committee evaluated all evidence from the pivotal SPRINT Phase II Stratum I study, the most relevant data source for selumetinib in NF1 PN.[1] The committee concluded that based on the clinical trial evidence, selumetinib is effective at reducing the volume and size of PN compared with best supportive care (Evaluation Consultation Document [ECD] Report page 4), and that the results from the SPRINT trial are generalisable to the UK population (ECD Report Section 3.10).
Patient Level Modelling *(see ECD Report recommendation 1.2 and Section 3.11)*	
2	**The development of a patient-level model is unfeasible** The committee stated that they would prefer to see a patient-level model. As discussed during the Committee Meeting, the available evidence package (Phase II Stratum I of the SPRINT clinical study and National Cancer Institute [NCI] Natural History study) does not support the development of a patient-level model. Very few Highly Specialised Technology (HST) appraisals have used patient-level models, likely due to the need to have sufficient quantities of patient-level data available to inform such cost-effectiveness analyses, and the challenge of recruiting patients to studies in ultra-rare conditions. The one HST appraisal identified by AstraZeneca in which a patient-level model was developed had a significantly longer-term evidence base (over 14-years) and larger clinical trial population of 112 patients to draw from.[2] This appraisal also used relatively well-established sub-models in different organs (e.g. pancreas, liver, cardiovascular, kidney, etc) and the well-established surrogate outcome of HBA1c to calculate transition probabilities.[2] While we acknowledge that a patient-level simulation would allow the development of a more detailed model which more closely reflects the heterogeneity of patients with NF1 PN, it would not have been feasible to meet this recommendation with the available data. We explored the feasibility of developing a regression-based patient level model at the stage of early model conceptualisation. However, the heterogeneity of NF1 PN, coupled with the limited sample size for the SPRINT Phase II Stratum I study (n=50),[1] made it unfeasible to establish a quantitative relationship between potential covariates sufficiently informative for decision-making purposes. It is worth emphasising that within the context of an rare condition, and, relative to the

total estimated number of children with NF1 PN in the UK and other related studies, the SPRINT Phase II trial achieved a good sample size. Covariates explored included: age, PN location, PN volume and quality of life (please see results included below the heading 'Further characterisation with regression analyses'). In addition, no patient-level health-related quality of life (HRQoL) data and other patient reported outcomes were available from the Natural History study to support such analysis; this also meant that we couldn't establish a quantitative relationship between potential covariates and HRQoL in patients treated with best supportive care (BSC).

The very high level of heterogeneity within the NF1 PN patient population also made it difficult to define a series of distinct health states. As multiple individual PN can occur anywhere on the body, combinations of treatment effect modifiers such as PN location, PN size, PN growth rate and age result in all patients having different and unique health states. [redacted].[3] It is also impossible to quantify the individual and combined impacts of each effect modifier on HRQoL, especially with data from 50 patients. For example, subgrouping the analysis by PN location would have reduced the maximum sample size to only [redacted].[1] The heterogeneity of NF1 PN was emphasised during the committee meeting in November 2021, where a patient expert explained that PN affect everyone differently, and can be unpredictable, making living with NF1 PN challenging.

We appreciate that a degree of simplification has been necessary in order to develop the current model. However, the modelling approach remains the most robust possible, given the available data and the heterogeneity of NF1 PN. The current modelling approach accounts for the overall improvements in clinical outcomes and quality of life seen at an individual and population level in selumetinib treated patients, alongside stabilisations and reductions in PN volume (see comment #7 for further details). **Patient-level modelling would result in a model associated with a significantly higher level of uncertainty**, due to a larger number of assumptions that would have to be made on the quantitative relationship between each effect modifier and outcome. This would impair the ability of the committee to draw a conclusion on the cost-effectiveness of selumetinib that improves on the existing approach.

During the open session of the Evaluation Committee Meeting (10th November 2021), there was lengthy discussion on the cost-effectiveness model during which we presented potential modelling approaches and the advantages and disadvantages of each, discussed our recommended modelling approach and provided an explanation as to why it was not feasible to develop a patient-level model. At that time, no concerns were raised by the Appraisal Committee and indeed, it was stated by the health economic expert on the committee that our model was likely to be conservative given the assumptions that we had made. Unfortunately, as discussed above, a patient-level model remains unfeasible, however we believe we have taken a pragmatic approach in developing the most robust model possible with the evidence package we have available.

Further characterisation of results with regression analysis

For full transparency, we have provided additional details of the analysis to assess whether quantitative relationships could be established between key variables, specifically: investigating the relationship between Pediatric Quality of Life Inventory™ (PedsQL) total scores and patient characteristics, disease characteristics or tumour size.

Regression analyses were performed using the PedsQL total scores collected from SPRINT Phase II Stratum I; self-reported values were used where available, otherwise parent/guardian reported scores were used. As patient and disease characteristics were only captured at baseline, the regressions were run using only baseline quality of life data.

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Patient and disease characteristics

The first analysis investigated the effect of NF1 PN disease duration and age on patient quality of life. It is logical that the longer a patient has had a given disease, the greater they are likely to have suffered from the effects of the disease; a patient cannot have had a disease for longer than they have been alive. In particular, once PN-related morbidities develop, they are extremely unlikely to resolve spontaneously.[4] As duration of disease is correlated with patient age, age was included as an explanatory variable, to accurately estimate the effect of the two different variables.

The regression showed insignificant coefficients, providing no evidence to suggest PedsQL score is predicted by age or disease duration (Figure 3). This result is unexpected, based on the natural history of NF1 PN. The inability to identify a significant relationship is likely due to the small dataset and heterogenous patient population, inevitable consequences of the rarity and complexity of NF1 PN. With a larger dataset it may be that a relationship would have been found between quality of life and age or disease duration.

Figure 3. Output of regression of PedsQL using age and duration of disease

Coefficient	Estimate	P-value

Footnotes: significance markers '***' 0.001; '**' 0.01; '*' 0.05.
Abbreviations: PedsQL: Pediatric Quality of Life Inventory; PN: plexiform neurofibroma.

The second analysis examined body surface area (BSA) and weight. Patient BSA is related to age, height, and weight, and thus may act as a good proxy for all these factors without using excessive statistical power by requiring three coefficients to be included. The regression analysis for BSA (Figure 4), however, indicates that **there is limited support for the hypothesis that PedsQL is linked to BSA**. In addition to a lack of significance, the interquartile range of BSA is only 0.5, meaning that any practical impact of PedsQL is half of the observed coefficient. Again, this finding is likely due to the inevitable limitations of data collected in rare and heterogenous patient population.

Figure 4. Output of regression for PedsQL using body surface area

Coefficient	Estimate	P-value

Footnotes: significance markers '***' 0.001; '**' 0.01; '*' 0.05.
Abbreviations: PedsQL: Pediatric Quality of Life Inventory; PN: plexiform neurofibroma.

In order to confirm the results of the analysis for BSA, a regression analysis was performed looking at the impact of weight on PedsQL, in light of evidence suggesting weight may be an important factor in patient reported outcomes for patients with NF1 PN. However, the results of the regression (Figure 5) indicate that weight is also a poor predictor of PedsQL score, when taken in isolation.

Figure 5. Output of regression for PedsQL using weight

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Coefficient	Estimate	P-value
[redacted]		

Footnotes: significance markers '***' 0.001; '**' 0.01; '*' 0.05.
Abbreviations: PedsQL: Pediatric Quality of Life Inventory; PN: plexiform neurofibroma.

In the SPRINT study, patients were classified according to whether their disease had progressed (≥20% increase in neurofibroma volume) in the 15-month period prior to enrolment in the study.[1] A regression analysis was conducted to evaluate whether progression status at baseline is a predictor of PedsQL score (Figure 6).

The coefficient associated with this was not significant; based on the available data, **progression status at baseline does not appear to predict patient PedsQL scores**. This was unexpected, as it was observed that patients who were classified as having 'progressed' at baseline had lower PedsQL scores. The inability to draw a significant correlation is likely due to the inevitable limitations of the available data, in particular the rarity of the NF1 PN and subsequent small sample size.

Figure 6. Output of regression for PedsQL using baseline progression status

Coefficient	Estimate	P-value
[redacted]		

Footnotes: significance markers '***' 0.001; '**' 0.01; '*' 0.05.
Abbreviations: PedsQL: Pediatric Quality of Life Inventory; PN: plexiform neurofibroma.

Tumour location

Tumour location was evaluated at baseline in the SPRINT study and has been suggested to be prognostic of patient quality of life. The regression analysis of PN location was first performed using PN locations as coded in SPRINT Phase II Stratum I (Figure 7). No reference group was used (the intercept was supressed) as it was not clear which group should constitute the intercept. The results were therefore difficult to interpret, due to both the small and highly variable sample size (ranging from [redacted]), and to the uncertainty over which group should be used as the intercept relative to which all other coefficients would be estimated.

Figure 7. Output of regression for PedsQL using tumour location as per the SPRINT trial coding

Coefficient	Estimate	P-value
[redacted]		

Footnotes: significance markers '***' 0.001; '**' 0.01; '*' 0.05.
Abbreviations: PedsQL: Pediatric Quality of Life Inventory; PN: plexiform neurofibroma.

PN locations were therefore reassigned to one of four categories, classifying PN as to whether there was involvement on the trunk, head, neck or extremity. This then allowed an intercept to be used in the equation and four coefficients to be estimated, by increasing the power for detecting a difference in each PN location (with patients potentially having more than one PN location depending on the extent of their PN; Figure 8).

Figure 8. Output of regression for PedsQL using recoded tumour location

Coefficient	Estimate	P-value

Footnotes: significance markers '***' 0.001; '**' 0.01; '*' 0.05.
Abbreviations: PedsQL: Pediatric Quality of Life Inventory; PN: plexiform neurofibroma.

In the recoded approach, the location of the PN and involvement of the trunk, head, neck or extremity does not predict PedsQL score. This is likely due to the extremely heterogenous nature of PN and the complex interplay of precise PN location and volume in determining the extent and severity of PN-associated morbidities.

Overall, of the different patient and disease characteristics evaluated at baseline in the SPRINT Phase II Stratum I and considered within these regression analyses, none can be linked to PedsQL total score.

Tumour volume

Regression analysis was also used to estimate the relationship between PedsQL scores and target tumour volume. Both PN volume measured by investigator (primary data) and measured by independent review (secondary data) were analysed (see SPRINT Clinical Study Report for further details).[5] For data from the central, independent review, where two values were available on the same date for a patient (Radiographer 1 and Radiographer 2 in the data), the mean of the values was taken.

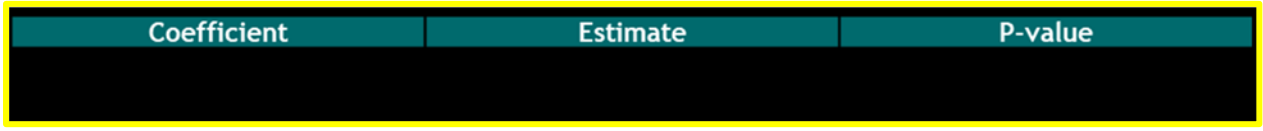
Using either volume measurement, PN volume does appear to be linked to PedsQL score (Figure 9 and Figure 10). However, the coefficients were small and the heterogeneity in tumour volume in this patient population should be noted.

Figure 9. Output of regression of PedsQL using target PN volume by central review

Coefficient	Estimate	P-value

Footnotes: significance markers '***' 0.001; '**' 0.01; '*' 0.05.
Abbreviations: PedsQL: Pediatric Quality of Life Inventory; PN: plexiform neurofibroma.

Figure 10. Output of regression for PedsQL using investigator-assessed target PN volume

	 **Footnotes:** significance markers '***' 0.001; '**' 0.01; '*' 0.05. **Abbreviations:** PedsQL: Pediatric Quality of Life Inventory; PN: plexiform neurofibroma. Given the heterogeneity in PN volume (and also body size between patients), a 'normalised PN volume' was constructed, in which PN volume was divided by the body weight of patients, to account for differences in both PN size and patient size. As only baseline weight was available in the raw data, this was used, but is not expected to vary substantially over the (relatively short) trial period. For consistency, total tumour volume measured by independent review was taken. In the regression analysis, the coefficient was found to be at a reasonable level (Figure 11). **Figure 11. Output of regression for PedsQL using normalised PN volume by central review**  **Footnotes:** significance markers '***' 0.001; '**' 0.01; '*' 0.05. **Abbreviations:** PedsQL: Pediatric Quality of Life Inventory; PN: plexiform neurofibroma. Though a reduction in PN size, both in absolute and normalised terms, appears to lead to an increase in PedsQL total score, the small coefficients associated with tumour size mean that changes in volume have a weak correlation with the PedsQL total score. As explained in the comment #7 of this response document, this weak relationship between tumour volume and PedsQL is *not* because the volume reduction does not improve HRQoL. Patients who experienced volume reduction also experienced HRQoL improvement in SPRINT Phase II Stratum I, and this effect was not observed in the Natural History study.[1] The weak relationship seen here is because **absolute** volume reduction is not directly linked to degree of HRQoL improvement; there is a complex interplay of many factors, and a high degree of heterogeneity within the NF1 PN patient population. *Summary* In conclusion, correlations between PedsQL total score and treatment effect modifiers could not be established or were weak in the regression analyses. This is likely due to the extremely heterogenous nature of PN and the complex interplay of precise PN location and volume in determining the extent and severity of PN-associated morbidities. This lack of correlation makes a development of a patient-level modelling challenging. Even if there were correlations, because of the challenges on mapping PedsQL to utility score (see comment #8 for further details), it would not be possible to assign corresponding utility score to each health state in a patient-level model. Therefore, the modelling approach in the company submission represents the best approach given the available evidence package.
3	**Addition of a progression-free state for the best supportive care arm** It was suggested that a progression-free state should be added to the BSC arm (see ECD Report recommendation 1.2 and Section 3.11). However, addition of a progression-free state for the best supportive care arm would imply that patients receiving best-supportive care experience the same rate of PN growth (or PN volume reduction) and quality of life as selumetinib treated patients in a

progression-free state. This would be neither accurate nor appropriate. However, we have implemented a progression-free survival (PFS) state in the model for the BSC arm as per the Committee's request.

Equivalent experience of PN growth

In the Gross et al. 2018 analysis of the NCI Natural History study, no patients aged ≤18 years experienced a reduction in tumour volume from baseline; across the study, a median growth rate of 15.9% per year was observed (lower quartile 10.1%, upper quartile 28.0%).[4] Whilst the PN growth rate experienced by individual patients varies, with some growing rapidly and others more slowly, the trend is for growth over of time.

In addition, patients treated with best supportive care experience persistent PN growth, even if this growth rate does not meet the formal definition of 'progressive disease' as used in the SPRINT Phase II Stratum I study (a ≥20% increase in PN volume).[1, 4] In total, eight PN in the Gross et al. 2018 analysis of the Natural History study had a <20% relative volume difference between baseline and maximum assessment (volumetric assessment at which the PN was at its maximum volume). However, median growth in these eight PN was 14.2% (5.7% per year), demonstrating that despite being classified as 'stable', these PN were still undergoing growth.[1]

As such, the experience of all patients treated with BSC is equivalent – patients experience continuous PN growth at varying rates. **It would therefore be inaccurate to model different patient experiences for those treated with BSC in progression or progression free health states; it is appropriate to assign the same utility to all patients in the BSC arm.**

Equivalent experience of PN-associated morbidity, and therefore quality of life

The addition of a PFS state for the BSC arm would imply that BSC-treated patients with progressive disease and those in the PFS state experienced a different quality of life. However, this is not supported by the evidence for the experience of patients within the Natural History study.

