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1. Title of the project

Imatinib at escalated doses of 600 mg/day or 800 mg/day for the treatment of people with unresectable and/or metastatic gastrointestinal stromal tumours whose disease has progressed on treatment with imatinib at a dose of 400 mg/day: systematic review and economic evaluation

2. Name of TAR team and 'lead'

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3. Plain english summary

GISTs (gastrointestinal stromal tumours) are a rare type of cancerous tumours that most commonly arise in the stomach or small intestine. People will be diagnosed with this type of cancer only if a biopsy of their tumours tests positive for a particular protein (called "KIT" or "CD117"). In around half of all cases it is possible to remove the tumour surgically, however overall at least 50% of those operated on will develop recurrent disease within 5 years. In these patients with recurrence, and other patients with inoperable disease at diagnosis survival beyond a period 2 years is uncommon without further treatment. The usual treatment for patients with inoperable GISTs is the drug imatinib, prescribed at a dose of 400 mg per day. This treatment is effective in 60-70% of

patients, in which it typically provides control of the GISTs for a period of 2-3 years. Approxiamtely 50% of patients will survive 5 or more years with this treatment. However in all patients resistance of the GISTs to imatinib will eventually occur, and the disease will then progress. Genetic differences, for example whether certain mutations in the c-kit or CD117 gene are present in patients or not, may help clincians' understanding of who is more likely to be able to tolerate the drug and/or have least resistance to it. FDG-PET scans may also be useful to detect early response or resistance to imatinib and these measures may allow more individulaised treatment approaches. At present, increasing the dose of imatinib, when 400 mg per day ceases to improve a patient's condition, is not officially recommended (though in practice it is usually tried). An alternative drug (sunitinib) is recommended to be prescribed in cases where imatinib has failed. The only other alternative to these treatments for patients with inoperable GISTs is to provide best supportive care through management of the patient's pain and other symptoms, and attend to their needs and general well-being, without providing treatment to actively fight the cancer itself. However, in reality it is likely that all patients (including those receiving active treatment) will receive supportive care as part of this treatment.

This review will look at two alternative doses of imatinib (600 mg per day and 800 mg per day) and compare these with the current recommended treatment alternatives (i.e. sunitinib and/or best supportive care) for those patients with inoperable GISTs whose disease progresses while on imatinib at a dose of 400 mg per day.

4. Decision problem

Gastrointestinal stromal tumours (GISTs) are tumours of the connective tissue of the gastrointestinal (GI) tract arising in the interstitial cells of Cajal. They are rare cancers and estimated to account for 1% of all tumours arising in the GI tract.[1] It is estimated that the vast majority (between 60 and 70%) will arise in the stomach, though they can also occur in the small bowel (25-35%), colon and rectum (5%), and, to a lesser extent, the oesophagus.[2] Estimates of the number of people affected by GIST vary, but it is thought that the annual incidence is unlikely to exceed 240.[3] However, previous estimates have suggested that it could be as high as 2000 cases per year.[3] The median age at time of first presentation is approximately 60 years.[4] Prognosis for patients with GISTs is highly dependent on the resectability of the tumour and approximately half of GIST patients will have resectable disease at first presentation. GISTs are resistant to 'conventional' oncology treatments of cytotoxic chemotherapy and radiotherapy. For resectable/non-metastatic tumours, prognosis gives a ten year survival rate of 30-50% of patients, and at least 50% will relapse within 5 years,[5] but for unresectable tumours, prognosis is poor with survival generally less than 2 years without further treatment.[6]

For a GIST to be diagnosed, it is widely accepted that a positive test result (at protein level), for the marker KIT (CD117) is required. KIT (CD117) is a tyrosine kinase receptor which provides a major pathogenic drive for the majority of GISTs by promoting tumor growth and inhibiting tumour cell death. There has been some debate on the definition of a GIST, as it has been noted that in extremely rare cases (<5%), a patient can have a GIST despite testing negative for c-Kit protein expression and in most of these cases a mutation of PDGFRAlpha gene has been detected.[7-9] However, the WHO classification of gastrointestinal tumours recommends that a diagnosis of GIST should only apply to those patients testing positive for the KIT (CD117) protein.[10]

