All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Form B guidance notes

This document provides guidance to applicant companies on how to complete the Form B. Separate guidance notes are available for completing the Form A and Form C, on the All Wales Therapeutics and Toxicology Centre (AWTTC) website under 'All appraisal documents'.

If you have any queries when filling in the Form B, please contact Ruth Lang, Head of Liaison and Administration for AWTTC, the All Wales Medicines Strategy Group (AWMSG) secretariat, on 029 218 26900 or email AWTTC@wales.nhs.uk.

Table of contents:

i. The function and timing of Form B

Form B contains the information required for an appraisal to proceed. It should be submitted to AWTTC as soon as marketing authorisation is granted and, at the very latest, within three months of receipt of marketing authorisation. Please refer to the AWMSG process for industry engagement document, available on the AWTTC website under '[All appraisal documents]'.

Applicant companies who are planning to submit a Form B should be aware that appraisal dates cannot be confirmed until AWTTC has received the completed submission and the scope of the appraisal has been agreed. A delay in submitting the Form B will delay the appraisal process.

ii. Completing Form B

You should complete the Form B in full, giving justification in places where this is not possible. Your information should be included in the relevant section of the Form B and any appendices should be clearly labelled with the corresponding question. The evidence quoted should be referenced throughout the form and you should provide AWTTC with a list of **all** references, together with electronic copies. If you have used a database to manage your references (for example, EndNote) please supply us with a copy of your reference library or use the 'travelling library' option.

It is vital that any data submitted (including prevalence, incidence and cost) are specific to Wales, for AWMSG to appropriately appraise medicines for use within NHS Wales. Data from any other UK country, or elsewhere, will not be accepted where Wales-specific data are available. The New Medicines Group (NMG) and AWMSG consider the basic NHS list price of medicines. Details of any proposed or negotiated discounts will not be considered and should not be submitted. Patient Access Schemes (PAS) will only be considered after positive advice from the Patient Access Scheme Liaison Unit (PASLU) and approval from the Department of Health (DOH) and incorporation into a National Institute for Health and Care Excellence (NICE) positive Final Appraisal Determination (FAD), or approval of a Wales Patient Access Scheme (WPAS) by Welsh Government.

It is important to clearly highlight any data or information that the applicant company consider to be commercial in confidence or academic in confidence and, where possible, to provide a date beyond which this data or information will no longer be considered confidential.

The relevant health economic model in Microsoft Excel (preferred) or TreeAge must be submitted electronically with the completed Form B. In addition, the applicant company should provide a list of all of the documents that they have submitted.

The following guidance notes are divided into 18 sections. You should refer to the notes when completing the corresponding sections of Form B.

1.0 Glossary of terms

Fill in the table with terms and acronyms used in the submission.

2.0 Product information

2.1 General information

a) Enter the details of the applicant company. If the applicant company is not the marketing authorisation (MA) holder then the MA holder should also be entered. Please also highlight any additional company name(s) to be included on documentation relating to the appraisal and recommendation if this differs from the MA holder.

b) The generic name should be entered under ‘Approved name of medicine’.

c) The brand or marketing name should be entered under ‘Trade name’.

d) The formulation(s), strength(s) and route(s) of administration should be entered accordingly.

e) The new licensed indication should be stated in full, in line with the Summary of Product Characteristics (SmPC).

f) Please state the indication covered in the submission if it differs from the full indication in section 1.1e. AWMSG appraises medicines for the full new licensed indication(s) as detailed in the SmPC and supporting evidence for the whole of the licensed indication, as agreed in the scope, should be submitted with a Form B submission. However, when parts of the licensed indication are in distinctly separate disease areas, AWTTC may request separate submissions for the separate parts of the licensed indication. AWMSG would then appraise the medicine for the two distinct areas separately.

   Where a medicine receives a licence extension, AWMSG appraises the medicine for the whole of the indication(s) covered by that licence extension.

g) Whether the medicine under consideration is newly licensed or has received a licence extension, the applicant company may highlight a specific population within the submission for which the medicine may be particularly advantageous, ensuring that evidence to support the subpopulation is included in the Form B. AWMSG may consider a restricted recommendation, whereby the medicine would not be endorsed for use outside of this restriction.

2.2 Regulatory status

Complete this section as fully as possible, ensuring that the information provided is specific to the full indication under consideration (for example, relates to the licence extension). Details will remain confidential until after licence. Launch date will only be used to prioritise workload by AWMSG; therefore, even an estimated time period would be acceptable.

2.3 Comparator and place in therapy

a) List the major comparator treatments, including medicines with similar indication(s) to the medicine under consideration. If appropriate, this can be restricted to those in the same or similar therapeutic class. The applicant company should provide information on comparator treatment(s) based on current standard care in NHS Wales, which is considered to be "routine practice" and may potentially be displaced. Comparators licensed for the indication under consideration should usually be included; however, AWMSG will also consider unlicensed comparators where it is deemed appropriate to do so. For some medicines, it may be appropriate to consider more than one comparator (for example, if practice is varied or if current therapy is unlicensed).