As previously described, patients in the Natural History study experienced a variety of PN growth rates. However, all PN included in the Gross et al. 2018 analysis which had associated morbidity present at baseline still had a morbidity present at maximum assessment. Furthermore, 30/57 PN had an increase in the number of associated morbidities between baseline and maximum assessment and morbidities increased in severity (Figure 12). In particular, 27 PN required an increased in the number of pain medications required over the same period; an increase in the number of PN requiring opioid and neuropathic painkillers was also observed.[4]

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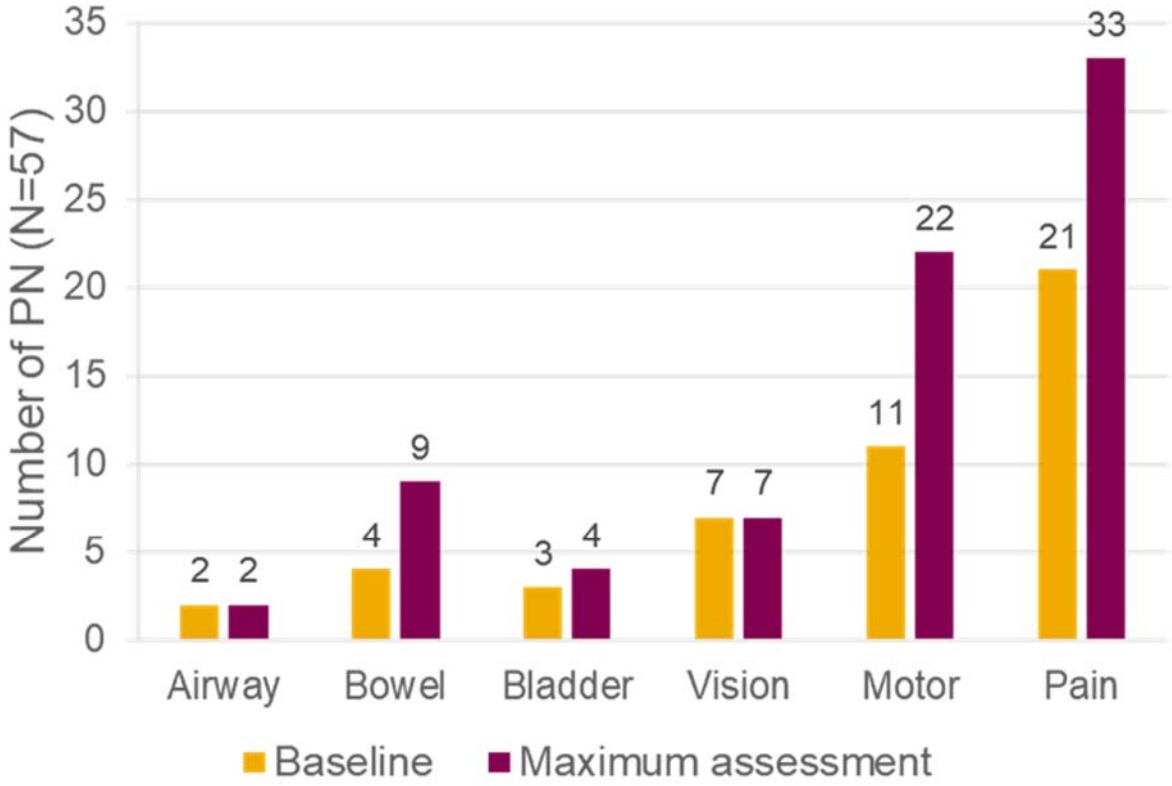
Figure 12. Number of PN with each type of PN-associated morbidity at baseline and maximum assessment



Footnotes: 'Maximum assessment' refers to the clinical assessment at which the PN reached its largest volume.
Abbreviation: PN: plexiform neurofibromas.
Source: Gross et al. 2018.[4]

The Natural History study demonstrates that in the absence of disease-modifying treatment, patients are extremely unlikely to experience an improvement in their existing PN-associated morbidities, regardless of PN growth rate.[4] Furthermore, the Natural History study demonstrates that PN-associated morbidities have a considerable negative impact on patients' HRQoL.[6-8] As emphasised by patient experts at the committee meeting, it is clinical outcomes such as improvements in pain, motor function, airway function, visual function and physical functioning, that are of greatest importance to individuals with PN and their carers. It is therefore reflective of the natural history of NF1 PN to model a constant utility for progressive disease for patients treated with BSC.

Application of the committee recommendation in the model

Whilst the company do not agree with using different utility scores in the BSC arm by progression state, due to the reasons outlined above, we have implemented the recommendation from the committee, in order to test the impact of using PFS in BSC arm.

To facilitate the committee's request to incorporate progression in the BSC arm, patients in the BSC-treated arm are assumed to enter in a stable (non-progressive state). However, as patients in the BSC arm do not experience the PN volume reduction or symptom improvement seen with selumetinib treatment,[1] they could not experience equivalent utility to patients with PFS in the

selumetinib arm (a utility score of xxxx). We have therefore applied a utility score of xxxx, which is the midpoint between the baseline utility (xxxx) and the utility score of selumetinib-treated patients in the progression-free state (xxxx). The updated model therefore takes a conservative approach, which favours the BSC arm and does not reflect the experience of patients in the SPRINT Phase II Stratum I.[1] The modelling assumes that patients in the BSC arm in the progression-free state have higher utility scores than baseline, however these patients would not have experienced any tumour reduction or symptom improvement from baseline.

Parametric survival analyses of time-to-progression data for the age-matched natural history cohort were conducted in line with the recommendations in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14.[9] Of the parametric distributions explored, the lognormal distribution had the best fit (as determined using goodness-of-fit statistics). Within the updated model, PFS follows this lognormal curve until patients reach the age of 18, after which point a lower progression rate is applied, representing the stabilisation of PN growth seen in adulthood (see comment #4 for further details).

The results from this revised modelling approach are shown in Figure 13. [redacted]

Figure 13. Cost-effectiveness model results, with PFS incorporated into the BSC arm, and using the revised PAS price for selumetinib

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
BSC	xxxx	xxxx	xxxx	-	-	-	-
Selumetinib	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	£74,795

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; PFS: progression-free survival; QALY: quality adjusted life years.

4

Only a very small proportion of adults with NF1 PN experience progression, and therefore including progression within the model after the age of 18 would not reflect the natural history of the disease

The committee recommended that the model should allow progression to happen after the age of 18 years (see ECD Report Section 3.12). In the Akshintala et al. 2020 analysis of the Natural History study, the median PN growth rate observed in patients aged ≥18 years was 0.7% per year; this is in significant contrast with a median tumour growth rate of 14.6% per year observed in patients aged <18 years, and substantially lower than a ≥20% increase used to define progressive disease. These data demonstrate that in adult patients, PN growth rates are generally very close to zero.[10] Indeed, the slowing and stabilisation of PN growth into adulthood was emphasised by clinical experts during the committee meeting. Whilst there might be some outliers, published data suggests that adults have an exceptionally low likelihood of progression.

However, to acknowledge the small potential of progression after the age of 18, we have revised the model to allow patients to experience progression after the age of 18. To reflect the slow growth rate of PN after the age of 18, we have applied an annual progression rate of xxxx for both the selumetinib arm and BSC arm after the age of 18. In the paediatric Natural History age matched cohort, 85% of patients experienced tumour progression over three years;[1] this equates to a rate of progression of 28.3%/year. As paediatric patients experience a tumour growth rate that is ~21 times higher than adult patients (14.6%/year versus 0.7%/year),[10] we used the simple calculation of xxxx to derive a progression rate of xxxx for patients aged >18 years. Tumour growth rate is even

lower in older adult patients (in line with general increase in height); we have therefore assumed that any further PN progression would stop by the age of 24, in both the selumetinib and BSC arms.

Clinical experts who had previously been consulted for the selumetinib appraisal were contacted again to give their input on assumptions around tumour progression after the age of 18. The assumptions were presented as follows:

Assumptions on tumour progression after the age of 18. *In a study analysing the Natural History study, the median PN growth rate observed in patients aged ≥18 years was 0.7% per year; this is in significant contrast with a median tumour growth rate of 14.6% per year observed in patients aged <18 years. Considering the slow PN growth rate in adulthood, we can arbitrarily assume that an additional* xxxx *of adult NF1 PN patients experience PN progression (>20% PN growth from baseline) every year until age of 24. This would mean that among adult patients who haven't had PN progression at the age of 18, about* xxxx *of them will eventually experience PN progression after age of 18.*

- *Would this be a reasonable assumption?*

Of the four clinical experts contacted, two responded and agreed that these assumptions are appropriate.

In acknowledgement of the potential for remaining uncertainties, we have used more conservative parameters (xxxx as a progression rate for patients aged >18 years) in the model. The results from this revised modelling approach are shown in Figure 14. Including progression after the age of 18 has minimal impact on the overall ICER xxxx it can therefore be concluded that this is not a key area of uncertainty within the modelling.

Figure 14. Cost-effectiveness model results, with progression after the age of 18 incorporated within the model, and using the revised PAS price for selumetinib

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
BSC	xxxx	xxxx	xxxx	-	-	-	-
Selumetinib	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	£76,491

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALY: quality adjusted life year.

5

Only a very small proportion of adults with NF1 PN experience progression, and therefore it is expected that very few patients would continue treatment beyond the age of 18

The committee requested that the possibility for selumetinib treatment to continue beyond the age of 18 years be included within the model (see ECD Report Recommendation 1.2 and Section 3.12). The marketing authorisation for selumetinib states that the treatment is indicated for paediatric patients aged 3 years and above, and that there are limited data in patients older than 18 years, therefore continued treatment in adulthood should be based on benefits and risks to the individual patient.[11] The authorisation also states that commencing treatment in adulthood is not appropriate; where there is continued benefit of selumetinib treatment beyond the age of 18 years, selumetinib treatment could be continued.[11] However, as discussed in comment #4, the number of adults with NF1 PN who experience progression beyond the age of 18 years is negligible. For this reason, it is expected that most, if not all patients would discontinue treatment when they reach adulthood.

Nonetheless, we have revised the model to incorporate patients who may continue to experience disease progression after the age of 18 (please see comment #4 for details). As a large portion of

patients would discontinue when they reach adulthood, we have assumed that xxxx of patients would stop treatment when they reach adulthood, and the remaining xxxx would continue treatment based on the Weibull curve for time-to-discontinuation. Clinical experts who had previously been consulted for the selumetinib appraisal were contacted again to give their input on this assumption; the assumption was presented as follows:

Treatment discontinuation after age of 18. *Among patients who started selumetinib treatment at the age of 10 and continued until age of 18, our modelling assumed xxxx would stop the treatment when they reach adulthood; the remaining xxxx would continue treatment into adulthood.*

- *Would this be a reasonable assumption?*

Of the four clinical experts contacted, two responded and agreed that this assumption was appropriate. In light of the potential uncertainty surrounding this assumption, we have used more conservative parameters (xxxx instead of xxxx stopping treatment when they reach adulthood) in the model.

The results from this revised modelling approach are shown in Figure 15. Whilst inclusion of treatment continuation after 18 does xxxx, selumetinib remains cost-effective in this scenario.

Figure 15. Cost-effectiveness model results, with selumetinib treatment continuation after the age of 18 incorporated within the model, and using the revised PAS price for selumetinib

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
BSC	xxxx	xxxx	xxxx	-	-	-	-
Selumetinib	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	£76,806

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALY: quality adjusted life year.

6

Accounting for age or PN location within the model would not be feasible due to a lack of correlations

The committee recommended development of a patient level simulation model which accounts for the age and location of PN (see ECD Report Recommendation 1.2 and Section 3.11).

As discussed in comment #2, in order to determine how age or PN location could be accounted for in the model, univariable regression analyses were carried out to investigate the relationship between PedsQL total scores, age and duration of disease, and PN location. These analyses used the PedsQL total scores collected from SPRINT Phase II Stratum I; self-reported values were used where available, otherwise parent/guardian reported scores were used. As age and duration of disease and PN location were only captured at baseline, the regressions were run using only baseline PedsQL scores.

Age

The first analysis investigated the effect of NF1 PN disease duration and age on patient quality of life. It follows logically that the longer a patient has had a given disease, the greater they are likely to have suffered from the effects of the disease; a patient cannot have had a disease for longer than they have been alive. As duration of disease is correlated with patient age, age was included as an explanatory variable, so as to accurately estimate the effect of the two different

variables. The regression showed insignificant coefficients, providing no evidence to suggest PedsQL score is predicted by age or disease duration (Figure 16).

As previously mentioned, this result is unexpected, based on the natural history of NF1 PN. The inability to identify a significant relationship is likely due to the small dataset and heterogenous patient population, inevitable consequences of the rarity and complexity of NF1 PN. With a larger dataset it may be that a relationship would have been found between quality of life and age or disease duration.

Figure 16. Output of regression of PedsQL using age and duration of disease

Coefficient	Estimate	P-value

Footnotes: significance markers '***' 0.001; '**' 0.01; '*' 0.05.
Abbreviations: PedsQL: Pediatric Quality of Life Inventory; PN: plexiform neurofibroma.

PN location

The analysis of PN location was first performed using PN locations as coded in SPRINT Phase II Stratum I (Figure 17). No reference group was used (the intercept was supressed) as it was not clear which group should constitute the intercept. The effect of not including an intercept is that the regression line passes through the origin, which tends to have the effect of misleading the results and removing the predictability of the analysis, which giving the model the appearance of significance. The results were therefore difficult to interpret, due to both the small and highly variable sample size xxxx and to the uncertainty over which group should be used as the intercept relative to which all other coefficients would be estimated.

Figure 17. Output of regression for PedsQL using tumour location as per the SPRINT trial coding

Coefficient	Estimate	P-value

Footnotes: significance markers '***' 0.001; '**' 0.01; '*' 0.05.
Abbreviations: PedsQL: Pediatric Quality of Life Inventory.

PN locations were therefore reassigned to one of four categories, classifying PN as to whether there was involvement on the trunk, head, neck or extremity. This then allowed an intercept to be used in the equation and four coefficients to be estimated, by increasing the power for detecting a difference in each PN location (with patients potentially having more than one PN location depending on the extent of their PN; Figure 18).