Imatinib is manufactured by Novartis under the names Glivec® (in Europe) and Gleevec® (in the USA). Having originally been licensed as a treatment for chronic myeloid leukaemia, it was first licensed for treatment of GIST in 2002, and is now the standard first line treatment for "locally advanced, inoperable patients and metastatic patients" with GIST.[11] The 2004 NICE Technology Appraisal 86 on the use of imatinib for

the treatment of unresectable and/or metastatic gastrointestinal stromal tumours recommends 400mg/day as first-line management. At present the NICE guidance does not recommend dose escalation of imatinib for those whose disease progresses after initially responding at the 400 mg per day dose, although dose escalation has been noted to be the standard approach to disease progression, where patient non-adherence or intolerance to imatinib are not factors in disease progression.[11]

The altermative treatments available for unresectable and/or metastatic GISTs are sunitinib (manufactured by Pfizer), and best supportive care. *Sunitinib is recommended for patients with unresectable and/or metastatic GISTs if treatment with imatinib has failed because of resistance or intolerance, and the drug cost for the first treatment cycle will be met by the manufacturer.*[12] Best supportive care is less well defined or standardised in different clinical trials or treatment protocols, and has also been referred to as "active symptom control".[2] It has been said to involve interventions to manage pain; treat fever, anaemia (due to GI haemorrhage) and GI obstruction[1] and can include palliative measures.[13] In a Cochrane review of supportive care for gastrointestinal cancer patients, supportive care was defined as "the multi-professional attention to the individual's overall physical, psychosocial, spiritual and cultural needs".[14] It was argued that this type of care should ethically be made available to all treatment groups, meaning that in practice for GIST patients, treatment with imatinib or sunitinib would not be provided without supportive care as well, though it is possible that treatment with best supportive care could be provided without additional drug treatment with either imatinib or sunitinib.

The survival of patients with GISTs is largely dependent on whether or not the tumour is resectable. For patients with unresectable and/or metastatic disease, the treatment options are imatinib, sunitinib or best supportive care. Guidance is available on the effectiveness of imatinib at the 400 mg per day dose.[1] However assessment is required of the clinical effectiveness of imatinib at higher dosages (i.e. 600 mg per day and 800 mg per day) in patients whose disease has progressed on treatment with the 400 mg dose, given that an estimated 16% of patients will experience primary resistance to imatinib, and all will develop resistance and progressive disease at a later stage.[15] In evaluating the effectiveness of escalated doses of imatinib or other alternate treatments it is also necessary to consider sub-groups of patients with specific gene KIT mutations who may respond differently to treatment, and also note how rapidly, and by what method (e.g. FDG-PET scans), these patients were identified.

This review will assess the clinical and cost-effectiveness of imatinib at escalated doses of 600 mg per day, and 800 mg per day, compared with treatment using sunitinib, or best supportive care, in patients with KIT (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours, whose disease has progressed on treatment with imatinib at a dose of 400 mg per day.

5. Report methods for synthesis of evidence of clinical effectiveness

A systematic review of the evidence of the clinical effectiveness of imatinib at escalated doses of 600 mg per day or 800 mg per day will be undertaken following the general principles of the CRD's guidance for undertaking reviews in health care[16] and reported in accordance with the PRISMA statement.[17]

5.1 Inclusion and exclusion criteria

- *Types of studies*

The types of studies considered will be randomised controlled trials (RCTs), non-randomised comparative studies and case series. If the number of studies meeting our inclusion criteria is sufficiently large, we may consider limiting them by type of study design and taking into account the importance of other factors such as sample size.

Scoping searches have already been conducted and fewer than 40 potentially relevant studies were found looking specifically at either of the named interventions (i.e. imatinib at 600 mg per day or 800 mg per day).

- *Population*

The population considered will be people with KIT (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST), whose disease has progressed on treatment with imatinib at a dose of 400 mg per day.

If there is sufficient evidence, sub-group analysis will be undertaken for those patients with different mutations of CD117, that are likely to affect their response to escalated doses of imatinib. Data will also be recorded on the methods used to identify response or resistance (e.g. FDG-PET or CT scanning), and whether or not imatinib had been prescribed in a neoadjuvant or adjuvant setting for patients with previously resectable GIST.

- *Intervention*

The intervention considered will be imatinib at escalated doses of 600 mg per day and 800 mg per day, being prescribed in addition to best supportive care

- *Comparators*

The comparators considered will be sunitinib, prescribed within its recommended dose range of 27-75 mg, and provided with best supportive care, and best supportive care only. Best supportive care has been defined in Section 4 above.

- *Outcomes*

The following outcomes will be considered:

- Overall response
- Overall survival
- Disease-free survival

- Progression-free survival
- Time to treatment failure
- Health-related quality of life
- Adverse effects of treatment

- *Exclusion criteria*

We will exclude the following types of studies:

- Animal models;
- Preclinical and biological studies;
- Reviews, editorials, opinions;
- Case reports;
- Reports investigating technical aspects of the intervention.