   The applicant company must justify their chosen comparator(s) based on evidence of current practice in NHS Wales. This usually requires advice from Welsh physicians, which should be sought by the applicant company.

b) Outline the anticipated place in therapy that this medicine will have.

c) State whether this medicine is indicated for conditions NOT previously treatable by another medicine; provide details accordingly.

d) Highlight any available guidelines that may be relevant to this submission.

3.0 Medicines developed to treat rare and very rare diseases

State if the medicine has been developed specifically to treat a rare or very rare disease.

AWMSG considers medicines for rare diseases to be orphan or orphan-equivalent, if:

- the prevalence for the full licensed population is ≤ 1 in 2,000 people in Wales (or the UK) and;
- the medicine meets the criteria for Medicines and Healthcare products Regulatory Agency (MHRA) orphan status.

To determine if a medicine has been developed specifically to treat a very rare disease, refer to the criteria detailed in AWMSG's 'Policy for appraising a medicine for a very rare disease' available on the AWTTC website under 'All appraisal documents'.

Please note that, before submitting a Form B to AWTTC, it is essential to have confirmation from AWTTC that the medicine is eligible for appraisal under AWMSG's very rare disease policy. Further information on completing and submitting the proforma for a medicine for a very rare disease is outlined in the policy.

When appraising a medicine for a rare or very rare disease, AWMSG recognises that evidence generation can be more challenging. Greater uncertainty is often associated with the clinical and cost-effectiveness evidence available for these medicines, due to the small numbers of patients on which it can be based. Therefore,

AWMSG has flexibility to accept a higher degree of uncertainty when making recommendations for these medicines. AWMSG also takes into account a broad range of considerations when appraising medicines for rare and very rare diseases; the cost per quality-adjusted life-year (QALY) is considered as only part of a wider judgement of a medicine's value.

Use sections 3.1a to 3.1d to provide details about MHRA orphan designation and the population for which the medicine was developed.

Use sections 3.1e and 3.1f to provide additional information that is specifically considered when appraising a medicine for a rare or very rare disease.

Use sections 3.1g and 3.1h to provide additional information that is specifically considered when appraising a medicine for a very rare disease only.

Complete section 15 to give additional information relating to important factors that may need to be considered during the appraisal process.

4.0 Severity of condition

To determine if a medicine is used to treat a severe condition, refer to the AWMSG 'Policy for appraising medicines for severe conditions' available on the AWTTC website under 'All appraisal documents'.

Complete section 4.1 in all cases, and section 4.2 (including Table 1) if applicable.

Both absolute and proportional QALY shortfall estimates should be taken into consideration when determining whether the severity of condition modifier should be applied. This is to avoid any inherent potential biases that could be associated with using a single estimate. If both shortfall estimates imply different levels of severity, QALY weighting selection is guided by the shortfall that shows greatest severity.

Use section 4.2 and Table 1 to provide details about both absolute and proportional QALY shortfall estimates, including recent and robust data sources for survival and health-related quality of life (EQ-5D). When the published literature has been used to inform QALY shortfall estimates, this must be supported by evidence that demonstrates the literature has been identified and selected systematically. Reference should be made to any relevant previous AWMSG Secretariat Assessment Reports or NICE Technology Appraisals (TAs), including details of health-related quality of life (HRQL) and survival estimates.

Calculations should be informed by the precise population for which the medicine will be used and by established practice within NHS Wales. Calculations should include an estimate of the total QALYs for the general population with the same age and sex distribution as the population with the condition. Fields should be cross referenced to relevant sections of the submission. An annual discount rate of 3.5% should be used to calculate QALY shortfall estimates. This section of the form can report the methods and results in full, or alternatively these can be provided as a separate report within the appendices.

Note: no additional severity modifier QALY weighting is applied to medicines developed to treat very rare diseases; severity is implicitly captured in the application of the policy for those medicines.

5.0 National Institute for Health and Care Excellence non-recommendation

In circumstances when NICE does not recommend a medicine for use within the NHS on the grounds of cost-effectiveness and the medicine is subsequently funded within England through alternative national commissioning routes, an opportunity exists for the MA holder to apply for the medicine to be appraised by AWMSG. The application must include a WPAS, but may also include additional information which may not have been submitted to NICE, or information specific to NHS Wales (perhaps highlighting a specific patient population or other societal benefits).

It is important that any additional evidence showing added value or benefit to NHS Wales, over and above that considered by NICE, is clearly identified and highlighted. The application should also reflect the context of an AWMSG appraisal which applies clinical and cost-effectiveness, in addition to considering broad strategic, societal and patient perspectives when making its recommendations. It is also important that confirmation and full details of the alternative funding route within the NHS in England are provided.

6.0 Cost and patient eligibility

6.1 Patient Access Schemes

Patient Access Schemes (PAS) will only be considered after positive advice from the Patient Access Schemes Liaison Unit (PASLU), approval from the Department of Health (DOH) and incorporation into a positive NICE FAD, or after approval of a Wales Patient Access Scheme (WPAS) by Welsh Government.

Please provide details relating to any DOH PAS or WPAS accordingly. Please also specify whether any of the comparators included in this submission have an approved DOH PAS or WPAS.