Figure 18. Output of regression for PedsQL using recoded tumour location

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	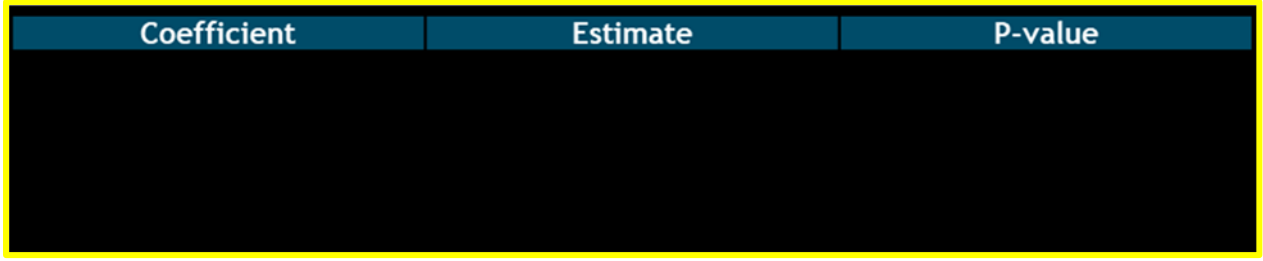 **Footnotes:** significance markers '***' 0.001; '**' 0.01; '*' 0.05. **Abbreviations:** PedsQL: Pediatric Quality of Life Inventory. In the recoded approach, the location of the PN and involvement of the trunk, head, neck or extremity does not predict PedsQL score. In conclusion, the analyses presented here demonstrate that quality of life, as measured by PedsQL, cannot be predicted either by age and duration of disease, or PN location, making it unfeasible to account for these variables within a patient level simulation model. This is likely due to the extremely heterogenous nature of PN and the complex interplay of precise PN location and volume in determining the extent and severity of PN-associated morbidities.
7	**Accounting for clinical outcomes (e.g. pain) within the model would require a large number of assumptions. The current modelling approach, whilst simplified, reflects the efficacy of selumetinib through the most robust methods** The committee requested that the cost-effectiveness model reflects clinical outcomes that are important to people with PN, carers and clinicians, such as pain, which were felt to be more important than PN volume reduction (see ECD Report Recommendation 1.2 and page 4). During model conceptualisation, the possibility of employing a modelling methodology that would incorporate clinical outcome measures was explored. However, a number of challenges were encountered in relation to the available data: – Very few patients had each type of morbidity at baseline within the SPRINT Phase II Stratum I. For example, clinical and patient experts explained that pain is a particularly important outcome, but only 52% of patients had pain at baseline (only 26 patients).[1] The very small data sets would have contributed a large degree of uncertainty to the modelling approach. To note, within the context of a rare condition, and, relative to the total estimated number of children with NF1 PN in the UK and other related studies, the SPRINT Phase II trial achieved a good sample size. The small data set is therefore an inevitable feature of a rare disease study – In addition, patients with NF1 PN will often experience multiple PN-associated morbidities, as a result of having PN in multiple locations.[4, 12-14] Indeed, patients in SPRINT Phase II Stratum I had a median of three morbidities at baseline (range 1–5).[1] Similarly, across the 57 patients of the Natural History study many of the observed PN were associated with multiple morbidities; more specifically, 23% of PN were associated with two morbidities and 10% of PN were associated with three or four morbidities at baseline.[4] As such, it is not feasible to correlate changes in patient quality of life with specific morbidities. It is even more challenging if other effect modifiers were also considered at the same time, such as PN size, location, growth rate and age, because of the very high heterogeneity of NF1 PN and the small sample size

Clinical experts commented that reducing the volume of PN by 20% may not result in a clinically meaningful improvement for some individuals with PN. Given the heterogeneity of the size and location of PN, as well as the heterogeneity of associated morbidities, it could be difficult to define a quantitative relationship between change in PN volume and each clinical outcome assessment at a population level. However, when taking a patient-level view, a quantitative relationship may still not be feasible but tumour volume reduction can be linked to improvements in HRQoL or clinical outcome measures such as pain.

The relationship between tumour volume reduction from baseline and patient-reported outcomes was evaluated in SPRINT Phase II Stratum I with a post-baseline scan. Scatter plots presenting the correlation between PedsQL total scores and tumour volume change, and between Numerical Rating Scale-11 (NRS-11) pain scores and tumour volume changes, show that in most cases volume reduction is linked to improvements in HRQoL or pain (Error! Reference source not found., Figure 19 and Figure 20). Whilst some patients treated with selumetinib experience symptom improvement without volume reduction, and absolute amounts of volume reduction cannot be correlated to the degree of symptom improvement, overall there is a trend for improved quality of life and pain outcomes with reduced tumour volume in each patient. It should be noted that in the Gross et al. 2018 analysis of the Natural History study, no spontaneous reductions in PN volume were observed in children aged <18 years and no improvements in PN-associated morbidities occurred. The Natural History study demonstrates that, in the absence of disease-modifying treatments, symptom improvements are extremely unlikely to occur.[4] It can therefore be concluded that the improvements in PedsQL scores observed in SPRINT Phase II Stratum I are due to treatment with selumetinib.

Figure 19. Correlation between change in PedsQL parent-report scores and percent change in tumour volume from baseline to pre-cycle 13 (full analysis set)

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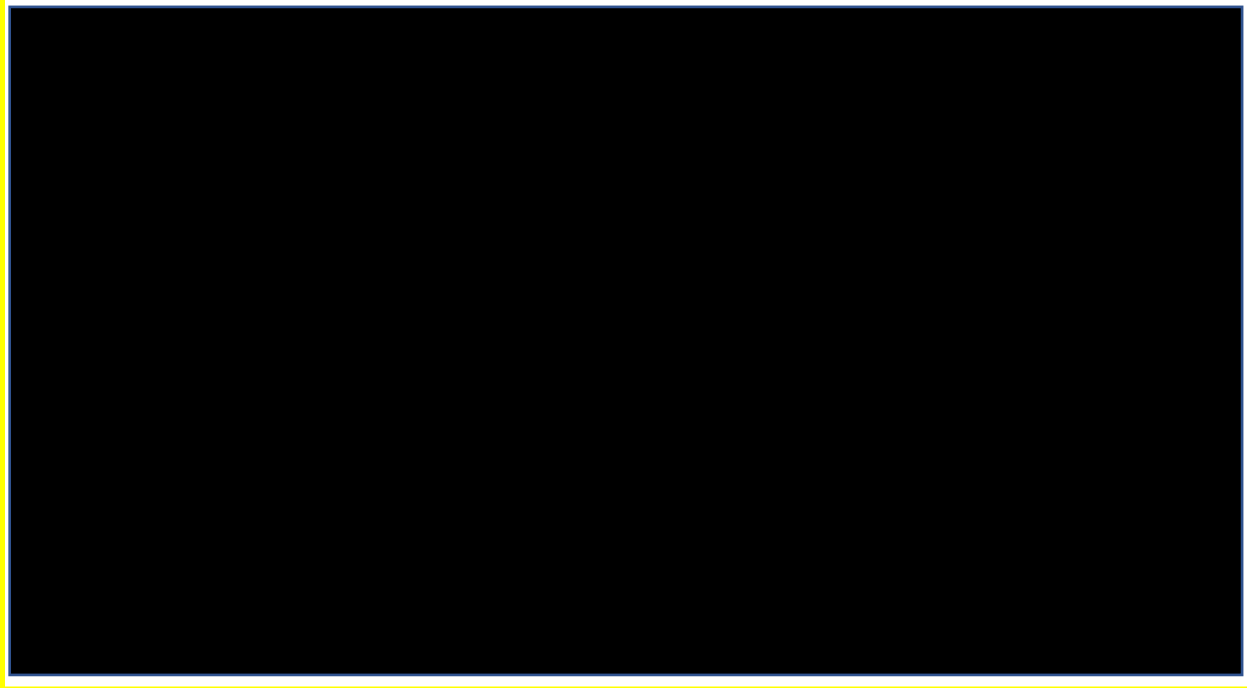
Footnotes: Parents or legal guardians of children 2–18 years of age at enrolment completed the parent proxy measures of the PedsQL.
Abbreviations: PedsQL: Pediatric Quality of Life Inventory.

Figure 20. Correlation between change in NRS-11 pain intensity score and percent change in tumour volume from baseline to pre-cycle 5, 9, 13 and 25 (full analysis set)



Footnotes: Children aged 8–18 years at enrolment completed self-report measures of NRS-11. Only patients with a pain score ≥2 at baseline were included.
Abbreviations: NRS-11: Numerical Rating Scale-11.

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	As stated above, PN volume change at an individual patient level is related to improvements in important symptoms such as pain and HRQoL. While the degree of volume reduction may not be directly corelated with the degree of pain and HRQoL improvement, we do know from the SPRINT Phase II Stratum I results that the volume reduction results in positive clinical outcomes in most patients. Therefore, we chose to include disease progression (representing change in PN volume) as a main driver of the model, as the most feasible and evidence-based approach.
Patient Utility Data *(see ECD Report recommendation 1.2 and 'Utility values' section)*	
8	**The mapping of PedsQL data from SPRINT to Child Health Utility 9D (CHU9D) would not appropriately reflect patient utility scores** The committee concluded it would have preferred to see an attempt at mapping and use of direct utility data from the trial included in the analysis or at the very least use the mapped values to validate the time trade off values (see ECD Report page 18). The committee acknowledged the challenges in mapping to EuroQol Five Dimensions (EQ-5D), but proposed that other mapping algorithms were available and the PedsQL data from SPRINT could have been mapped to the CHU9D. Similar to the previously discussed issues of mapping the PedsQL to EQ-5D, to our knowledge there are only a limited number of validated algorithms for the mapping of PedsQL to the CHU9D: Lambe *et al*., Mpundu-Kaambwa *et al*. and Sweeney *et al*.[15-17] Furthermore, the different studies raised similar limitations regarding the development and/or validation of such algorithms, such as the poor performance for certain age groups or for patients with a severe disease and low quality of life. For example, whilst a study by Lambe *et al*. for estimating CHU9D index scores from PedsQL data was based on a UK cohort of children with health issues (cortico-sensitive nephrotic syndrome) and could therefore be theoretically considered suitable in this case, the age range of included patients was comparatively narrow with 5–12 years and a considerable number of children had (near) perfect health; Lambe *et al*. therefore concluded for the resulting mapping algorithm that "caution should be exercised when using this with children younger than five years, older adolescents (>13 years) or patient groups with particularly poor quality of life".[15] Correspondingly, when we applied the Lambe *et al.* algorithm to baseline PedsQL data obtained from the SPRINT study population (3–18 years of age), the resulting utility overall value for patients with NF1 PN was unrealistically high, with a median score of [redacted]; Figure 21). Other available mapping algorithms by Mpundu-Kaambwa *et al.* and Sweeney *et al.* were also limited to comparatively narrow age bands, in terms of the included patient populations (e.g. 10–12 years or 15–17 years of age) and based on Australian general population cohorts.[16, 17] In this context, it should also be noted that it was already acknowledged during the committee meeting that it is difficult to extrapolate from healthy individuals to patients with NF1 PN when mapping utility values. In addition, another study by Mpundu-Kaambwa *et al*. aimed to assess the validity and generalisability of five mapping algorithms (for predicting CHU9D utilities from PedsQL scores), with the finding that all algorithms performed worse amongst children with disabilities/health conditions (relative to children without disabilities/health conditions).[19] Similarly, when developing their mapping algorithm as well as validating existing algorithms by Lambe *et al.* and Mpundu-Kaambwa *et al.*, Sweeney *et al.* clearly stated that "This work again confirms that mapping algorithms generally perform poorly in children with relatively poor HRQoL; as such, the use of any

of these mapping algorithms will underestimate any actually experienced HRQoL gains and this bias increases with disease severity".[17]

In line with this, when we also applied the two additional mapping algorithms available from Mpundu-Kaambwa *et al.* and Sweeney *et al.*, resulting median utility scores were also unrealistically high (Figure 21), and are thus not considered reflective of the actual HRQoL experienced by patients with NF1 PN.

Figure 21. Utilities generated from SPRINT Phase II Stratum I PedsQL data via different CHU9D mapping algorithms (using baseline values only)

Mapping algorithm	Generated utility score, median (range)
Lambe *et al*	[redacted]
Mpundu-Kaambwa *et al.*	
Sweeney *et al.*	

Abbreviations: CHU9D: Child Health Utility 9D; PedsQL: Pediatric Quality of Life Inventory.
Source: AstraZeneca Data on File. Further information available upon request; Lambe et al. 2018;[15] Mpundu-Kaambwa et al. 2017;[16] Sweeney et al. 2020.[17]

In consequence, and as demonstrated by the application of existing mapping algorithms, the mapping of PedsQL data obtained from the SPRINT study population (3–18 years of age)[1] into CHUD9 would not appropriately reflect patient utility scores or take into account the full evidence available from the SPRINT PedsQL data. We therefore maintain that the utility scores from the performed vignette study should be considered a more appropriate option for the application of quality of life data in the economic analysis.

We further believe that this approach is also in line with precedence from previous NICE appraisals of orphan drugs that faced similar challenges regarding the collection of suitable utility data:

- For the appraisal of nusinersen in spinal muscular atrophy (TA588), the committee noted that "identifying robust utility values in babies and young children is exceptionally challenging"; correspondingly, the final economic analysis was based on patient utilities mainly generated by the company from their clinical advisers, which was also considered the most appropriate approach by the Evidence Review Group (ERG) given the issues with and limited face validity of existing preference-based utility estimates[20]
- The appraisal of asfotase alfa in paediatric-onset hypophosphatasia (HST6) included utility values estimated by nine clinical experts as part of a vignette study; whilst some methodological limitations were flagged by the ERG, the provided utility values were considered overall reasonable estimates[21]
- Similarly, the appraisal of burosumab in X-linked hypophosphataemia (HST8) included utility values obtained from a dedicated vignette study, with the committee concluding that "the utility values were uncertain but, in the absence of an alternative, were acceptable for decision-making"[22]
- For the appraisal of cerliponase alfa in neuronal ceroid lipofuscinosis (HST12), the committee discussed that it would generally prefer to include values directly collected in trials; however, it acknowledged that the available PedsQL data from the relevant trials may not be realistic and considered EQ-5D values from the company-provided vignette study instead[23]