In addition, we may consider excluding non-English language papers, and/or reports published as meeting abstracts, if the evidence base containing English language and/or full text reports is sufficiently large.

5.2 Search strategy

Extensive sensitive electronic searches will be conducted to identify reports of published and ongoing studies on the clinical effectiveness of imatinib The searches will also be designed to retrieve clinical effectiveness studies of the comparator treatments. Databases to be searched will include: Medline, Medline In-Process, Embase, CINAHL, Science Citation Index, Biosis, Health Management Information Consortium, and the Cochrane Controlled Trials Register for primary research and the Database of Abstracts of Reviews of Effects (DARE), the Cochrane Database of Systematic Reviews (CDSR) and the HTA database for relevant evidence synthesis.

A preliminary Medline search strategy is provided in the Appendix and will be adapted for use in the other databases. Current research registers, including Clinical Trials, Current Controlled Trials, NIHR Portfolio, WHO International Clinical Trials Registry Platform, IFPMA Clinical Trials and the ABPI database will be searched to identify ongoing and recently completed trials. Recent conference proceedings of key oncology and gastrointestinal organisations will also be screened and will include the American Society for Clinical Oncology (ASCO), the International Society of Gastrointestinal Oncology (ISGIO), and the National Cancer Research Institute.

In addition, an Internet search using Copernic Agent will be undertaken and will include the websites of key professional organisations, GIST Support International, and the drug manufacturers Pfizer and Novartis.

There will be no language restriction and all databases will be searched from 2000 onwards.

The reference lists of all identified studies and evidence syntheses, as well as submissions from industry and other consultees, will be checked for additional references.

5.3 Data extraction strategy

One reviewer will screen the titles (and abstracts if available) of all reports identified by the search strategy. Full text copies of all studies deemed to be potentially relevant will be obtained, and two reviewers will independently assess them for inclusion. Any disagreements will be resolved by consensus or arbitration by a third party.

A data extraction form will be developed and piloted. One reviewer will extract details of study design, participants, intervention, comparator and outcomes. A second reviewer

will check the data extraction. Any disagreements will be resolved by consensus or arbitration by a third party.

5.4 Quality assessment strategy

Two reviewers will independently assess the methodological quality of the included studies. Any disagreements will be resolved by consensus or arbitration by a third party. Studies will not be included or excluded on the basis of methodological quality.

RCTS will be assessed using the Cochrane Collaboration's tool for assessing risk of bias.[18] The tool addresses six specific domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and 'other issues'. Non-randomised comparative studies will be assessed using an 18-question checklist, with the same checklist minus four questions used to assess the quality of case series. The checklist for non-randomised studies and case series was adapted from several sources, including the Centre for Reviews and Dissemination's guidance for those carrying out or commissioning reviews,[16] Verhagen and colleagues,[19] Downs and Black[20] and the Generic Appraisal Tool for Epidemiology (GATE). It assesses bias and generalisability, sample definition and selection, description of the intervention, outcome assessment, adequacy of follow-up, and performance of the analysis. The checklist was developed through the Review Body for Interventional Procedures (ReBIP). ReBIP is a joint venture between Health Services Research at Sheffield University and the Health Services Research Unit at the University of Aberdeen and works under the auspices of the National Institute for Health and Clinical Excellence (NICE) Interventional Procedures Programme (IPP).

5.5 Methods of analysis/synthesis

For relevant outcomes from randomised studies, where appropriate, meta-analysis will be employed to estimate a summary measure of effect. Dichotomous outcome data for the overall response outcome will be combined using the Mantel-Haenszel relative risk (RR) method and continuous outcomes will be combined using the inverse-variance weighted mean difference (WMD) method. For the estimates of RR and WMD 95% confidence intervals (CIs) and p-values will be calculated. Chi-squared tests and I-squared statistics will be used to explore statistical heterogeneity across studies. Possible reasons for heterogeneity will be explored using sensitivity analysis. Where there is no obvious reason for heterogeneity, the implications will be explored using random effects methods.