6.2 Commercial Access Agreements and Market Access Agreements

Please indicate whether the medicine is associated with a commercial access agreement (CAA) or a market access agreement (MAA) within NHS England, and, where this is the case, whether a similar arrangement will be offered to NHS Wales.

6.3 Cost overview

Provide estimates related to the condition for which this medicine is likely to be prescribed. The figures provided must be as accurate as possible and reference sources must be stated, highlighting paragraphs and page numbers accordingly.

It is vital that applicant companies submit data specific to Wales, for AWMSG to appropriately appraise medicines for use within NHS Wales. Data from any other UK country, or elsewhere, will not be accepted if Wales-specific data are available.

The applicant company should provide details of any additional tests or investigations needed for selection or monitoring of patients above the usual clinical practice for this condition.

See below for an example:

Efficacy:

- To establish eligibility for treatment (for example, in subtypes of the condition at a specified level of severity or after failure of other therapy).
- For monitoring of effect (for example, if continuation of treatment is dependent on assessment of early response).

Safety:

- To identify patients in whom the treatment is contraindicated and/or who are particularly at risk of or from known adverse effects.
- Monitoring to detect potential adverse effects.

If there are recommended testing or monitoring regimens please specify. This may be included as an Appendix if it is extensive.

State the costs associated with any additional tests.

6.4 Patient eligibility

The figures provided must be as accurate as possible and reference sources must be stated, highlighting paragraphs and page numbers accordingly.

It is vital that applicant companies submit data specific to Wales for AWMSG to appropriately appraise medicines for use within NHS Wales. Data from any other UK country, or elsewhere, will not be accepted if Wales-specific data are available.

7.0 Executive summary

This should constitute a summary of the main points from the submission in under 300 words. It should include:

- Reasons why this medicine should be prescribed in Wales for the licensed indication;
- The suggested place in therapy with respect to treatments currently available and;
- Any subpopulation analysis proposed.

8.0 Efficacy

This section should contain evidence that is relevant to the indication described in section 1.1f. Randomised controlled trials, systematic reviews, meta-analyses and other studies should be described, drawing on published sources, data on file, and other supporting evidence. This should include regulatory summaries such as the relevant sections from the MHRA's Public Assessment Report, the European Medicines Agency (EMA) European Public Assessment Report (EPAR), Food and Drug Administration (FDA) documentation, etc.

a) This need not be comprehensive, and should provide only brief details of the trial programme, particularly phase III studies. Phase II and other studies should be mentioned if they have been pivotal, for example, in establishing the dose and design for major phase III trials.

b) This section asks for a referenced description of each of the most relevant studies. It need not include all of the studies referred to in section 8.0a, but it should include confirmatory studies. Where peer-reviewed evidence is available, it should be given prominence. Where data on file or regulatory summaries are quoted this should be clearly stated and, as with other references, they should be provided with the submission.

   A strict pro-forma has not been provided, as a certain amount of discretion is appropriate in this section. The aim should be to give a balanced, coherent description of the appropriate trials. Each trial can be described individually in the order suggested, and this is most appropriate where the trial programme consists of heterogeneous trials which may have, for example, different endpoints and/or methodology. This may lend itself to tabulation. However, where a number of trials are reasonably homogeneous, it is helpful to group common features, for example, listing the methodology, inclusion and exclusion criteria which they share, then presenting the results for individual trials.

   Objective:
   - Study objectives should be provided.

   Methods:
   - A brief description of trial methodology should be provided.
   - Dosing information for the study medicine and comparators should be given.

   Study design:
   - Inclusion and exclusion criteria should be included.
   - The therapeutic outcomes investigated, and the primary and secondary outcome measures used to investigate those outcomes. Where appropriate, a description of the principal outcome measure(s) including details of scoring methods, evidence of validity and current status (for example, approval by professional bodies, licensing authority, etc.).

   Results:
   - Results from primary outcome measure(s) should be presented as tables with appropriate measures of spread whenever available. Please note that 95% confidence intervals are preferred. Graphical presentation may sometimes be

appropriate, but this should be considered as a supplement to tabulated data rather than an alternative.

- Results from secondary outcome measures, subgroup information and other significant findings should be presented where appropriate. Subgroups should be defined *a priori* in pivotal clinical trials and have a clear clinical relevance or significance.
- Patient numbers should be given at appropriate stages in such a way as to account for all patients entered into the study and the number included at each stage of analysis described.
- Where results are presented in terms of the number of patients who fall into a particular category (for example, responders) the preferred format is:
  - number of patients responding/number of patients in analysis (%), for example 25/100 (25%).
- Where interim trial data are quoted this should be clearly stated along with the point at which data were taken and the time remaining until completion of that trial. Analytical adjustments should be described to cater for the interim nature of the data.