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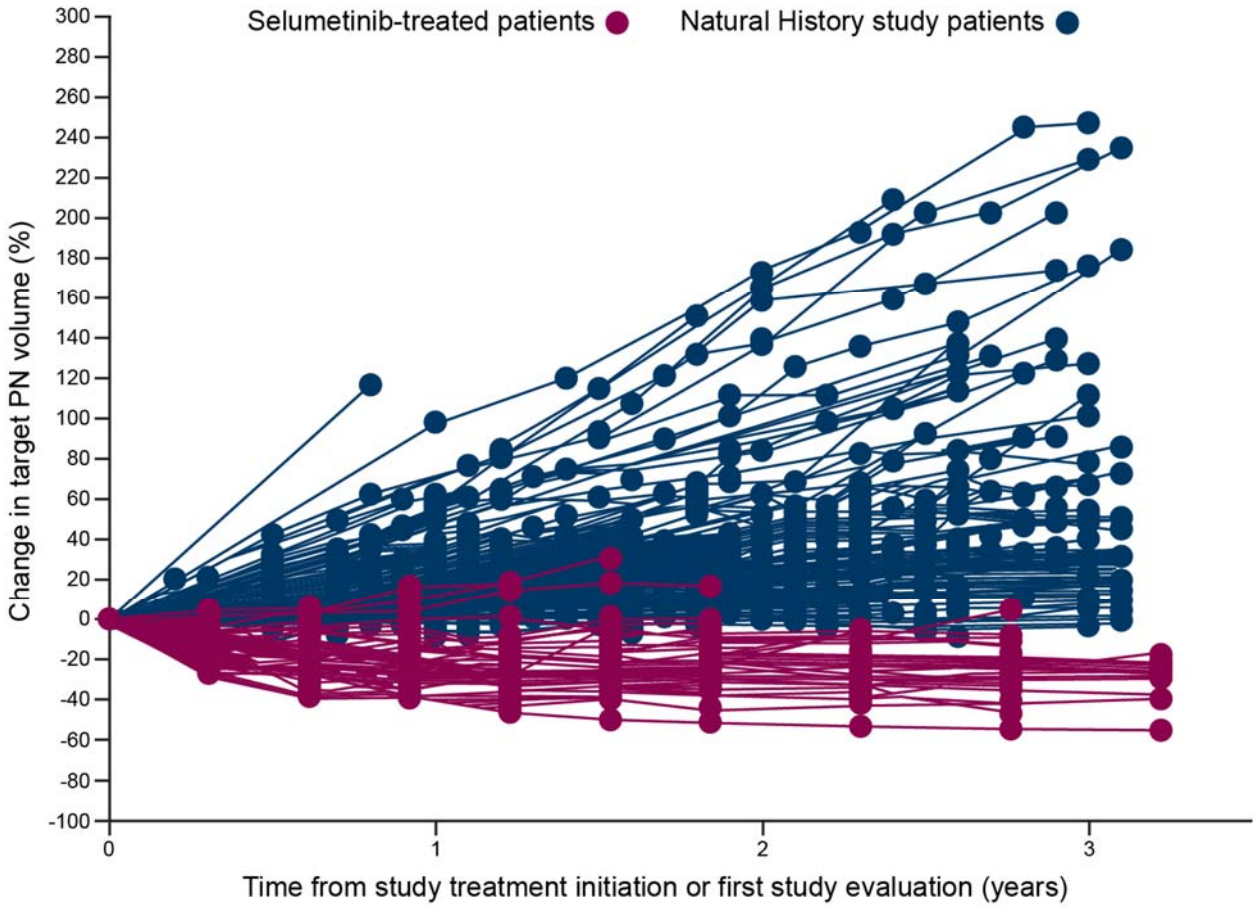
9	**Five years of utility waning after discontinuation can be considered to appropriately reflect selumetinib treatment benefits, however the base case analysis has been adjusted to three years of waning and a scenario based on waning over one year has been provided** The committee concluded that a waning of utility one year after progression was reasonable (see ECD Report Section 3.19). When considering the most likely decline in patients' quality of life following treatment discontinuation, it is important to also account for the preventative nature of treatment with selumetinib. Whilst untreated patients with NF1 PN experience continuous PN growth, the majority of patients treated with selumetinib instead experience a degree of tumour reduction (Figure 22). As such, the difference in tumour volume when compared to untreated patients is expected to steadily increase for the entire period a patient is on treatment with selumetinib; more importantly, this difference would also be reflected in the associated patient burden. **Figure 22. Percentage change in target PN volume during selumetinib treatment in SPRINT Phase II Stratum I compared to an age-matched Natural History study control cohort**  **Abbreviations:** PN: plexiform neurofibroma. **Source**: Gross et al. 2020.[1]

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	For example, propensity score analyses demonstrated a mean difference in annual PN growth rate between untreated patients from the Natural History Study and treated patients from SPRINT Phase II Stratum I of [redacted] % to [redacted] % (Figure 23); correspondingly, patients being on treatment for three years can be expected to have a target tumour volume less than half of what would be expected for an untreated patient.

Figure 23. Percentage change in target PN volume (mean difference by propensity score adjustment method) – SPRINT Phase II Stratum I vs Natural History comparator cohort

Propensity score adjustment method	Group	n	Time period, years, Mean (95% CI)	PN volume % change/year, Mean (95% CI)	Estimated annual PN growth rate, Mixed model Adjusted mean (95% CI)
1:1 match	SPRINT	[redacted]			
	Natural History				
1:2 match	SPRINT				
	Natural History				
IPTW	SPRINT				
	Natural History				
Stabilised IPTW	SPRINT				
	Natural History				

Abbreviations: CI: confidence interval; IPTW: inverse probability of treatment weighting; PN: plexiform neurofibroma.
Source: AstraZeneca Data on File. Further information available upon request.

Therefore, even if a patient should experience tumour growth again following discontinuation of selumetinib their PN would, at this point, be substantially smaller and pose less of a burden than if they had not been treated to begin with; this residual benefit on the patient's quality of life can also be expected to persist in the long term, as PN volume and associated burden continue to be comparatively smaller in discontinued patients than in untreated patients of the same age.

However, to acknowledge the committee's recommendation, we have adjusted the model base case to apply a reduced duration of utility waning of 3 years (Figure 24); in addition, we present below the results of a scenario based on decreasing the duration of utility waning even further to a minimum of 1 year (Figure 25).

[redacted]

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Figure 24. Cost-effectiveness model results, with three years duration of utility waning and using the revised PAS price for selumetinib

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£73,677

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALY: quality adjusted life year.

Figure 25. Cost-effectiveness model results, with one year duration of utility waning and using the revised PAS price for selumetinib

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£77,397

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALY: quality adjusted life year.

Caregiver Utility Data (see ECR Report Recommendation 1.2 and 'Utility values' section)

10

Estimating caregiver utility dependent on PN location and morbidity is not feasible

Estimating caregiver quality of life based on a respective patient's PN location and associated morbidity faces similar challenges as the estimation of patient quality of life by PN location or morbidity (see comment #7 and ECD Report Section 3.15).

Although all patients in SPRINT Phase II Stratum I had PN-related symptoms at baseline, per the eligibility criteria, there was considerable heterogeneity in the types of symptoms observed and related severity reported. More importantly, patients in SPRINT Phase II Stratum I had an average of three (range, 1–5) different target PN morbidities.[1] Similarly, across the 57 patients of the Natural History Study many of the observed PN were associated with multiple morbidities; more specifically, 23% of PN were associated with two morbidities and 10% of PN were associated with three or four morbidities at baseline.[4]

Therefore, it is unfeasible to derive (and subsequently model) the specific impact of single locations/morbidities and, in particular, account for the likely interplay of different combinations of morbidities.

As such, and based on the available evidence regarding a general relationship between target PN volume reduction and improvements in some aspects of quality of life, we considered it more practical and appropriate to apply broader utility estimates for treated/untreated patients with unspecified PN locations. In consequence, caregiver utility should be equally applied independent of specific PN locations/morbidities.

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11

The model has been revised and caregiver disutility has now been applied in both the selumetinib and BSC arm

The committee reiterated the stated ERG preference of using a utility decrement for parents and carers (0.07) based on previous NICE HST reviews; it further stated that, in consideration of carers of children with activity limitations, the carer disutility as submitted for selumetinib ([redacted]) was too high. The committee also advised that the carer disutility should be applied to the selumetinib arm too. However, patients and carers dealing with NF1 PN face more challenges than just activity limitations, due to the heterogeneous and pervasive nature of the disease; this was confirmed by the patient group representatives present at the committee meeting. For example, NF1 PN has a significant negative impact on patients' emotional and social wellbeing;[24] patients with NF1 PN may experience [redacted]. In addition, caregivers have reported [redacted] and the emotional impact of NF1 PN, particularly anxiety which results from uncertainty surrounding PN growth and PN-associated morbidities.[24, 25] As such, it is highly probable that the utility decrement for parents and carers suggested by ERG (0.07) does not fully reflect the burden for parents and carers of patients with NF1 PN; we therefore still maintain that a carer disutility of [redacted] appropriately reflects the carer burden presented by uncontrolled NF1 PN treated with BSC only.

We acknowledge the committee's preference to also include caregiver disutility in the selumetinib arm; however, this should also reflect the impact of effective disease control with selumetinib when compared to BSC, by applying a correspondingly lower disutility value. As such, we have included a caregiver disutility value of [redacted] in the selumetinib arm, which represents a reasonable point between the disutility still applied in the BSC arm ([redacted]) and the ERG preferred value based on NICE HST precedence (0.07). In consequence, the absolute difference in carer disutility between the two treatment arms, reflecting the impact of disease control with selumetinib on caregiver QoL, would therefore be reduced to [redacted] (compared to the previously modelled difference of [redacted]).

We have revised the model accordingly, applying a disutility of [redacted] to the carers of BSC-treated patients and a disutility of [redacted] to the carers of selumetinib-treated patients (Figure 26). [redacted]

Figure 26. Cost-effectiveness model results, with revised caregiver disutility and using the revised PAS price for selumetinib

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£82,736

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALY: quality adjusted life year.

12

Caregiver utility scores should be applied to more than one carer (see ECD Report Section 3.18)

Patient and caregiver expert feedback provided during the first committee meeting supports the assumption that care for a patient with NF1 PN is likely to place a burden on the entire family, and not just one single family member who may provide the majority of physical caregiving. In addition, in the patient expert statements submitted to NICE in November 2021 (prior to the first committee

meeting), it was emphasised that the impact of NF1 PN is on the whole family, which can include a patient's parents and siblings.[27]

As such we maintain that the originally submitted approach for estimating parent/carer burden (applying it to 1.4 people, based on the average UK household size being 2.4 people and one person being the patient) still provides the most appropriate estimate and may potentially be a conservative assumption.

Cost and Resource Use Data (see ECD Report Recommendation 1.2)

13

Full resource use costings have been applied conservatively

The committee concluded that it would like to see analyses with full resource use included for both arms of the model (see ECD Report Section 3.13).

Based on the committee's recommendation, additional cost items have been included within the model, with most of these being additional monitoring costs for selumetinib treated patients. NF1 PN patients require regular monitoring to check their disease status and patients treated with selumetinib would also need additional monitoring before starting and during treatment. We have collected information on the frequency of additional monitoring items, by treatment status and year, from a clinical expert and calculated the corresponding cost (Figure 27 and Figure 28).

Figure 27. Additional monitoring costs (baseline to Year 1)

Monitoring items	£ per unit	BSC		Selumetinib (on treatment)		Selumetinib (off treatment)	
		Frequency per year	£ per year	Frequency per year	£ per year	Frequency per year	£ per year
Physical/skin exam	£587.96	[redacted]					
X-ray of left wrist and tibial growth plate	£32.73						
Ophthalmology test	£28.35						
ECG/Echo	£91.73						
Blood test	£2.53						
Total	-						

Abbreviations: BSC: best supportive care; ECG: electrocardiogram.

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Figure 28. Additional monitoring costs (from Year 2)

Monitoring items	£ per unit	BSC		Selumetinib (on treatment)		Selumetinib (off treatment)	
		Frequency per year	£ per year	Frequency per year	£ per year	Frequency per year	£ per year
Physical/skin exam	£587.96	[redacted]					
X-ray of left wrist and tibial growth plate	£32.73						
Ophthalmology test	£28.35						
ECG/Echo	£91.73						
Blood test	£2.53						
Total	-						

Abbreviations: BSC: best supportive care; ECG: electrocardiogram.

We did not assume potential cost savings from symptom improvement due to treatment with selumetinib, even if this could be expected. This is because we did not have enough quantitative data to support this. As such, this can still be considered a very conservative approach.

The results from this revised modelling approach are shown in Figure 29. [redacted]

Figure 29. Cost-effectiveness model results, with full resource use costings and using the revised PAS price for selumetinib

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Selumetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£70,888

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALY: quality adjusted life year.

14

Addition of two magnetic resonance imaging (MRI) scans per year

The committee requested that two additional MRIs are included within the selumetinib arm of the model (see ECD Report section 3.14).

During the first committee meeting, clinical experts confirmed that patients who receive selumetinib will most likely receive two MRIs per year while patients treated with BSC will receive only one MRI; this would effectively result in one additional MRI per year for selumetinib-treated patients. Committee members also noted that the use of two additional MRI in the company submission base case was a conservative approach.

However, in the evaluation consultation document it is stated that the clinical expert consulted during the committee meeting envisaged that "in NHS clinical practice, two 'additional' MRI scans per year would be the most needed by people having selumetinib unless any acute changes happened." Therefore, the committee concluded the company assumption of two additional MRI scans per year was reasonable.

As we already used two additional MRIs in the model base case analysis, there was no need to update the model based on this recommendation. However, we would like to emphasise that two

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	additional MRIs (therefore total of three MRIs per year) can be considered a conservative assumption.

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Summary of the impact of performed model revisions

The impact of each of the revisions described above on the cost-effectiveness model results is summarised in Figure 30. The accumulated impact of all model revisions is further summarised in Figure 31, resulting in a final revised ICER of £[redacted]. Therefore, with the model revised as far as possible/feasible in light of the committee's recommendations, selumetinib remains a cost-effective treatment for the NHS.

Figure 30. Summary of model revisions (impact of each revision individually; with revised PAS)

	BSC			Selumetinib			Incremental: Selumetinib vs BSC		
	Costs	QALYs	LYG	Costs	QALYs	LYG	Costs	QALYs	ICER (£/QALY)
New PAS Discount [1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£70,471
PAS plus additional costs [1,2]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£70,888
PAS plus 3-year to revert to baseline utility [1,3]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£73,677
PAS plus 1-year to revert to baseline utility [1, 3b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£77,379
PAS plus treatment continuation after 18 years of age [1,4]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£76,806
PAS plus progression after 18 years of age [1.5]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£76,491
PAS plus inclusion of PFS for BSC arm [1,6]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£74,795
PAS plus alternative caregiver disutility (absolute decrement of 0.115 applied to 1.4 caregiver [1,7]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£82,736

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; PFS: progression-free survival; QALY: quality adjusted life year.

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Figure 31. Summary of model revisions (accumulated impact and final revised results; with revised PAS)

	BSC			Selumetinib			Incremental: Selumetinib vs BSC		
	Costs	QALYs	LYG	Costs	QALYs	LYG	Costs	QALYs	ICER (£/QALY)
New PAS Discount [1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£70,471
PAS plus additional costs [1,2]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£70,888
PAS plus 3-year to revert to baseline utility [1,3]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£74,113
PAS plus treatment continuation after 18 years of age [1,4]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£76,544
PAS plus progression after 18 years of age [1.5]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£81,141
PAS plus inclusion of PFS for BSC arm [1,6]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£87,246
PAS plus alternative caregiver disutility (absolute decrement of 0.115 applied to 1.4 caregiver [1,7]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£99,827

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; PFS: progression-free survival; QALY: quality adjusted life year.

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- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology evaluation (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the evaluation consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Selumetinib for treating symptomatic and inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in children aged 3 years and over [ID1590]

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Selumetinib for treating symptomatic and inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in children aged 3 years and over

1) Selumenitib could possibly help more children than initially indicated.
    a. There is no national database recording numbers with NF and plexiform tumours.
    b. There is also no indication of what criteria a child has to meet to be eligible for the drug so it is impossible to clearly indicate numbers

2) Clear criteria must be in place for indicating who can receive the drug.

    a. The use of the wording "inoperable tumour" as a criteria is misleading as most plexiform tumours are inoperable by nature, but not all of these tumours will meet the criteria for this treatment- the phrase needs to be expanded upon. In explanation I (CB) have a facial plexiform that has had multiple surgeries it is now classed as inoperable, my child has a plexiform that cannot be removed as the bulk of the tumour is inoperable though a small part can be surgically removed, he has two other plexiform tumours which are inoperable around major vessels in his neck, does this mean we would be candidates for treatment with the drug or do we need to meet further criteria?
    b. Symptomatic is also misleading as this could cover a myriad of things or not as the case may be. How does someone never experiencing a plexiform gauge the pain level of someone who has one?