Pooled weighted ratio of median survival will be derived for overall, disease-free and progression-free survival. The hazard ratio (HR) is the most appropriate statistic for time-to-event outcomes (i.e. for time to treatment failure). If available, the HR will be extracted directly from the trial publications. If not reported the HR will be extracted from other available summary statistics or from data extracted from published Kaplan-Meier curves using methods described by Parmar et al.[21] A pooled HR from available RCTs will be obtained by combining the observed (O) minus expected (E) number of events and the variance obtained for each trial using a fixed effects model.[22] A weighted average of survival duration across studies will then be calculated. The chi square test for heterogeneity will be used to test for statistical heterogeneity between studies. If no RCT data are available, but non-randomised studies have reported relevant data for this outcome, assessment of the risk of bias and heterogeneity will be undertaken using meta-regression analysis.

Data on adverse effects of treatment and quality of life (QoL) will be collected and combined, ideally using standardised mean difference to compare QoL, where there are available data to do so.

It is expected that studies with direct comparisons of the intervention and comparators are likely to be limited. If feasible, and appropriate where we have non-randomised evidence, meta-anlysis models will be used to model survival rates for interventions and comparators. A "cross design" approach will be adopted to allow non-randomised evidence to be included, whilst avoiding the strong assumption of the equivalence of studies. This approach will enable evidence from RCTs, non-randomised comparative studies and case-series to be included.[23] Differences between treatments for survival outcomes will be assessed by the corresponding odds ratio and 95% credible intervals. These results will be "unadjusted odds ratios", but meta-analysis models adjusting for study type will also be used. The results from these models will produce "adjusted" odds ratios. WinBUGS software.[24]

If appropriate, and where there is sufficient data to do so, we will consider using a mixed treatment comparison model for indirect comparisons.

Where a quantitative synthesis is considered to be inappropriate or not feasible, a narrative synthesis of results will be provided.

6. Report methods for synthesising evidence of cost-effectiveness

6.1 Economic evaluation

The economic impact of GISTs for the NHS is associated with its incidence rate, and the proportion of patients who may have unresectable disease (and the consequent resource use by the health systems), and burden in terms of patient outcome. Information from the work on an economic model for the UK, mainly from an industry submission, is based on the assumption that the incidence rate is 15 per million population, and 10-30% of all GIST patients are likely to have resectable disease. If these patients (between 80-240 people) are treated with imatinib, the annual drug costs per patient to the NHS, have been estimated at £18,896 and £24,368 for patients on 400 and 600 mg per day, respectively. Other associated yearly costs with the treatment (including the treatment of adverse events) were estimated at £2730. The model estimates suggest that in two years it would cost the NHS £31,160 to treat a patient with imatinib, and in 10 years it would cost the NHS £56,146.[2,25] An estimate suggests that the total yearly costs to the NHS (England and Wales) for treating with imatinib would be between £5.6 million and £11.2 million. The cost to the NHS would differ when patients who fail to progress with imatinib are provided with higher doses, or other alternative treatments, (e.g. treatment with sunitinib). NICE estimates suggest the number of new cases of unresectable and/or metastatic GISTs to be around 240 people per year.[3] The economic impact of different treatment strategies needs thorough investigation for a robust economic evaluation.

- *Objectives*

The aim is to assess the clinical and cost-effectiveness of alternative treatment strategies for people with KIT (CD117) positive unresectable and/or metastatic gastrointestinal tumours (GISTs), whose disease has progressed on treatment with imatinib at a dose of 400 mg per day.

The specific objectives are:

a) To determine, by undertaking a systematic review of the literature, the clinical and cost-effectiveness of using imatinib at an escalated dose of 600 mg per day or 800 mg per day to treat patients with GISTs (whose disease has progressed with imatinib at a dose of 400 mg per day), compared with treating them with sunitinib and best supportive care.

b) To develop an economic model to compare the cost-effectiveness and cost-utility of use of imatinib at a dose of 600 mg per day or 800 mg per day, or use of sunitinib, or best supportive care only, for treating people with KIT (CD117) positive unresectable and/or metastatic gastrointestinal tumours (GISTs) whose disease has progressed on treatment with imatinib at a dose of 400 mg per day.

The economic assessment will be a comparison of alternative treatments for people with GISTs whose disease has progressed in spite of treatment with imatinib at a dose of 400 mg per day, or those whose treatment with imatinib has failed due to resistance or intolerance. The alternative treatments that will be considered are i) treating with escalated doses of 600 mg per day or 800 mg per day, ii) treating with sunitinib (within its recommended dosage) and iii) providing best supportive care to manage symptoms. It should be noted here that best supportive care is often not provided exclusively. For treatment with imatinib, and treatment with sunitinib, it will be assumed that best supportive care would be provided alongside these treatments.