Summary:

- A short summary should be provided.

c) Where appropriate, this section should summarise the results from the trial programme, mainly through tabulation of the results of primary endpoints. This may not always be necessary; for example, where only one trial has been described, or where the results have been sufficiently summarised under section 8b.

d) Use this section to describe the methods and results of any systematic reviews and direct pairwise meta-analyses (i.e. those based solely on evidence from head-to-head trials) included in the submission. State the purpose and relevance of these analyses in the context of the submission. AWTTC recommends that you report the methods and results of systematic reviews and meta-analyses as outlined in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. This section of the form can either report the methods and results in full, or provide a summary, supplemented by appendices containing, for example, details of the search strategy, study selection, and full details of all included and excluded studies.

e) Use this section to describe the methods and results of any indirect comparisons, mixed treatment comparisons, network meta-analysis, or any other analysis conducted to indirectly estimate the comparative effectiveness of interventions of interest. State the purpose and relevance of these analyses in the context of the submission. AWTTC recommends that you report the methods and results of indirect analyses as outlined in the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons Good Research Practices (Part 1 and Part 2). This section of the form can either report the methods and results in full, or provide a summary, supplemented by appendices containing, for example, details of the type of analysis conducted and the full results for all pairwise comparisons.

Where a systematic review has identified insufficient evidence to allow indirect analysis to be carried out, use this section to summarise and justify this

conclusion.

f) The applicant company should include additional evidence from studies for which interim results were presented, as well as studies not included in the previous section. Include patient type and endpoints to be measured and the likely timescale for production of evidence from proposed trials. AWMSG is interested in trials that may provide further evidence concerning the use of the new medicine for the same indication as in this assessment.

   The inclusion of new evidence into the appraisal process is at the discretion of AWTTC and will be on a case-by-case basis. If additional information (highlighted in this section) becomes available after submission of Form B, the applicant company should contact AWTTC, who will inform as to whether the information can be included in the AWMSG Secretariat Assessment Report. This is dependent on timelines. No other information will be accepted after completion of the AWMSG Secretariat Assessment Report. If “new evidence” is not accepted, a subsequent resubmission will be timetabled pragmatically into the work programme. A resubmission would be timetabled at the earliest convenience; however, there is no guarantee of a definite slot and this could take up to 12 months.

9.0 Comparative safety

Identify whether studies demonstrate clinically significant differences in the adverse events profile of this treatment compared to alternative treatments. Give incidence rates if appropriate.

Whilst in general, evidence from comparative trials and regulatory summaries are preferred, findings from noncomparative trials may sometimes be relevant. For example, they may demonstrate a relative lack of adverse effects commonly associated with a competitor or the occurrence of adverse effects not significantly associated with other treatments.

Information on adverse effects, contraindications, precautions, interactions, etc. will be available from the SmPC or draft SmPC and need not be listed in full in this section. Only a brief overview of comparative safety, drawing on information from the SmPC and from clinical studies, is required.

10.0 Clinical effectiveness

a) The response to this question should be based on the outcomes studied in clinical trials. It should discuss whether trials have directly measured health outcomes such as mortality, survival, incidence of disease, morbidity, functional performance, quality of life, etc. or whether surrogate markers have been measured such as reduction in blood pressure, increase in FEV1, peak flow, etc. In the latter case, it should be possible to discuss the association between these

measures and health benefits or disadvantages to patients.

b) This question is concerned with whether benefits associated with the treatment in the controlled conditions of a clinical trial are likely to be applicable in routine clinical practice. If there are any specific issues relating to clinical practice in Wales, these should be identified. State any criteria that would be used in clinical practice to select suitable patients based on the evidence submitted.

c) The applicant company is required to explain the approach used where there may be, for example, a disputed surrogate endpoint. If data are not specific to Wales and, for example, a different comparator has been used, the approach and rationale must be clearly explained.

d) A brief statement is required detailing any advantages in safety and/or efficacy of the new medicine over current therapy. Advantages should be concerned with health gains and be evidence based. If those given are, as yet, theoretical, this should be clearly stated.

   A brief statement of the disadvantages associated with this medicine is needed. This may include highlighting any adverse effects not experienced with current therapy, reduced efficacy in certain circumstances, special reconstitution or administration requirements.

   Put these in the context of existing therapy, for example:
   - State if the medicine should be used as a first-, second-, or third-line therapy.
   - State which medicines it would replace or compete with and how it compares.
   - Include any algorithm or protocol for use (insert as an appendix if required).

11.0 Pharmacoeconomic evaluation

This section should be completed by reporting the context, design, methods and results of the economic evaluation. It is important that submissions include a plausible base case and a range of alternatives (combinations of sensitivity and scenario analyses) for AWMSG to consider.

a) The context of the economic evaluation needs to be summarised, including details of the treatment pathway being modelled, the place of therapy within that pathway, and how this relates to the licensed indication(s), and other treatments available for managing the condition. The population should be described, and a justification given for any differences between patients who were included in the trials and those represented in the economic evaluation.

b) The applicant company should provide information on comparator treatment(s) based on current standard care in NHS Wales, that is what is considered to be “routine practice” and may potentially be displaced. Comparators licensed for the indication under consideration should usually be included; however, AWMSG will also consider unlicensed comparators where it is deemed appropriate to do so. For some medicines, it may be appropriate to consider more than one comparator (for example, if practice is varied or if current therapy is unlicensed). In such cases, economic evaluations should include different scenarios, presenting

cost-effectiveness estimates for each. The comparator may also relate to a “care package” that might vary between locations, or “best supportive care” which would need to be described in full.