Clear criteria should be published, and a guide made available to explain this to the lay person (children and families or carers).

    i. It is important that there is good communication between the Highly Specialised centres and the NF community via all patient groups so that expectations can be managed well, as many will see this as a wonder drug and feel it would help them or their child and that correct information is given.
    ii. Many children are not seen by an NF specialist, and many are not in the system (undiagnosed children/families).

These guidelines should enable anyone who feels they meet the criteria to request, through their primary care practitioner, an appointment at one of the Highly Specialised centres, or outreach hospitals to discuss possible use of the drug. There then should be a clear referral pathway to the relevant treatment centre.

3) Is there a support pathway (counselling/psychological support) and a care pathway in place for those who don't meet criteria/ have to stop the drug due to toxicity/ the drug doesn't work for or stops working? NF has a huge psychological impact upon a person, even more so if they have a debilitating or disfiguring and painful plexiform tumour, to be told that a drug could help them and for this then to fail will have a huge impact upon the child/Young person and their families and carers. They will need support throughout the whole process to manage expectations and deal with any fallout from treatment/lack of treatment.

4) It is important to note that although Selumetinib can have an impact in the short term on quality of life due to additional tests and hospital visits the long-term overall outcome should improve quality of life for those with plexiform tumours.

Q2

1) The committee mentions comparing the use of Selumetinib with BEST SUPPORTIVE CARE. It is important to note current practices aren't necessarily best supportive care and costs to provide this could be in excess of current recommendations.

2) Can AZ clarify what is best supportive care and

Is best supportive care receiving annually MRI's for a known plexiform and being under a highly specialised centre? As this is certainly not the case for everyone.

As parents of children with inoperable Plexiform Tumours we can clearly state our children do not receive yearly MRIs of their plexiform tumours, I (CB) can also clarify as a person with an inoperable plexiform tumour at no time during childhood or as a adult did I or do I have yearly MRI scans. My (CB) son is under one of the Highly Specialised centres and does not get annual scans, my daughter (CB) daughter and I are seen locally.

The costs of ongoing holistic care of a patient with NF and an inoperable plexiform tumour overtime could be greater than that of a patient treated successfully with Selumetinib. If a tumour is successfully treated then there would be reduced psychological burden, reduced need for pain relief and pain management, reduced need for therapies specifically associated with loss of function due to the plexiform tumour, reduced impact on schooling (less time off school for medical care), hopefully reducing the need for limb amputation due to plexiform tumours. A knock on impact of the regular MRI's would mean any other plexi forms would be identified early and the drug would also work on these tumours as some children will have multiple plexiform neurofibromas.

3) MRI scans – General anaesthetic is generally avoided post 6 years of age and in some cases a sedative can be used instead of a GA. Not needing a general anaesthetic will significantly reduce costs of the MRI scans The number of children they are talking about treating currently is a tiny amount in comparison to the general population of people with NF, therefore comparatively the cost is small as they all have to be over the age of 3.

Q3

We feel Black and Ethnic Minorities are significantly under represented NF does not discriminate race, ethnicity, gender, religion yet we find that we see lower numbers of children and younger people from the Black and Ethnic Minority Communities, this could because NF can be harder to pick up or maybe due to the use of the term coffee coloured marks (café au lait) as in people with black skin the marks are not coffee coloured, so it could be people are not picked up at the routine screening appointments. Religion can also have an impact as can cultural values and beliefs. Some children will not be taken to the doctors/hospital and some will not agree with certain treatments. Whilst the committee cannot ensure that these people are reached we can ensure clear guidelines are available to be distributed by the nhs and charities to give these children and young people an opportunity to have equal care.

A 20 year old had to have her leg amputated due to an MPNST. (Cancerous Plexiform Tumour) Although she was known to have NF1 from the age of 7, it took 18 months of her mother fighting to get the 'large red and painful lump' looked at. The cancer has now spread to her lungs and no more treatment is available. We don't know if the Selumetinib may have helped this young girl, but the point is she would never have had the opportunity, as by the time she had reached the Highly specialised centres it was too late.

It needs to be very specific who meets the criteria. We need detailed criteria that is clear and easy to follow. Parents/Young people/carers and practitioners need to be able to easily see who is eligible and how to move forward. Criteria cannot just say inoperable plexiform tumours unless the intention is to offer the treatment to everyone in the age range with an inoperable plexiform tumour. Inoperable could also be open to interpretation - does it mean totally inoperable as in no surgery is viable or does it include those that could be de-bulked but cannot he fully removed - those that grow back post-surgery -most plexiforms will continue to grow after de-bulking.

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Selumetinib for treating symptomatic and inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in children aged 3 years and over [ID1590]

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Evaluation Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	The Neurofibromatosis Association t/a Nerve Tumours UK Charity Registration. 1078790/ SCO45051
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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	It is exciting that there is a drug treatment available to help in managing this distressing complication.
2	Surgery has been the main treatment till MEK inhibitors became available (i.e. selumetnib and related drugs). Many plexiforms cannot be entirely removed by surgery, but surgery can improve function and quality of life. a) What is the definition of inoperable? b) Is there a plan to use selumetinib in conjunction with surgery, either before or after, to improve outcome?
3	We believe that the decision making about who should receive selumetinib, should be undertaken by the national neurofibromatosis teams at Guy's Hospital, London and St. Mary's Hospital, Manchester, where there is already a joint, established MDT in combination with Great Ormond St. Hospital. This would tap into existing experience and expertise and avoid over or under treatment.
4	We think that treatment could be carried out in conjunction with local centres as this avoids unnecessary disruption to schooling, parents' employment and family life.
5	We believe that the measures that look at effectiveness of treatment should be robust and weight should be given to patient perceived quality of life.
6	We do not know how long the drug should be given for and whether there will be a need for ongoing treatment in adult clinics.

Insert extra rows as needed

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Highly Specialised Technology Evaluation

Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee	AstraZeneca	[redacted] SPRINT Phase II Stratum I is the most relevant data source for selumetinib in the licensed indication of paediatric patients with neurofibromatosis type 1 (NF1) with symptomatic, inoperable plexiform neurofibroma (PN). The evidence from this clinical trial is supportive of the effectiveness of selumetinib at stabilising and reducing PN volume, compared with best supportive care.[1] However, there are limitations associated with this evidence base; these limitations are inevitable consequences of the ultra-rarity and heterogeneity of NF1 PN. In light of the available evidence, we maintain that the modelling approach in the company submission represents the best approach and only feasible approach. The rationale behind the modelling approaches taken has been further explained within this response, and we have adopted a large extent of the recommendations within this response (where feasible). However, use of some assumptions in the modelling remains inevitable and we acknowledge that this may contribute a degree of uncertainty. [redacted] [redacted] **[Figure 1 received but not reproduced in this table]**	Comment noted.

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			[Figure 2 received but not reproduced in this table] Selumetinib represents a step-change in the management of paediatric patients with symptomatic, inoperable NF1 PN, a patient population where this is a substantial unmet need for an effective treatment. Selumetinib treatment results in durable stabilisations and reductions in PN volume in paediatric patients, preventing or reducing the most rapid stage of PN volume growth.[1] In the following responses, AstraZeneca have sought to implement the committee's feedback wherever feasible. [redacted]	
2	Consultee	AstraZeneca	**The conclusions regarding the clinical evidence are sound, and an accurate interpretation of the evidence** The committee evaluated all evidence from the pivotal SPRINT Phase II Stratum I study, the most relevant data source for selumetinib in NF1 PN.[1] The committee concluded that based on the clinical trial evidence, selumetinib is effective at reducing the volume and size of PN compared with best supportive care (Evaluation Consultation Document [ECD] Report page 4), and that the results from the SPRINT trial are generalisable to the UK population (ECD Report Section 3.10).	Comment noted.
3	Consultee	AstraZeneca	**The development of a patient-level model is unfeasible** The committee stated that they would prefer to see a patient-level model. As discussed during the Committee Meeting, the available evidence package (Phase II Stratum I of the SPRINT clinical study and National Cancer Institute [NCI] Natural History study) does not support the development of a patient-level model. Very few Highly Specialised Technology (HST) appraisals have used patient-level models, likely due to the need to have sufficient quantities of patient-level data available to inform such cost-effectiveness analyses, and the challenge of recruiting patients to studies in ultra-rare conditions. The one HST appraisal identified by AstraZeneca in which a patient-level model was developed had a significantly longer-term evidence base (over 14-years) and larger clinical trial population of 112 patients to draw from.[2] This appraisal also used relatively well-established sub-models in different organs (e.g. pancreas, liver, cardiovascular, kidney, etc) and the well-established surrogate outcome of HBA1c to calculate transition probabilities.[2] While we acknowledge that a patient-level simulation would allow the development of a more detailed model which more closely reflects the heterogeneity of patients with NF1 PN, it would not have been feasible to meet this recommendation with the available data. We explored the feasibility of developing a regression-based patient level model at the stage of early model conceptualisation. However, the heterogeneity of NF1 PN, coupled with the limited sample size for the SPRINT Phase II Stratum I study (n=50),[1] made it unfeasible to establish a quantitative relationship between potential covariates sufficiently informative for decision-making purposes. It is worth emphasising that within the context of an rare condition, and, relative to the total estimated number of children with NF1 PN in the UK and other related studies, the SPRINT Phase II trial achieved	Comment noted. Although it would have preferred a model structure that represents the disease and includes outcomes that clinical and patient experts advised were important, the committee recognised the difficulty of including clinical outcomes in the model due to the heterogeneity of NF1 PN and this would require many

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			a good sample size. Covariates explored included: age, PN location, PN volume and quality of life (please see results included below the heading 'Further characterisation with regression analyses'). In addition, no patient-level health-related quality of life (HRQoL) data and other patient reported outcomes were available from the Natural History study to support such analysis; this also meant that we couldn't establish a quantitative relationship between potential covariates and HRQoL in patients treated with best supportive care (BSC). The very high level of heterogeneity within the NF1 PN patient population also made it difficult to define a series of distinct health states. As multiple individual PN can occur anywhere on the body, combinations of treatment effect modifiers such as PN location, PN size, PN growth rate and age result in all patients having different and unique health states. [redacted].[3] It is also impossible to quantify the individual and combined impacts of each effect modifier on HRQoL, especially with data from 50 patients. For example, subgrouping the analysis by PN location would have reduced the maximum sample size to only [redacted].[1] The heterogeneity of NF1 PN was emphasised during the committee meeting in November 2021, where a patient expert explained that PN affect everyone differently, and can be unpredictable, making living with NF1 PN challenging. We appreciate that a degree of simplification has been necessary in order to develop the current model. However, the modelling approach remains the most robust possible, given the available data and the heterogeneity of NF1 PN. The current modelling approach accounts for the overall improvements in clinical outcomes and quality of life seen at an individual and population level in selumetinib treated patients, alongside stabilisations and reductions in PN volume (see comment #7 for further details). **Patient-level modelling would result in a model associated with a significantly higher level of uncertainty**, due to a larger number of assumptions that would have to be made on the quantitative relationship between each effect modifier and outcome. This would impair the ability of the committee to draw a conclusion on the cost-effectiveness of selumetinib that improves on the existing approach. During the open session of the Evaluation Committee Meeting (10th November 2021), there was lengthy discussion on the cost-effectiveness model during which we presented potential modelling approaches and the advantages and disadvantages of each, discussed our recommended modelling approach and provided an explanation as to why it was not feasible to develop a patient-level model. At that time, no concerns were raised by the Appraisal Committee and indeed, it was stated by the health economic expert on the committee that our model was likely to be conservative given the assumptions that we had made. Unfortunately, as discussed above, a patient-level model remains unfeasible, however we believe we have taken a pragmatic approach in developing the most robust model possible with the evidence	assumptions. It concluded the company revised model structure is suitable for decision making. See FED section 3.9 and 3.11.

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			package we have available. <u>Further characterisation of results with regression analysis</u> For full transparency, we have provided additional details of the analysis to assess whether quantitative relationships could be established between key variables, specifically: investigating the relationship between Pediatric Quality of Life Inventory™ (PedsQL) total scores and patient characteristics, disease characteristics or tumour size. Regression analyses were performed using the PedsQL total scores collected from SPRINT Phase II Stratum I; self-reported values were used where available, otherwise parent/guardian reported scores were used. As patient and disease characteristics were only captured at baseline, the regressions were run using only baseline quality of life data. *Patient and disease characteristics* The first analysis investigated the effect of NF1 PN disease duration and age on patient quality of life. It is logical that the longer a patient has had a given disease, the greater they are likely to have suffered from the effects of the disease; a patient cannot have had a disease for longer than they have been alive. In particular, once PN-related morbidities develop, they are extremely unlikely to resolve spontaneously.[4] As duration of disease is correlated with patient age, age was included as an explanatory variable, to accurately estimate the effect of the two different variables. **The regression showed insignificant coefficients, providing no evidence to suggest PedsQL score is predicted by age or disease duration** ([Figure **3 received but not reproduced in this table]**). This result is unexpected, based on the natural history of NF1 PN. The inability to identify a significant relationship is likely due to the small dataset and heterogenous patient population, inevitable consequences of the rarity and complexity of NF1 PN. With a larger dataset it may be that a relationship would have been found between quality of life and age or disease duration. **[Figure 3 received but not reproduced in this table]** The second analysis examined body surface area (BSA) and weight. Patient BSA is related to age, height, and weight, and thus may act as a good proxy for all these factors without using excessive statistical power by requiring three coefficients to be included. The regression analysis for BSA (**Error! Reference source not found.**), however, indicates that **there is limited support for the hypothesis that PedsQL is linked to BSA**. In addition to a lack of significance, the interquartile range of BSA is only 0.5, meaning that any practical impact of PedsQL is half of the observed coefficient. Again, this	

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			finding is likely due to the inevitable limitations of data collected in rare and heterogenous patient population. **[Figure 4 received but not reproduced in this table]** In order to confirm the results of the analysis for BSA, a regression analysis was performed looking at the impact of weight on PedsQL, in light of evidence suggesting weight may be an important factor in patient reported outcomes for patients with NF1 PN. However, the results of the regression ([Figure 5 received but not reproduced in this table]) indicate that weight is also a poor predictor of PedsQL score, when taken in isolation. **[Figure 5 received but not reproduced in this table]** In the SPRINT study, patients were classified according to whether their disease had progressed (≥20% increase in neurofibroma volume) in the 15-month period prior to enrolment in the study.[1] A regression analysis was conducted to evaluate whether progression status at baseline is a predictor of PedsQL score ([Figure **6 received but not reproduced in this table]**). The coefficient associated with this was not significant; based on the available data, **progression status at baseline does not appear to predict patient PedsQL scores**. This was unexpected, as it was observed that patients who were classified as having 'progressed' at baseline had lower PedsQL scores. The inability to draw a significant correlation is likely due to the inevitable limitations of the available data, in particular the rarity of the NF1 PN and subsequent small sample size. **[Figure 6 received but not reproduced in this table]** *Tumour location* Tumour location was evaluated at baseline in the SPRINT study and has been suggested to be prognostic of patient quality of life. The regression analysis of PN location was first performed using PN locations as coded in SPRINT Phase II Stratum I ([Figure 7 received but not reproduced in this table]). No reference group was used (the intercept was supressed) as it was not clear which group should constitute the intercept. The results were therefore difficult to interpret, due to both the small and highly variable sample size (ranging from [redacted]), and to the uncertainty over which group should be used as the intercept relative to which all other coefficients would be estimated. **[Figure 7 received but not reproduced in this table]**	