The economic assessment will be based on two components, (i) a systematic review of existing economic evaluations of the above alternative treatments and (ii) an economic evaluation modelling exercise.

- Systematic review of economic evaluations, and cost analyses of alternative treatment strategies used for treatment of GISTs, (particularly for patients whose disease has progressed with imatinib at a dose of 400 mg per day)

The purpose of the review of studies on economic analysis, or economic evaluation, will be to identify published studies and assess their quality and usefulness for comparisons of alternative treatment of GISTs; inform the methodology of the proposed economic model; and identify data on the parameters of the proposed economic model (e.g. utilities for different health states, costs and epidemiological data).

- *Data sought*

With respect to costs, data will be sought to gather information on costs to the health services (NHS) in treating GIST patients and on costs to patients, in order to estimate overall mean-costs. Specific information will also be collected on (a) the cost of treating the different clinical outcomes (e.g. cost of achieving total survival for the GIST patients whose disease has progressed on treatment with imatinib at a dose of 400 mg per day - the base case), (b) the costs of maintaining GIST patients at a disease progression-free state for a specific period of time under alternative treatment strategies, and (c) the cost per life year gained under alternative treatment strategies. Data will be sought on the costs associated with each alternative. For costs to the health services this will include, for example, the mean number of visits to the oncologist, number of laboratory tests and examinations, radiology examination, the number of inpatient days, and the costs of drugs. Costs associated with the treatment of adverse effects[i] will be included within the

[i] Most of the adverse effects noted in the literature include fatigue and fever, hypertension, gastrointestinal illnesses, dermatological, haemorrhagic events etc.

costs of treatment under different strategies, and data will be sought accordingly. Data on costs to patients in seeking care and for best supportive care under different strategies will also be collected.

With respect to effectiveness, data will be sought on the same outcomes (overall survival, disease-free or progression-free survival, adverse effects of the treatments, time to treatment failure or time to tumour progression, and overall response rate) as noted in the review of effectiveness of different strategies (see section 5.1). This will aid comparison of the results of individual economic evaluations with pooled estimates of effectiveness. In addition to this, we will also seek information on the quality adjusted life years (QALYs) associated with each treatment strategy, and for different relevant health states noted.

More specifically we will seek to identify any data on the QALY loss caused by gastro-intestinal cancer or gastrointestinal stromal tumours, tumour progression, and adverse effects of the different treatment strategies.

- *Types of studies*

Economic evaluations and cost analyses comparing the above mentioned alternative treatment strategies will be included. Non-UK studies will also be included provided they report interventions or involve populations relevant to the scope of the study.

- *Search strategy for identification of published reports*

A comprehensive search will be undertaken to identify studies that assess the cost or cost-effectiveness of the alternative treatments used for GISTs. Databases to be searched will include: Medline, Medline In Process, Embase Science Citation Index Health Management Information Consortium, NHS Economic Evaluations database, the HTA database, CEA Registry and RePeC. There will be no language restriction and all databases will be searched from 2000 onwards.

A preliminary Medline search strategy is provided in the Appendix and will be adapted for use in the other databases. In addition, an Internet search using Copernic Agent will be undertaken and will include the websites of key professional organisations, GIST Support International and the drug manufacturers Pfizer and Novartis.

The references lists of all identified studies and evidence syntheses, as well as submissions from industry and other consultees will be checked for additional potentially relevant references.

The description of how the industry submissions will be handled is described in Section 7 below.

- *Quality assessment*

All included studies will be assessed using the guidelines of the Centre for Reviews and Dissemination.[16] Modelling studies will also be quality assessed against the Phillips checklist.[27]

- *Report methods for synthesising evidence of cost-effectiveness*

The titles and abstracts of all published reports, literature and industry submissions identified by the search strategy will be examined to select relevant studies. The full

texts of potentially relevant reports, publications and industry submissions will be obtained and assessed in terms of their relevance to the economic evaluation or cost-analysis. Data will be extracted by an economist according to the guidelines produced by the Centre for Reviews and Dissemination for the critical appraisal of economic evaluations. Where the economic evaluation has been based on a modelling exercise, additional data extraction criteria developed by Phillips and colleagues will apply.[26,27]

Data from the included studies on economic analysis and economic evaluation will be summarised in order to identify common results, and to summarise the variations and weaknesses between studies. The studies that use economic modelling will be critically reviewed with regard to, for example, model structure use, parameterisation and how these models have dealt with uncertainty. This critical review will assist us in developing methods that can be used to structure our model.