The applicant company must justify their chosen comparator(s) based on evidence of current practice in NHS Wales. This usually requires advice from Welsh physicians, which should be sought by the applicant company.

It is recognised that comparators used in clinical trials may not be those used in Wales. In such circumstances it will be necessary to conduct some form of bridging assessment to an appropriate comparator (for example, using an indirect or mixed-treatment comparison) together with sensitivity analyses to assess the impact of assumptions about comparators and discussion of possible biases.

c) The costing perspective should be that of the NHS in Wales and personal social services. Therefore, the main analysis should focus on those changes in resource use and costs (or savings) that affect the Welsh healthcare system and, where applicable, services such as provision of residential care, day and domiciliary services or assessment and care management (covering the process of receiving referrals, assessing need, defining eligibility, arranging for packages of care to be provided, etc.).

d) The time horizon for estimating clinical and cost-effectiveness should be sufficiently long to capture all important differences in costs or outcomes between the treatments being compared. A lifetime horizon analysis is usually appropriate for chronic conditions, and required for any mortality component, to quantify the implications of any differential survival effect between alternative treatments.

   The approach used to select a time horizon and the resulting issues that the timeframe presents for any modelling of long-term health outcomes and resource use should be explained, together with an account of the reasons for and effects of its adoption over its alternatives. If the model is sensitive to the choice of timeframe or the approach used to extrapolate data over time, then details of sensitivity analyses should be provided.

e) Economic evaluations should take the form of cost-utility analyses, with results expressed as incremental costs per QALY gained. The QALY provides a “common currency” which allows different medicines to be compared for different conditions. This allows AWMSG to make its decisions consistently, transparently and fairly.

   There are some exceptions where cost-minimisation analyses, also sometimes known as cost-comparison analyses, may be acceptable. These include cases where there are no clinically meaningful differences in the distribution of effects between the medicine and its comparator(s). Effects include all dimensions of health, including impact on HRQL, survival, as well as adverse events, patient preference and adherence. This would ideally require well-designed equivalence trials for the evaluation of efficacy (effectiveness) and evidence of close comparability of other effects, which were not the subject of the equivalence analysis. If alternative methods are applied to support a claim of equivalence, these must be fully transparent, rigorous and justified.

Modelling provides an important framework for synthesising available evidence and generating estimates of clinical and cost-effectiveness in a format relevant to AWMSG's decision-making process. Models are required for most appraisals. Situations when modelling is likely to be required include those where:

- all the relevant evidence is not contained in a single trial;
- patients participating in trials do not match the typical patients likely to be prescribed the medicine within NHS Wales;
- intermediate outcome measures are used rather than effect on HRQL and survival;
- relevant comparators have not been used or trials do not include evidence on relevant subgroups and;
- the long-term costs and benefits of the medicine extend beyond trial follow-up.

All structural assumptions should be transparent and fully justified, and data inputs should be clearly documented and justified in the context of a valid review of the alternatives. All model parameter values should be clinically plausible. Alternative scenarios should be considered to compare the implications of different assumptions (for example, duration of treatment effect, sustained or diminished treatment effects over time, etc.). Modelling techniques should be described in sufficient detail and results should be fully reported to allow independent scrutiny of methods and replication of results. Standard guidelines on health economic modelling, statistical analyses and reporting should be adhered to.

f) Resource implications should be identified, measured and valued within a Welsh context (i.e. using data for NHS Wales on resource utilisation and unit costs). Submitted economic evaluations that do not include data from Wales are required to include a comment on the validity of using resource data from outside Wales, and make reference to any relevant differences in the healthcare environments. Data from any other UK country, or elsewhere, will not be accepted if Wales-specific data are available.

The main analysis should present direct healthcare resource usage for the medicine and its comparator(s) separately and in natural units (for example, hospital days, volume of medicines, number of screenings, etc.), with data sources cited. Any resource use arising from clinical trials, as opposed to that in routine care, should be excluded from the analysis. When long-term effects are modelled, future resource use should include treatment of the condition under consideration but not resource use from treating unrelated conditions.

Total costs should be calculated for the medicine and its comparator(s) by the application of standardised unit costs to resource use data. For most direct healthcare resource use, the actual price paid will be an acceptable estimate of opportunity cost. Staffing costs should include employers' costs such as superannuation etc.

The date of the study or reference time period spanning the collection of cost, expenditure or price data used to value resource quantities should be clearly stated along with the inflation indices used to calculate current costs.

g) The value of health effects should be expressed in terms of QALYs. The measurement of changes in HRQL should be reported directly from patients.

When it is not possible to obtain information on changes in patients' HRQL directly from patients, then data should be obtained from their carer (not from healthcare professionals). The value of changes in patients' HRQL (that is, utilities) should be based on public preferences using a choice-based method (for example, time-trade off or standard gamble).

The EQ-5D is the preferred measure of HRQL in adults. The EQ-5D-3L value set should be used to generate utility values. EQ-5D-5L data should be mapped onto 3L where necessary.