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			PN locations were therefore reassigned to one of four categories, classifying PN as to whether there was involvement on the trunk, head, neck or extremity. This then allowed an intercept to be used in the equation and four coefficients to be estimated, by increasing the power for detecting a difference in each PN location (with patients potentially having more than one PN location depending on the extent of their PN; [Figure 8 received but not reproduced in this table]). **[Figure 8 received but not reproduced in this table]** In the recoded approach, the location of the PN and involvement of the trunk, head, neck or extremity does not predict PedsQL score. This is likely due to the extremely heterogenous nature of PN and the complex interplay of precise PN location and volume in determining the extent and severity of PN-associated morbidities. Overall, of the different patient and disease characteristics evaluated at baseline in the SPRINT Phase II Stratum I and considered within these regression analyses, none can be linked to PedsQL total score. *Tumour volume* Regression analysis was also used to estimate the relationship between PedsQL scores and target tumour volume. Both PN volume measured by investigator (primary data) and measured by independent review (secondary data) were analysed (see SPRINT Clinical Study Report for further details).[5] For data from the central, independent review, where two values were available on the same date for a patient (Radiographer 1 and Radiographer 2 in the data), the mean of the values was taken. Using either volume measurement, PN volume does appear to be linked to PedsQL score (**Error! Reference source not found.** and [Figure **10 received but not reproduced in this table]**). However, the coefficients were small and the heterogeneity in tumour volume in this patient population should be noted. **[Figure 9 received but not reproduced in this table]** **[Figure 10 received but not reproduced in this table]** Given the heterogeneity in PN volume (and also body size between patients), a 'normalised PN volume' was constructed, in which PN volume was divided by the body weight of patients, to account for differences in both PN size and patient size. As only baseline weight was available in the raw data, this was used, but is not expected to vary substantially over the (relatively short) trial period. For consistency, total tumour volume measured by independent review was taken. In the regression analysis, the coefficient was found to be at a reasonable level ([Figure **11 received but not reproduced**	

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			in this table]). **[Figure 11 received but not reproduced in this table]** Though a reduction in PN size, both in absolute and normalised terms, appears to lead to an increase in PedsQL total score, the small coefficients associated with tumour size mean that changes in volume have a weak correlation with the PedsQL total score. As explained in the comment #7 of this response document, this weak relationship between tumour volume and PedsQL is *not* because the volume reduction does not improve HRQoL. Patients who experienced volume reduction also experienced HRQoL improvement in SPRINT Phase II Stratum I, and this effect was not observed in the Natural History study.[1] The weak relationship seen here is because **absolute** volume reduction is not directly linked to degree of HRQoL improvement; there is a complex interplay of many factors, and a high degree of heterogeneity within the NF1 PN patient population. *Summary* In conclusion, correlations between PedsQL total score and treatment effect modifiers could not be established or were weak in the regression analyses. This is likely due to the extremely heterogenous nature of PN and the complex interplay of precise PN location and volume in determining the extent and severity of PN-associated morbidities. This lack of correlation makes a development of a patient-level modelling challenging. Even if there were correlations, because of the challenges on mapping PedsQL to utility score (see comment #8 for further details), it would not be possible to assign corresponding utility score to each health state in a patient-level model. Therefore, the modelling approach in the company submission represents the best approach given the available evidence package.	
4	Consultee	AstraZeneca	**Addition of a progression-free state for the best supportive care arm** It was suggested that a progression-free state should be added to the BSC arm (see ECD Report recommendation 1.2 and Section 3.11). However, addition of a progression-free state for the best supportive care arm would imply that patients receiving best-supportive care experience the same rate of PN growth (or PN volume reduction) and quality of life as selumetinib treated patients in a progression-free state. This would be neither accurate nor appropriate. However, we have implemented a progression-free survival (PFS) state in the model for the BSC arm as per the Committee's request. <u>Equivalent experience of PN growth</u> In the Gross et al. 2018 analysis of the NCI Natural History study, no patients aged ≤18 years experienced a reduction in tumour volume from baseline; across the study, a median growth rate of 15.9% per year was observed (lower quartile 10.1%, upper quartile 28.0%).[4] Whilst the PN growth rate experienced by individual patients varies, with some growing rapidly and others more slowly, the trend is for growth over of time.	Comment noted. The committee welcomed the addition of a progression-free state to the best supportive care arm. It concluded utility values for health-states defined by the presence or absence of disease progression,

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			In addition, patients treated with best supportive care experience persistent PN growth, even if this growth rate does not meet the formal definition of 'progressive disease' as used in the SPRINT Phase II Stratum I study (a ≥20% increase in PN volume).[1, 4] In total, eight PN in the Gross et al. 2018 analysis of the Natural History study had a <20% relative volume difference between baseline and maximum assessment (volumetric assessment at which the PN was at its maximum volume). However, median growth in these eight PN was 14.2% (5.7% per year), demonstrating that despite being classified as 'stable', these PN were still undergoing growth.[1] As such, the experience of all patients treated with BSC is equivalent – patients experience continuous PN growth at varying rates. **It would therefore be inaccurate to model different patient experiences for those treated with BSC in progression or progression free health states; it is appropriate to assign the same utility to all patients in the BSC arm.** <u>Equivalent experience of PN-associated morbidity, and therefore quality of life</u> The addition of a PFS state for the BSC arm would imply that BSC-treated patients with progressive disease and those in the PFS state experienced a different quality of life. However, this is not supported by the evidence for the experience of patients within the Natural History study. As previously described, patients in the Natural History study experienced a variety of PN growth rates. However, all PN included in the Gross et al. 2018 analysis which had associated morbidity present at baseline still had a morbidity present at maximum assessment. Furthermore, 30/57 PN had an increase in the number of associated morbidities between baseline and maximum assessment and morbidities increased in severity ([Figure **12 received but not reproduced in this table]**). In particular, 27 PN required an increased in the number of pain medications required over the same period; an increase in the number of PN requiring opioid and neuropathic painkillers was also observed.[4] **[Figure 12 received but not reproduced in this table]** The Natural History study demonstrates that in the absence of disease-modifying treatment, patients are extremely unlikely to experience an improvement in their existing PN-associated morbidities, regardless of PN growth rate.[4] Furthermore, the Natural History study demonstrates that PN-associated morbidities have a considerable negative impact on patients' HRQoL.[6-8] As emphasised by patient experts at the committee meeting, it is clinical outcomes such as improvements in pain, motor function, airway function, visual function and physical functioning, that are of greatest importance to individuals with PN and their carers. It is therefore reflective of the natural history of NF1 PN to model a constant utility for progressive disease for patients treated with BSC.	should be consistent between the selumetinib and best supportive care arms See FED section 3.12

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			Application of the committee recommendation in the model Whilst the company do not agree with using different utility scores in the BSC arm by progression state, due to the reasons outlined above, we have implemented the recommendation from the committee, in order to test the impact of using PFS in BSC arm. To facilitate the committee's request to incorporate progression in the BSC arm, patients in the BSC-treated arm are assumed to enter in a stable (non-progressive state). However, as patients in the BSC arm do not experience the PN volume reduction or symptom improvement seen with selumetinib treatment,[1] they could not experience equivalent utility to patients with PFS in the selumetinib arm (a utility score of [redacted]). We have therefore applied a utility score of [redacted], which is the midpoint between the baseline utility ([redacted]) and the utility score of selumetinib-treated patients in the progression-free state ([redacted]). The updated model therefore takes a conservative approach, which favours the BSC arm and does not reflect the experience of patients in the SPRINT Phase II Stratum I.[1] The modelling assumes that patients in the BSC arm in the progression-free state have higher utility scores than baseline, however these patients would not have experienced any tumour reduction or symptom improvement from baseline. Parametric survival analyses of time-to-progression data for the age-matched natural history cohort were conducted in line with the recommendations in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14.[9] Of the parametric distributions explored, the lognormal distribution had the best fit (as determined using goodness-of-fit statistics). Within the updated model, PFS follows this lognormal curve until patients reach the age of 18, after which point a lower progression rate is applied, representing the stabilisation of PN growth seen in adulthood (see comment #4 for further details). The results from this revised modelling approach are shown in [Figure **13 received but not reproduced in this table**]. [redacted]. **[Figure 13 received but not reproduced in this table]**	
5	Consultee	AstraZeneca	**Only a very small proportion of adults with NF1 PN experience progression, and therefore including progression within the model after the age of 18 would not reflect the natural history of the disease** The committee recommended that the model should allow progression to happen after the age of 18 years (see ECD Report Section 3.12). In the Akshintala et al. 2020 analysis of the Natural History study, the median PN growth rate observed in patients aged ≥18 years was 0.7% per year; this is in significant contrast with a median tumour growth rate of 14.6% per year observed in patients aged <18 years, and substantially lower than a ≥20% increase used to define progressive disease. These data demonstrate	Comment noted. The committee recognised that there would be progression after the age of 18 but noted some uncertainty in the assumption of

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			that in adult patients, PN growth rates are generally very close to zero.[10] Indeed, the slowing and stabilisation of PN growth into adulthood was emphasised by clinical experts during the committee meeting. Whilst there might be some outliers, published data suggests that adults have an exceptionally low likelihood of progression. However, to acknowledge the small potential of progression after the age of 18, we have revised the model to allow patients to experience progression after the age of 18. To reflect the slow growth rate of PN after the age of 18, we have applied an annual progression rate of [redacted] for both the selumetinib arm and BSC arm after the age of 18. In the paediatric Natural History age matched cohort, 85% of patients experienced tumour progression over three years;[1] this equates to a rate of progression of 28.3%/year. As paediatric patients experience a tumour growth rate that is ~21 times higher than adult patients (14.6%/year versus 0.7%/year),[10] we used the simple calculation of [redacted] to derive a progression rate of [redacted] for patients aged >18 years. Tumour growth rate is even lower in older adult patients (in line with general increase in height); we have therefore assumed that any further PN progression would stop by the age of 24, in both the selumetinib and BSC arms. Clinical experts who had previously been consulted for the selumetinib appraisal were contacted again to give their input on assumptions around tumour progression after the age of 18. The assumptions were presented as follows: ***Assumptions on tumour progression after the age of 18.*** *In a study analysing the Natural History study, the median PN growth rate observed in patients aged ≥18 years was 0.7% per year; this is in significant contrast with a median tumour growth rate of 14.6% per year observed in patients aged <18 years. Considering the slow PN growth rate in adulthood, we can arbitrarily assume that an additional [redacted] of adult NF1 PN patients experience PN progression (>20% PN growth from baseline) every year until age of 24. This would mean that among adult patients who haven't had PN progression at the age of 18, about [redacted] of them will eventually experience PN progression after age of 18.* - *Would this be a reasonable assumption?* Of the four clinical experts contacted, two responded and agreed that these assumptions are appropriate. In acknowledgement of the potential for remaining uncertainties, we have used more conservative parameters ([redacted] as a progression rate for patients aged >18 years) in the model. The results from this revised modelling approach are shown in [Figure **14 received but not reproduced in this table]**. Including progression after the age of 18 has minimal impact on the overall ICER [redacted]); it can therefore be concluded that this is not a key area of uncertainty within the modelling. **[Figure 14 received but not reproduced in this table]**	stopping exactly at the age of 24. See FED section 3.13

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6	Consultee	AstraZeneca	**Only a very small proportion of adults with NF1 PN experience progression, and therefore it is expected that very few patients would continue treatment beyond the age of 18** The committee requested that the possibility for selumetinib treatment to continue beyond the age of 18 years be included within the model (see ECD Report Recommendation 1.2 and Section 3.12). The marketing authorisation for selumetinib states that the treatment is indicated for paediatric patients aged 3 years and above, and that there are limited data in patients older than 18 years, therefore continued treatment in adulthood should be based on benefits and risks to the individual patient.[11] The authorisation also states that commencing treatment in adulthood is not appropriate; where there is continued benefit of selumetinib treatment beyond the age of 18 years, selumetinib treatment could be continued.[11] However, as discussed in comment #4, the number of adults with NF1 PN who experience progression beyond the age of 18 years is negligible. For this reason, it is expected that most, if not all patients would discontinue treatment when they reach adulthood. Nonetheless, we have revised the model to incorporate patients who may continue to experience disease progression after the age of 18 (please see comment #4 for details). As a large portion of patients would discontinue when they reach adulthood, we have assumed that [redacted] of patients would stop treatment when they reach adulthood, and the remaining [redacted] would continue treatment based on the Weibull curve for time-to-discontinuation. Clinical experts who had previously been consulted for the selumetinib appraisal were contacted again to give their input on this assumption; the assumption was presented as follows: ***Treatment discontinuation after age of 18.*** *Among patients who started selumetinib treatment at the age of 10 and continued until age of 18, our modelling assumed [redacted] would stop the treatment when they reach adulthood; the remaining [redacted] would continue treatment into adulthood.* - *Would this be a reasonable assumption?* Of the four clinical experts contacted, two responded and agreed that this assumption was appropriate. In light of the potential uncertainty surrounding this assumption, we have used more conservative parameters ([redacted] instead of [redacted] stopping treatment when they reach adulthood) in the model. The results from this revised modelling approach are shown in [Figure **15 received but not reproduced in this table]**. Whilst inclusion of treatment continuation after 18 does [redacted], selumetinib remains cost-effective in this scenario. **[Figure 15 received but not reproduced in this table]**	Comment noted. The committee concluded that the percentage of people continuing selumetinib treatment beyond the age of 18 provided by the company was reasonable. See FED section 3.14
7	Consultee	AstraZeneca	**Accounting for age or PN location within the model would not be feasible due to a lack of correlations**	Comment noted. The committee recognised the

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			The committee recommended development of a patient level simulation model which accounts for the age and location of PN (see ECD Report Recommendation 1.2 and Section 3.11). As discussed in comment #2, in order to determine how age or PN location could be accounted for in the model, univariable regression analyses were carried out to investigate the relationship between PedsQL total scores, age and duration of disease, and PN location. These analyses used the PedsQL total scores collected from SPRINT Phase II Stratum I; self-reported values were used where available, otherwise parent/guardian reported scores were used. As age and duration of disease and PN location were only captured at baseline, the regressions were run using only baseline PedsQL scores. Age The first analysis investigated the effect of NF1 PN disease duration and age on patient quality of life. It follows logically that the longer a patient has had a given disease, the greater they are likely to have suffered from the effects of the disease; a patient cannot have had a disease for longer than they have been alive. As duration of disease is correlated with patient age, age was included as an explanatory variable, so as to accurately estimate the effect of the two different variables. The regression showed insignificant coefficients, providing no evidence to suggest PedsQL score is predicted by age or disease duration ([Figure **16 received but not reproduced in this table]**). As previously mentioned, this result is unexpected, based on the natural history of NF1 PN. The inability to identify a significant relationship is likely due to the small dataset and heterogenous patient population, inevitable consequences of the rarity and complexity of NF1 PN. With a larger dataset it may be that a relationship would have been found between quality of life and age or disease duration. **[Figure 16 received but not reproduced in this table]** PN location The analysis of PN location was first performed using PN locations as coded in SPRINT Phase II Stratum I ([Figure **17 received but not reproduced in this table]**). No reference group was used (the intercept was supressed) as it was not clear which group should constitute the intercept. The effect of not including an intercept is that the regression line passes through the origin, which tends to have the effect of misleading the results and removing the predictability of the analysis, which giving the model the appearance of significance. The results were therefore difficult to interpret, due to both the small and highly variable sample size ([redacted], and to the uncertainty over which group should be used as the intercept relative to which all other coefficients	difficulty of including clinical outcomes in the model due to the heterogeneity of NF1 PN and this would require many assumptions. It concluded the company revised model structure is suitable for decision making. See FED section 3.9 and 3.11.