However, there may be occasions when EQ-5D data are not available or the EQ-5D may be considered inappropriate. In such cases, methods can be used to estimate EQ-5D utility data by mapping EQ-5D utility data from other HRQL measures included in the relevant clinical trial(s). This can be done if an adequate mapping function can be demonstrated and validated. Mapping should be based on empirical data and the statistical properties of the mapping function should be clearly described. Alternatively, direct valuations of descriptions of health states based on standardised and validated HRQL measures included in the relevant clinical trial(s) may be submitted. The use of condition-specific, preference-based measures may also be acceptable.

If the EQ-5D is considered inappropriate, empirical evidence should be provided on why the properties of the EQ-5D are not suitable for the particular patient population. These properties may include the content validity, construct validity, responsiveness and reliability of the EQ-5D. Alternative validated generic measure instruments, preferably with a UK value set, can be used for children and adolescents. Choice of measure should be explained.

The use of utility estimates from published literature must be supported by evidence that demonstrates that they have been identified and selected systematically.

When reporting any relevant health effects for carers, explain how the technology affects carers and give supporting evidence to clearly demonstrate that the condition is associated with a substantial effect on carer's HRQL.

h) The timing of the costs and benefits should be outlined before their discounting. Costs and benefits should be discounted at the same rate using an annual discount rate of 3.5%.

   However, if the medicine is likely to restore people, who would otherwise die or have a severely impaired life, to near-full or full health and if these benefits are likely to be sustained over a long time, applying a discount rate of 1.5% per year for costs and health effects may be acceptable to AWMSG. Applying this alternative discount rate in a scenario analysis should be fully justified and supported by evidence.

i) It is important to identify potential selection bias in the inputs to the model and for the model to quantify the decision uncertainty associated with the medicine (that is, the probability that a different decision would be reached if the true cost-effectiveness of each medicine could be ascertained before making the decision).

The three main sources of uncertainty and bias which need careful consideration are:

- structural uncertainty, which may include the categorisation of different states of health and the representation of different pathways of care;
- selection bias, such as those that might occur with different sources of costs and utilities, estimates of relative effectiveness and their longevity; and
- parameter uncertainty, which is the uncertainty around the mean health and cost inputs in the model.

The impact of structural uncertainty on estimates of cost-effectiveness should be explored by separate analyses of a representative range of plausible scenarios. The implications of different estimates of key parameters must be reflected in sensitivity analyses (for example, one-way and multi-way sensitivity analyses). Uncertainty in parameters is best characterised by use of probabilistic sensitivity analysis. Full justification for the choice of scenarios, parameter estimates, mean values and distribution around the means should be provided.

Outputs should be presented numerically, indicating the total costs and QALYs, the ICER and associated 95% confidence intervals, and the probability of being cost-effective at threshold willingness-to-pay values of £20,000 and £30,000 per QALY; and graphically, for example, cost-effectiveness plane and cost-effectiveness acceptability curves. This should be repeated for different scenarios, where applicable.

j) If there is an approved WPAS/DOH PAS for the comparator(s), the impact of this should be explored. Conduct additional sensitivity analyses and report the impact of discounts ranging between 5% and 95% in increments of 5%. Include a discount field in the economic model to enable the user to input any value between 0% and 100%.

k) Summarise the key methods in a table according to the headings listed below.

Table 4. Key methods

Item	Description
Comparator(s)	Provide details of medicine and comparator(s) and dosing regimens.
Population	Describe the patient populations represented in the economic evaluation and any subgroups.
Model type and description	Describe the modelling approach, including details of health states and cycle length.
Perspective	State the costing perspective used.
Time horizon	State the time horizon of analysis, with justification.
Discount rate	State the discount rates, and which values were used in the sensitivity analysis.
Efficacy	Describe the sources of efficacy/effectiveness data, including any indirect comparisons. State the methods used to model treatment effect (e.g. Weibull extrapolation) and any impact of other aspects (e.g. influence of variable adherence, patient preference).
Adverse effects	Describe how adverse effects were considered in the model (cost impact and health disutility).
Utility values	Describe the methods of utility elicitation and valuation.
Resource use	Describe the methods of resource identification and measurement.
Costs	Describe the sources of unit costs.
Uncertainty	Describe the methods for considering parameter, structural and other sources of uncertainty.
Scenarios	Describe the approaches taken to scenario and subgroup analyses. Please refer to details of scenario required for the appraisal of life-extending, end of life treatments, where considered applicable.
Assumptions	List the main assumptions of the health economic evaluation.

l) Provide a full, detailed description of the results, with and without discounting applied. Include a plausible base case analysis, and a range of alternatives (combinations of sensitivity and scenario analyses). Conduct threshold analysis to identify relevant parameter boundaries and to explore influential parameters associated with a high degree of uncertainty. If scenario analyses are submitted that explore the impact of apportioning or adjusting a particular cost, or the removal of background care costs, the inclusion of these analyses for consideration by AWMSG should be explained and justified.

When appropriate, expected net health benefits should be reported alongside ICERs for the base case and for any scenario analyses conducted, to enhance the transparency of the potential effects of a decision on overall population health.

Net health benefits should be calculated valuing a QALY gain at both £20,000 and £30,000. The inclusion of net health benefits is particularly beneficial in instances when a decision modifier is applied; comparators have only small differences in associated QALYs or costs; subgroup analysis is done; or a medicine provides less health benefit at lower costs (i.e. the ICER falls in the south-west quadrant of the cost-effectiveness plane). Expected net monetary benefits can also be reported.

m) Summarise the key results in the key economic evaluation summary results table (Table 5).

12.0 Budget impact and resource implications

The purpose of this section is to give an estimate of the potential budget impact (BI), in a way that a health board in Wales could identify, for example, how much money they might have to find if the new medicine replaces (or is used in addition to) current treatments. Your analysis should include all direct costs and be specific to Wales. The following websites may be useful:

https://statswales.gov.wales/Catalogue/Population-and-Migration/Population/Estimates

https://statswales.gov.wales/Catalogue/Population-and-Migration/Population/Estimates/Ethnicity/PopulationEstimates-by-Localauthority-Ethnicity

https://statswales.gov.wales/Catalogue/Health-and-Social-Care/NHS-Primary-and-Community-Activity/GMS-Contract/quality-and-outcomes-framework/

https://phw.nhs.wales/services-and-teams/welsh-cancer-intelligence-and-surveillance-unit-wcisu/

https://dhcw.nhs.wales/information-services/health-intelligence/pedw-data-online/

Use the AWTTC BI template to estimate the budget impact for Wales. All worksheets included in the template must be completed, including data sources and assumption rationale (where applicable). If data for Wales are not readily available, UK data may be adapted based on Welsh population statistics. All your assumptions must be justified, and supported with referenced evidence. Data from any other UK country, or elsewhere, will not be accepted where Wales-specific data are available.

a) Please estimate the total number of patients in Wales who have the condition relating to the indication under consideration (current prevalence), and indicate the source of estimated numbers.

b) Please estimate the number of newly diagnosed patients each year over the first five years after introduction of the medicine (yearly incidence), and the source of estimated numbers.

c) The net number should, where appropriate, take account of changing patterns associated with the condition under consideration. In some cases, the prevalence

may remain constant from one year to the next. In others, it may be likely to change; for example, because of changes in incidence and/or prognosis and survival. There may be assumptions that some of these changes will be influenced by the new treatment.

d) Estimate the number of people in Wales currently treated for this condition and who would be eligible for treatment according to the medicine's licence. There may be direct evidence, but this may have to be based on epidemiology and assumptions about the proportion of patients who are currently treated. If the appraisal indication under consideration reflects a subpopulation of the licensed eligible patient population, the eligible subpopulation should be identified.

e) This estimate may be based on assumptions about the proportion of patients with the condition who will receive the new medicine as newly treated patients or as a result of being switched from current treatment. It may involve making assumptions about market share and uptake changing with time; for example, an analysis of each of the five years after introduction of the medicine. The estimate should allow for any patients who discontinue treatment.

f) For the medicine under consideration and each of the principal alternative treatments identified in section 2.3a, estimate the cost per patient per year, or other appropriate time period (for example, the acquisition cost of 28 days of chronic treatment, or cost per treatment episode) stating any assumptions made.

   This should consider the following (which should be stated):
   - the average length of treatment (or range);
   - average dose anticipated (or range), and
   - whether treatment is continuous, one-off or given cyclically, but for a finite time.

g) For the medicine under consideration in this submission, and for the principal alternative treatments, give details of other resources and direct costs (or savings) associated with treatment over a defined time period.

h) Summarise the net cost implications for Wales in each of the first five years after introduction of the new medicine (Table 6). This should combine the data for sections 12.0d, 12.0e and 12.0f, and should be presented according to the same categories, and as annual totals. This table content should be the same as the 'Summary acquisition costs' table in AWTTC's BI template.

i) Resource implications, data from section 12.0g, should be captured and summarised in a separate table (Table 7). This table content should be the same as the 'Summary resource' table in the BI template. Resource use should be disaggregated under the headings below.
   - Costs of administration (for example, administration sets and diluents for a parenteral preparation);
   - Diagnostic tests and monitoring;
   - Adverse events costs;
   - Primary care resources and costs (including associated staff and infrastructure changes);

- Secondary and tertiary care resources and costs (for example, changes to average inpatient length of stay; the number of bed days per year required to support any new service; and associated staff and infrastructure changes);
- Costs of personal social services.

j) The BI calculations should include one-way and multi-way sensitivity analyses together with scenario analyses, as deemed appropriate. Plausible ranges of values for the sensitivity analyses should be selected and justified. Tables with appropriate calculations should be provided on the 'Sensitivity analysis' worksheet of the BI template. If there is an approved WPAS or DOH PAS for the comparator(s), conduct sensitivity analysis to explore the impact of discounts ranging between 5% and 95% in increments of 5%.

13.0 Comparative unit costs

The purpose of this section is to compare medicine costs per year (or medicine costs per course of treatment) for treatment regimens available to the patient population targeted. The selection of medicines included in this table (Table 8) may be wider than those included as comparators in the economic analysis. Inclusion in the table does not imply therapeutic equivalence.