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			would be estimated. **[Figure 17 received but not reproduced in this table]** PN locations were therefore reassigned to one of four categories, classifying PN as to whether there was involvement on the trunk, head, neck or extremity. This then allowed an intercept to be used in the equation and four coefficients to be estimated, by increasing the power for detecting a difference in each PN location (with patients potentially having more than one PN location depending on the extent of their PN; [Figure **18 received but not reproduced in this table]**). **[Figure 18 received but not reproduced in this table]** In the recoded approach, the location of the PN and involvement of the trunk, head, neck or extremity does not predict PedsQL score. In conclusion, the analyses presented here demonstrate that quality of life, as measured by PedsQL, cannot be predicted either by age and duration of disease, or PN location, making it unfeasible to account for these variables within a patient level simulation model. This is likely due to the extremely heterogenous nature of PN and the complex interplay of precise PN location and volume in determining the extent and severity of PN-associated morbidities.	
8	Consultee	AstraZeneca	**Accounting for clinical outcomes (e.g. pain) within the model would require a large number of assumptions. The current modelling approach, whilst simplified, reflects the efficacy of selumetinib through the most robust methods** The committee requested that the cost-effectiveness model reflects clinical outcomes that are important to people with PN, carers and clinicians, such as pain, which were felt to be more important than PN volume reduction (see ECD Report Recommendation 1.2 and page 4). During model conceptualisation, the possibility of employing a modelling methodology that would incorporate clinical outcome measures was explored. However, a number of challenges were encountered in relation to the available data: – Very few patients had each type of morbidity at baseline within the SPRINT Phase II Stratum I. For example, clinical and patient experts explained that pain is a particularly important outcome, but only 52% of patients had pain at baseline (only 26 patients).[1] The very small data sets would have contributed a large degree of uncertainty to the modelling approach. To note, within the context of a rare condition, and, relative to the total estimated number of children with NF1 PN in the UK and other related studies, the SPRINT Phase II trial achieved a good sample size. The small data set is therefore an inevitable feature of a	Comment noted. The committee recognised the difficulty of including clinical outcomes in the model due to the heterogeneity of NF1 PN and this would require many assumptions. It concluded the company revised model structure is suitable for decision making. See FED section

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			rare disease study – In addition, patients with NF1 PN will often experience multiple PN-associated morbidities, as a result of having PN in multiple locations.[4, 12-14] Indeed, patients in SPRINT Phase II Stratum I had a median of three morbidities at baseline (range 1–5).[1] Similarly, across the 57 patients of the Natural History study many of the observed PN were associated with multiple morbidities; more specifically, 23% of PN were associated with two morbidities and 10% of PN were associated with three or four morbidities at baseline.[4] As such, it is not feasible to correlate changes in patient quality of life with specific morbidities. It is even more challenging if other effect modifiers were also considered at the same time, such as PN size, location, growth rate and age, because of the very high heterogeneity of NF1 PN and the small sample size Clinical experts commented that reducing the volume of PN by 20% may not result in a clinically meaningful improvement for some individuals with PN. Given the heterogeneity of the size and location of PN, as well as the heterogeneity of associated morbidities, it could be difficult to define a quantitative relationship between change in PN volume and each clinical outcome assessment at a population level. However, when taking a patient-level view, a quantitative relationship may still not be feasible but tumour volume reduction can be linked to improvements in HRQoL or clinical outcome measures such as pain. The relationship between tumour volume reduction from baseline and patient-reported outcomes was evaluated in SPRINT Phase II Stratum I with a post-baseline scan. Scatter plots presenting the correlation between PedsQL total scores and tumour volume change, and between Numerical Rating Scale-11 (NRS-11) pain scores and tumour volume changes, show that in most cases volume reduction is linked to improvements in HRQoL or pain ([Figure **19 received but not reproduced in this table]** , [Figure **20 received but not reproduced in this table]** and **Error! Reference source not found.**). Whilst some patients treated with selumetinib experience symptom improvement without volume reduction, and absolute amounts of volume reduction cannot be correlated to the degree of symptom improvement, overall there is a trend for improved quality of life and pain outcomes with reduced tumour volume in each patient. It should be noted that in the Gross et al. 2018 analysis of the Natural History study, no spontaneous reductions in PN volume were observed in children aged <18 years and no improvements in PN-associated morbidities occurred. The Natural History study demonstrates that, in the absence of disease-modifying treatments, symptom improvements are extremely unlikely to occur.[4] It can therefore be concluded that the improvements in PedsQL scores observed in SPRINT Phase II Stratum I are due to treatment with selumetinib. **[Figure 19 received but not reproduced in this table]**	3.9 and 3.11.

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			[Figure 20 received but not reproduced in this table] **[Figure 21 received but not reproduced in this table]** As stated above, PN volume change at an individual patient level is related to improvements in important symptoms such as pain and HRQoL. While the degree of volume reduction may not be directly corelated with the degree of pain and HRQoL improvement, we do know from the SPRINT Phase II Stratum I results that the volume reduction results in positive clinical outcomes in most patients. Therefore, we chose to include disease progression (representing change in PN volume) as a main driver of the model, as the most feasible and evidence-based approach.	
9	Consultee	AstraZeneca	**The mapping of PedsQL data from SPRINT to Child Health Utility 9D (CHU9D) would not appropriately reflect patient utility scores** The committee concluded it would have preferred to see an attempt at mapping and use of direct utility data from the trial included in the analysis or at the very least use the mapped values to validate the time trade off values (see ECD Report page 18). The committee acknowledged the challenges in mapping to EuroQol Five Dimensions (EQ-5D), but proposed that other mapping algorithms were available and the PedsQL data from SPRINT could have been mapped to the CHU9D. Similar to the previously discussed issues of mapping the PedsQL to EQ-5D, to our knowledge there are only a limited number of validated algorithms for the mapping of PedsQL to the CHU9D: Lambe *et al*., Mpundu-Kaambwa *et al*. and Sweeney *et al*.[15-17] Furthermore, the different studies raised similar limitations regarding the development and/or validation of such algorithms, such as the poor performance for certain age groups or for patients with a severe disease and low quality of life. For example, whilst a study by Lambe *et al*. for estimating CHU9D index scores from PedsQL data was based on a UK cohort of children with health issues (cortico-sensitive nephrotic syndrome) and could therefore be theoretically considered suitable in this case, the age range of included patients was comparatively narrow with 5–12 years and a considerable number of children had (near) perfect health; Lambe *et al*. therefore concluded for the resulting mapping algorithm that "caution should be exercised when using this with children younger than five years, older adolescents (>13 years) or patient groups with particularly poor quality of life".[15] Correspondingly, when we applied the Lambe *et al.* algorithm to baseline PedsQL data obtained from the SPRINT study population (3–18 years of age), the resulting utility overall value for patients with NF1 PN was unrealistically high, with a median score of [redacted]; [Figure **22 received but not reproduced in this table]**). Other available mapping algorithms by Mpundu-Kaambwa *et al.* and Sweeney *et al.* were also limited to comparatively narrow age bands, in terms of the included patient populations (e.g. 10–12 years or 15–	Comment noted. The committee would have preferred to see direct utility data from the trial included in the analysis. It recognised that there remains considerable uncertainty relating to the utility values estimated from the time trade off interviews but concluded in the absence of any plausible mapped utilities they would have to use them for decision making. See FED section 3.17

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			17 years of age) and based on Australian general population cohorts.[16, 17] In this context, it should also be noted that it was already acknowledged during the committee meeting that it is difficult to extrapolate from healthy individuals to patients with NF1 PN when mapping utility values. In addition, another study by Mpundu-Kaambwa *et al*. aimed to assess the validity and generalisability of five mapping algorithms (for predicting CHU9D utilities from PedsQL scores), with the finding that all algorithms performed worse amongst children with disabilities/health conditions (relative to children without disabilities/health conditions).[19] Similarly, when developing their mapping algorithm as well as validating existing algorithms by Lambe *et al.* and Mpundu-Kaambwa *et al.*, Sweeney *et al.* clearly stated that "This work again confirms that mapping algorithms generally perform poorly in children with relatively poor HRQoL; as such, the use of any of these mapping algorithms will underestimate any actually experienced HRQoL gains and this bias increases with disease severity".[17] In line with this, when we also applied the two additional mapping algorithms available from Mpundu-Kaambwa *et al.* and Sweeney *et al.*, resulting median utility scores were also unrealistically high ([Figure **22 received but not reproduced in this table]**), and are thus not considered reflective of the actual HRQoL experienced by patients with NF1 PN. **[Figure 22 received but not reproduced in this table]** In consequence, and as demonstrated by the application of existing mapping algorithms, the mapping of PedsQL data obtained from the SPRINT study population (3–18 years of age)[1] into CHUD9 would not appropriately reflect patient utility scores or take into account the full evidence available from the SPRINT PedsQL data. We therefore maintain that the utility scores from the performed vignette study should be considered a more appropriate option for the application of quality of life data in the economic analysis. We further believe that this approach is also in line with precedence from previous NICE appraisals of orphan drugs that faced similar challenges regarding the collection of suitable utility data: – For the appraisal of nusinersen in spinal muscular atrophy (TA588), the committee noted that "identifying robust utility values in babies and young children is exceptionally challenging"; correspondingly, the final economic analysis was based on patient utilities mainly generated by the company from their clinical advisers, which was also considered the most appropriate approach by the Evidence Review Group (ERG) given the issues with and limited face validity of existing preference-based utility estimates[20] – The appraisal of asfotase alfa in paediatric-onset hypophosphatasia (HST6) included utility values estimated by nine clinical experts as part of a vignette study; whilst some methodological limitations were flagged by the ERG, the provided utility values were	

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			considered overall reasonable estimates[21] – Similarly, the appraisal of burosumab in X-linked hypophosphataemia (HST8) included utility values obtained from a dedicated vignette study, with the committee concluding that "the utility values were uncertain but, in the absence of an alternative, were acceptable for decision-making"[22] – For the appraisal of cerliponase alfa in neuronal ceroid lipofuscinosis (HST12), the committee discussed that it would generally prefer to include values directly collected in trials; however, it acknowledged that the available PedsQL data from the relevant trials may not be realistic and considered EQ-5D values from the company-provided vignette study instead[23]	
10	Consultee	AstraZeneca	**Five years of utility waning after discontinuation can be considered to appropriately reflect selumetinib treatment benefits, however the base case analysis has been adjusted to three years of waning and a scenario based on waning over one year has been provided** The committee concluded that a waning of utility one year after progression was reasonable (see ECD Report Section 3.19). When considering the most likely decline in patients' quality of life following treatment discontinuation, it is important to also account for the preventative nature of treatment with selumetinib. Whilst untreated patients with NF1 PN experience continuous PN growth, the majority of patients treated with selumetinib instead experience a degree of tumour reduction ([Figure **23 received but not reproduced in this table]**). As such, the difference in tumour volume when compared to untreated patients is expected to steadily increase for the entire period a patient is on treatment with selumetinib; more importantly, this difference would also be reflected in the associated patient burden. **[Figure 23 received but not reproduced in this table]** For example, propensity score analyses demonstrated a mean difference in annual PN growth rate between untreated patients from the Natural History Study and treated patients from SPRINT Phase II Stratum I of [redacted]% to [redacted]% ([Figure **24 received but not reproduced in this table]**); correspondingly, patients being on treatment for three years can be expected to have a target tumour volume less than half of what would be expected for an untreated patient.	Comment noted. The committee preferred a more rapid decline in utility that matches the time to obtain on-treatment utility after starting selumetinib. See FED section 3.20

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			[Figure 24 received but not reproduced in this table] Therefore, even if a patient should experience tumour growth again following discontinuation of selumetinib their PN would, at this point, be substantially smaller and pose less of a burden than if they had not been treated to begin with; this residual benefit on the patient's quality of life can also be expected to persist in the long term, as PN volume and associated burden continue to be comparatively smaller in discontinued patients than in untreated patients of the same age. However, to acknowledge the committee's recommendation, we have adjusted the model base case to apply a reduced duration of utility waning of 3 years ([Figure **25 received but not reproduced in this table]**); in addition, we present below the results of a scenario based on decreasing the duration of utility waning even further to a minimum of 1 year ([Figure **26 received but not reproduced in this table]**). [redacted] **[Figure 25 received but not reproduced in this table]** **[Figure 26 received but not reproduced in this table]**	
11	Consultee	AstraZeneca	**Estimating caregiver utility dependent on PN location and morbidity is not feasible** Estimating caregiver quality of life based on a respective patient's PN location and associated morbidity faces similar challenges as the estimation of patient quality of life by PN location or morbidity (see comment #7 and ECD Report Section 3.15). Although all patients in SPRINT Phase II Stratum I had PN-related symptoms at baseline, per the eligibility criteria, there was considerable heterogeneity in the types of symptoms observed and related severity reported. More importantly, patients in SPRINT Phase II Stratum I had an average of three (range, 1–5) different target PN morbidities.[1] Similarly, across the 57 patients of the Natural History Study many of the observed PN were associated with multiple morbidities; more specifically, 23% of PN were associated with two morbidities and 10% of PN were associated with three or four morbidities at baseline.[4] Therefore, it is unfeasible to derive (and subsequently model) the specific impact of single locations/morbidities and, in particular, account for the likely interplay of different combinations of morbidities. As such, and based on the available evidence regarding a general relationship between target PN	Comment noted. The committee would have preferred to see disutility values dependent on PN location and the associated morbidity. See FED section 3.18.