Please complete the table in the 'Comparative unit costs' worksheet in AWTTC's BI template, following the instructions given in the 'General guidance' worksheet. Costs should be based on list prices except where there is an approved WPAS or DOH PAS. Please include WPAS or DOH PAS unit costs where these are known. If there is a WPAS or DOH PAS on any of the medicines included in the table where the level of discount is unknown, please show this by including 'WPAS/PAS price unknown' in the corresponding unit cost/pack price cell of the table. Do not include other costs such as administration and monitoring. The approximate costs per patient should be calculated allowing for any natural wastage of the medicine. Annual costs should be calculated for medicine usage over 365.25 days.

14.0 Homecare

Homecare is a service that delivers ongoing medicine supplies and, where necessary, associated care. It is initiated by a hospital prescriber and the medicine is delivered direct to the patient's home. The purpose of the homecare service is to improve patient care and choice for their clinical treatment.

Complete section 14.0a, and, if applicable, sections 14.0b, 14.0c and 14.0d.

15.0 Additional information for all medicines

AWMSG may consider factors in addition to clinical effectiveness, cost-effectiveness and budgetary impact as part of the appraisal process for the medicine (including medicines developed to treat rare and very rare diseases). Please provide this information where applicable.

a) Where applicable, describe the innovativeness of the medicine. This might include evidence that the medicine can treat a condition where there was previously no effective treatment, no consistently satisfactory treatment, treatment that was less safe, or treatment that was less convenient.

   Evidence supporting innovation should also include an estimate of the health gain attributable to the medicine, compared with an appropriate comparator and over an appropriate time. This should be extracted from the results of the economic evaluation and the BI analysis, and include:
   - the expected (mean) discounted QALY gain; and
   - the total (population) expected number of QALYs gained, calculated as the above number, multiplied by the annualised number of people likely to start treatment with the medicine (average over Years 1 to 5).

b) Describe any particular features of the condition and population receiving the medicine that might be relevant to the appraisal process.

c) Outline the degree of severity of the disease as presently managed, in terms of survival and quality of life of patients and their carers that might be relevant to the appraisal process.

d) Describe whether the medicine addresses an unmet need.

e) Outline any added value to the patient which may not be adequately captured in the QALY (for example, convenience of treatment, ability to socialise, maintenance of dignity, etc.).

f) Provide details about any added value to the patient's family (for example, impact on a carer or on family life) that might be relevant to the appraisal process.

g) Where considered applicable, outline any proposed stopping criteria.

h) Describe any potential equity and equality issues that might need to be considered for this medicine. For example, any potential positive and/or negative impacts on people on the basis of a protected characteristic (such as age; disability; gender; gender reassignment; marriage and civil partnership; pregnancy and maternity; race; religion or belief; or sexual orientation); or according to their income group or where they live; or on people who face health inequalities. Please provide any evidence that would help to identify and consider any equity and equality issues.

i) State any wider societal costs and benefits of this medicine. Supplementary analyses which consider benefits and costs (or savings) to patients and their families may also be considered. Patient resource use in accessing treatment should be included where felt to be significant, particularly where this differs

between the medicine and its comparator(s). Other resource use may also be presented separately where differences arise between the medicine and its comparator(s); for example, direct non-healthcare resource use, such as that by social and educational services, and productivity losses attributable to changes in health outcomes.

An indication of the nature and likely magnitude of any included benefits and costs that would arise from adopting a wider societal perspective and the effect of these on the cost-effectiveness estimates may be provided, even where these are difficult to quantify.

j) Describe any potential environmental impacts, positive and/or negative, associated with the medicine and/or comparators.

16.0 References

You are required to provide AWTTC with an electronic copy of all references included in your submission (on CD or USB or datastick). If you have used a database to manage your references (e.g. EndNote) please supply us with a copy of your reference library or use the “travelling library” option.

17.0 Identification of patient organisations

AWMSG is committed to involving patient organisations in its decision-making process. The main objective will be to provide AWMSG with a patient and carer perspective on the condition being considered. AWTTC has a process for identifying relevant patient organisations. However, it would be helpful if you (the applicant company) could indicate any patient organisations you feel may be relevant in relation to this appraisal. Patient organisation(s) will be asked to declare any interests.

18.0 Contact details

Please supply contact details accordingly. Please enter the date of submission of Form B, or the date of any resubmission if applicable.

Please note that representatives of patient organisations may wish to obtain information from the applicant company about the treatment(s) under consideration. AWMSG will channel enquiries from patient organisations to the applicant company making the submission. If these requests should be directed to someone other than the main contact person, please give alternative details.

THE FOLLOWING DOCUMENTS SHOULD BE SUBMITTED ELECTRONICALLY:

- **LIST OF DOCUMENTS SUBMITTED**
- **FORM B**
- **MEDICINES FOR A VERY RARE DISEASE FORM (when applicable)**
- **REFERENCES**
- **HEALTH ECONOMIC MODEL**
- **BUDGET IMPACT MODEL**
- **SmPC**

A SIGNED HARD COPY OF FORM B MUST FOLLOW BY POST.

AWMSG Secretariat:
All Wales Therapeutics and Toxicology Centre
The Routledge Academic Centre
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