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			volume reduction and improvements in some aspects of quality of life, we considered it more practical and appropriate to apply broader utility estimates for treated/untreated patients with unspecified PN locations. In consequence, caregiver utility should be equally applied independent of specific PN locations/morbidities.	
12	Consultee	AstraZeneca	**The model has been revised and caregiver disutility has now been applied in both the selumetinib and BSC arm** The committee reiterated the stated ERG preference of using a utility decrement for parents and carers (0.07) based on previous NICE HST reviews; it further stated that, in consideration of carers of children with activity limitations, the carer disutility as submitted for selumetinib ([redacted]) was too high. The committee also advised that the carer disutility should be applied to the selumetinib arm too. However, patients and carers dealing with NF1 PN face more challenges than just activity limitations, due to the heterogeneous and pervasive nature of the disease; this was confirmed by the patient group representatives present at the committee meeting. For example, NF1 PN has a significant negative impact on patients' emotional and social wellbeing;[24] patients with NF1 PN may experience [redacted] XXXXXX. In addition, caregivers have reported [redacted] and the emotional impact of NF1 PN, particularly anxiety which results from uncertainty surrounding PN growth and PN-associated morbidities.[24, 25] As such, it is highly probable that the utility decrement for parents and carers suggested by ERG (0.07) does not fully reflect the burden for parents and carers of patients with NF1 PN; we therefore still maintain that a carer disutility of [redacted] appropriately reflects the carer burden presented by uncontrolled NF1 PN treated with BSC only. We acknowledge the committee's preference to also include caregiver disutility in the selumetinib arm; however, this should also reflect the impact of effective disease control with selumetinib when compared to BSC, by applying a correspondingly lower disutility value. As such, we have included a caregiver disutility value of [redacted] in the selumetinib arm, which represents a reasonable point between the disutility still applied in the BSC arm ([redacted]) and the ERG preferred value based on NICE HST precedence (0.07). In consequence, the absolute difference in carer disutility between the two treatment arms, reflecting the impact of disease control with selumetinib on caregiver QoL, would therefore be reduced to [redacted] (compared to the previously modelled difference of [redacted]). We have revised the model accordingly, applying a disutility of [redacted] to the carers of BSC-treated patients and a disutility of [redacted] to the carers of selumetinib-treated patients (**Error! Reference source not found.**). [redacted]	Comment noted. The committee noted it had not been presented with supportive evidence for the company's carer disutility value. It also recalled that this value is unjustifiably higher than carer disutility values used in previous NICE appraisals. See FED section 3.18

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			[redacted] **[Figure 27 received but not reproduced in this table]**	
13	Consultee	AstraZeneca	**Caregiver utility scores should be applied to more than one carer (see ECD Report Section 3.18)** Patient and caregiver expert feedback provided during the first committee meeting supports the assumption that care for a patient with NF1 PN is likely to place a burden on the entire family, and not just one single family member who may provide the majority of physical caregiving. In addition, in the patient expert statements submitted to NICE in November 2021 (prior to the first committee meeting), it was emphasised that the impact of NF1 PN is on the whole family, which can include a patient's parents and siblings.[27] As such we maintain that the originally submitted approach for estimating parent/carer burden (applying it to 1.4 people, based on the average UK household size being 2.4 people and one person being the patient) still provides the most appropriate estimate and may potentially be a conservative assumption.	Comment noted. The committee concluded there was not enough evidence to assume the carer disutility applies to more than 1 carer. See FED section 3.19.
14	Consultee	AstraZeneca	**Full resource use costings have been applied conservatively** The committee concluded that it would like to see analyses with full resource use included for both arms of the model (see ECD Report Section 3.13). Based on the committee's recommendation, additional cost items have been included within the model, with most of these being additional monitoring costs for selumetinib treated patients. NF1 PN patients require regular monitoring to check their disease status and patients treated with selumetinib would also need additional monitoring before starting and during treatment. We have collected information on the frequency of additional monitoring items, by treatment status and year, from a clinical expert and calculated the corresponding cost ([Figure 28 received but not reproduced in this table] **[Figure 29 received but not reproduced in this table]** and **Error! Reference source not found.**). **[Figure 28 received but not reproduced in this table]** **[Figure 29 received but not reproduced in this table]** We did not assume potential cost savings from symptom improvement due to treatment with selumetinib, even if this could be expected. This is because we did not have enough quantitative data to support this. As such, this can still be considered a very conservative approach.	Comment noted. The committee recognised the uncertainty in the estimates but concluded the resource use costs associated with selumetinib treatment compared with best supportive care provided in the company revised model were suitable for decision making. See FED section 3.15

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			The results from this revised modelling approach are shown in [Figure 30 received but not reproduced in this table]. [redacted] **[Figure 30 received but not reproduced in this table]**	
15	Consultee	AstraZeneca	**Addition of two magnetic resonance imaging (MRI) scans per year** The committee requested that two additional MRIs are included within the selumetinib arm of the model (see ECD Report section 3.14). During the first committee meeting, clinical experts confirmed that patients who receive selumetinib will most likely receive two MRIs per year while patients treated with BSC will receive only one MRI; this would effectively result in one additional MRI per year for selumetinib-treated patients. Committee members also noted that the use of two additional MRI in the company submission base case was a conservative approach. However, in the evaluation consultation document it is stated that the clinical expert consulted during the committee meeting envisaged that "in NHS clinical practice, two 'additional' MRI scans per year would be the most needed by people having selumetinib unless any acute changes happened." Therefore, the committee concluded the company assumption of two additional MRI scans per year was reasonable. As we already used two additional MRIs in the model base case analysis, there was no need to update the model based on this recommendation. However, we would like to emphasise that two additional MRIs (therefore total of three MRIs per year) can be considered a conservative assumption.	Comment noted. The committee concluded that the company assumption of 2 additional MRI scans per year was reasonable. See FED section 3.16.
16	Consultee	AstraZeneca	**Summary of the impact of performed model revisions** The impact of each of the revisions described above on the cost-effectiveness model results is summarised in [Figure 31 received but not reproduced in this table]. The accumulated impact of all model revisions is further summarised in **Error! Reference source not found.**, resulting in a final revised ICER of £[redacted]. Therefore, with the model revised as far as possible/feasible in light of the committee's recommendations, selumetinib remains a cost-effective treatment for the NHS. **[Figure 31 received but not reproduced in this table]** **[Figure 32 received but not reproduced in this table]**	Comment noted . The committee preferred the assumptions used by the ERG in their revised base case. Some of these assumptions were the same as the company's. Some of the

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				assumptions differed from the company's in relation to: • inclusion of a progression-free state in the best supportive care arm, with the same utility as those applied to the progression-free state in the selumetinib arm • a carer disutility value of 0.07 applied to carers of people in the best supportive care arm and a carer disutility value of 0.035 applied to carers of people in the

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				selumetinib arm • carer disutility values applied to 1 carer • linear decline in utility over 1 year after progression in the selumetinib arm See FED section 3.22.
17	Consultee	The Neurofibromatosis Association	Surgery has been the main treatment till MEK inhibitors became available (i.e. selumetnib and related drugs). Many plexiforms cannot be entirely removed by surgery, but surgery can improve function and quality of life. a) What is the definition of inoperable? b) Is there a plan to use selumetinib in conjunction with surgery, either before or after, to improve outcome?	Comment noted. Inoperable is defined as PN which cannot be completely resected without risk of substantial morbidity because of encasement of, or close proximity to, vital structures, invasiveness, or high vascularity. See FED section 3.5. Technology appraisals only appraise within the products marketing

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				authorisation, therefore cannot comment further on the use of selumetinib.
18	Consultee	The Neurofibromatosis Association	We believe that the decision making about who should receive selumetinib, should be undertaken by the national neurofibromatosis teams at Guy's Hospital, London and St. Mary's Hospital, Manchester, where there is already a joint, established MDT in combination with Great Ormond St. Hospital. This would tap into existing experience and expertise and avoid over or under treatment.	Comment noted. The committee recognised that children with PN associated with NF1 are managed within 2 nationally commissioned services in Manchester and London. See FED section 3.5 and 3.6
19	Consultee	The Neurofibromatosis Association	We think that treatment could be carried out in conjunction with local centres as this avoids unnecessary disruption to schooling, parents' employment and family life.	Comment noted
20	Consultee	The Neurofibromatosis Association	We believe that the measures that look at effectiveness of treatment should be robust and weight should be given to patient perceived quality of life.	Comment noted. The reference case stipulates that the perspective on outcomes should be all direct health effects whether for patients or, where relevant, other individuals (principally carers). The perspective adopted on cost

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				should be that of the NHS and PSS. If the inclusion of a wider set of costs or outcomes is expected to influence the results significantly, such analysis should be presented in addition to the reference case analysis; see section 5.1.7–5.1.10 of the Guide to the methods of technology appraisal.
21	Consultee	The Neurofibromatosis Association	We do not know how long the drug should be given for and whether there will be a need for ongoing treatment in adult clinics.	Comment noted. The committee concluded that the percentage of people continuing selumetinib treatment beyond the age of 18 provided by the company was reasonable. See FED section 3.14
22	Consultee	Childhood Tumour Trust	1Selumenitib could possibly help more children than initially indicated. a. There is no national database recording numbers with NF and plexiform tumours. b. There is also no indication of what criteria a child has to meet to be eligible for the drug so it is	Comment noted. The marketing authorisation for selumetinib

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			impossible to clearly indicate numbers	includes treating symptomatic and inoperable plexiform neurofibromas (PN) associated with type 1 neurofibromatosis (NF1) in children aged 3 and over.
23		Childhood Tumour Trust	Clear criteria must be in place for indicating who can receive the drug. a. The use of the wording “inoperable tumour” as a criteria is misleading as most plexiform tumours are inoperable by nature, but not all of these tumours will meet the criteria for this treatment- the phrase needs to be expanded upon. In explanation I (CB) have a facial plexiform that has had multiple surgeries it is now classed as inoperable, my child has a plexiform that cannot be removed as the bulk of the tumour is inoperable though a small part can be surgically removed, he has two other plexiform tumours which are inoperable around major vessels in his neck, does this mean we would be candidates for treatment with the drug or do we need to meet further criteria? b. Symptomatic is also misleading as this could cover a myriad of things or not as the case may be. How does someone never experiencing a plexiform gauge the pain level of someone who has one?	Comment noted. Inoperable is defined as PN which cannot be completely resected without risk of substantial morbidity because of encasement of, or close proximity to, vital structures, invasiveness, or high vascularity. See FED section 3.5
24	Consultee	Childhood Tumour Trust	Clear criteria should be published, and a guide made available to explain this to the lay person (children and families or carers). i. It is important that there is good communication between the Highly Specialised centres and the NF community via all patient groups so that expectations can be managed well, as many will see this as a wonder drug and feel it would help them or their child and that correct information is given. ii. Many children are not seen by an NF specialist, and many are not in the system (undiagnosed children/families). These guidelines should enable anyone who feels they meet the criteria to request, through their primary care practitioner, an appointment at one of the Highly Specialised centres, or outreach hospitals to	Comment noted. The committee noted that NF1 PN is currently managed in 2 specialist centres in England. Selumetinib would be started at the specialist

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			discuss possible use of the drug. There then should be a clear referral pathway to the relevant treatment centre.	centres, with the potential for treatment to continue in conjunction with local healthcare providers if safe and useful. See FED section 3.25
25	Consultee	Childhood Tumour Trust	Is there a support pathway (counselling/psychological support) and a care pathway in place for those who don't meet criteria/ have to stop the drug due to toxicity/ the drug doesn't work for or stops working? NF has a huge psychological impact upon a person, even more so if they have a debilitating or disfiguring and painful plexiform tumour, to be told that a drug could help them and for this then to fail will have a huge impact upon the child/Young person and their families and carers. They will need support throughout the whole process to manage expectations and deal with any fallout from treatment/lack of treatment.	Comment noted
26	Consultee	Childhood Tumour Trust	It is important to note that although Selumetinib can have an impact in the short term on quality of life due to additional tests and hospital visits the long-term overall outcome should improve quality of life for those with plexiform tumours.	Comment noted..
27	Consultee	Childhood Tumour Trust	The committee mentions comparing the use of Selumetinib with BEST SUPPORTIVE CARE. It is important to note current practices aren't necessarily best supportive care and costs to provide this could be in excess of current recommendations.	Comment noted. The committee concluded the resource use costs associated with selumetinib and best supportive care provided in the company revised model were suitable for decision making. See FED section 3.15.
28	Consultee	Childhood Tumour Trust	Can AZ clarify what is best supportive care and Is best supportive care receiving annually MRI's for a known plexiform and being under a highly	Comment noted. The committee concluded that the assumption

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			specialised centre? As this is certainly not the case for everyone. As parents of children with inoperable Plexiform Tumours we can clearly state our children do not receive yearly MRIs of their plexiform tumours, I (CB) can also clarify as a person with an inoperable plexiform tumour at no time during childhood or as a adult did I or do I have yearly MRI scans. My (CB) son is under one of the Highly Specialised centres and does not get annual scans, my daughter (CB) daughter and I are seen locally. The costs of ongoing holistic care of a patient with NF and an inoperable plexiform tumour overtime could be greater than that of a patient treated successfully with Selumetinib. If a tumour is successfully treated then there would be reduced psychological burden, reduced need for pain relief and pain management, reduced need for therapies specifically associated with loss of function due to the plexiform tumour, reduced impact on schooling (less time off school for medical care), hopefully reducing the need for limb amputation due to plexiform tumours. A knock on impact of the regular MRI's would mean any other plexi forms would be identified early and the drug would also work on these tumours as some children will have multiple plexiform neurofibromas.	of 2 additional MRI scans per year for people receiving selumetinib was reasonable. See FED section 3.16
29	Consultee	Childhood Tumour Trust	MRI scans – General anaesthetic is generally avoided post 6 years of age and in some cases a sedative can be used instead of a GA. Not needing a general anaesthetic will significantly reduce costs of the MRI scans The number of children they are talking about treating currently is a tiny amount in comparison to the general population of people with NF, therefore comparatively the cost is small as they all have to be over the age of 3.	Comment noted The committee concluded that the assumption of 2 additional MRI scans per year for people treated with selumetinib was reasonable. See FED section 3.16
30	Consultee	Childhood Tumour Trust	We feel Black and Ethnic Minorities are significantly under represented NF does not discriminate race, ethnicity, gender, religion yet we find that we see lower numbers of children and younger people from the Black and Ethnic Minority Communities, this could because NF can be harder to pick up or maybe due to the use of the term coffee coloured marks (café au lait) as in people with black skin the marks are not coffee coloured, so it could be people are not picked up at the routine screening appointments. Religion can also have an impact as can cultural values and beliefs. Some children will not be taken to the doctors/hospital and some will not agree with certain treatments. Whilst the committee cannot ensure that these people are reached we can ensure clear guidelines are available to be distributed by the nhs and charities to give these children and young people an opportunity to have equal care.	Comment noted. The NHS aims to provide free, necessary and appropriate treatment to the whole UK population. Legislation on human rights,

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			A 20 year old had to have her leg amputated due to an MPNST. (Cancerous Plexiform Tumour) Although she was known to have NF1 from the age of 7, it took 18 months of her mother fighting to get the 'large red and painful lump' looked at. The cancer has now spread to her lungs and no more treatment is available. We don't know if the Selumetinib may have helped this young girl, but the point is she would never have had the opportunity, as by the time she had reached the Highly specialised centres it was too late. It needs to be very specific who meets the criteria. We need detailed criteria that is clear and easy to follow. Parents/Young people/carers and practitioners need to be able to easily see who is eligible and how to move forward. Criteria cannot just say inoperable plexiform tumours unless the intention is to offer the treatment to everyone in the age range with an inoperable plexiform tumour. Inoperable could also be open to interpretation - does it mean totally inoperable as in no surgery is viable or does it include those that could be de-bulked but cannot he fully removed - those that grow back post-surgery - most plexiforms will continue to grow after de-bulking.	discrimination and equality requires that patients are not denied access, or have different or restricted access, to NHS care because of their race, disability, age, sex/gender, sexual orientation, religion, beliefs, or socioeconomic or other status (Social Value Judgements; 'Principles for the development of NICE guidance', principle 6).