6.2 Economic modelling

- *Model structure*

The structure of the model will be informed by the modelling studies identified as part of the systematic review of economic evaluations, the review of clinical effectiveness and other existing evidence including previous NICE TARs. We will also draw upon advice from health care professional members of our research team. However, the scope of the study suggests that treatment strategies to be compared in the models are:

i) Treatment of GIST patients (whose disease has progressed on treatment with imatinib at a dose of 400 mg per day) with an escalated dose of 600 mg per day, regulating symptoms with best supportive care

ii) Treatment of GIST patients (whose disease has progressed on treatment with imatinib at a dose of 400 mg per day) with an escalated dose of 800 mg per day, regulating symptoms with best supportive care

iii) Treatment with sunitinib (within its recommended dose range), regulating symptoms with best supportive care

iv) Regulating symptoms with best supportive care only

The model will consider the above treatment strategies as different types of intervention, and will consider the costs and consequences of patients following these different pathways of care. When building the model we will also consider whether the use of FDG-PETs to predict non-response should be built into the model. The inclusion of this imaging technology may alter estimates of cost-effectiveness because (i) it is costly and (ii) it may provide an early indication of non-responders who may benefit from the early introduction of an alternative therapy.

Consideration will be given to estimating relative differences between treatments based on non-directly comparative data, if direct evidence is not identified within the literature.

The model used will be a Markov model, where the following health states will be considered (all are associated with clinical effectiveness); overall survival; treatment failure; time to tumour progression, and progression-free survival. In an earlier HTA of imatinib at a dose of 400 mg per day,[2] and other studies,[28] the health states within the economic model were (i) “imatinib treatment” with different doses or “sunitinib treatment that stops disease progression, or at least leads to a partial response; (ii) progressive disease, (iii) death. It is likely that the health states used in our model will be similar to

these analyses, although the final choice will depend upon advice and also the literature as described in Section 6.1. Where evidence is available, sub-group analysis will be undertaken on patients with different gene mutation types that may affect their response to escalated doses of imatinib.

- *Data requirements*

For our model, data on the relative effectiveness of interventions will be based upon the systematic review. Resource use of the selected treatment strategies, and for baseline (patients whose disease has progressed on treatment with imatinib at a dose of 400 mg/day) will be identified from relevant sources (NHS cost data, NHS tariff), the review of economic evaluations and advice from experts. Data on resource use can generally be classified into different groups: e.g. resource use in the treatment strategy of the escalated doses of imatinib, secondary care resource use related to secondary level of care or services other than the interventions e.g. side-effect management and other associated treatments, laboratory and other examinations, and resource use for other health care. Data/information on unit costs will be obtained from NHS National Reference Costs and from studies that will be identified as described in Section 6.1. Additional focused searching for relevant cost data will also be conducted.

A cost-utility analysis will be conducted, with outcomes estimated in terms of quality-adjusted life years (QALYs) for patients, where EQ-5D health state profile can be used from the information expected to be available from the review of economic evaluation studies on such treatments. Each health state of the state transition model will require a utility estimated using the best available data (EQ-5D, ECOG category mapped to QALY). These data will be identified from the systematic review, additional focused searches and routine data sources. Where necessary we may need to make assumptions in order to use utility values derived from different patient populations.

- *Time horizon for the model*

The model will look at the costs and consequences directly attributable to the events to the GIST patients (whose disease progression takes place in spite of treatment with imatinib at 400 mg per day) and treating them with alternative strategies up to the end of the patient's lifetime. Although the time horizon used will be the patient's lifetime, it is expected that this is unlikely to exceed 6 years (the maximum number of years patients are expected to live after they are diagnosed with unresectable and/or metastatic gastrointestinal stromal tumours).

- *Analysis methods*

The results of the model will be presented in terms of a cost-consequence analysis and cost-utility analysis. The cost-consequence analysis will examine the costs and effects on natural and clinical measures. The likely consequences that are expected to be included in the analysis would include overall survival and progression-free survival. In the cost-utility analysis, results will be presented in terms of an incremental cost per QALY, incremental cost per overall survival (life years gained) and incremental cost per months/year of progression-free survival.

Where appropriate, costs and outcomes will be discounted at 3.5% for both the cost-consequence and cost-utility analyses.[26] The economic evaluation will consider the different sub-groups noted earlier.

Both deterministic and probabilistic sensitivity analysis will be conducted for the uncertainty surrounding parameters, and a net benefit framework will be used to compare the different treatment strategies.

7. Handling the company submission(s)

Information from the manufacturer will be considered if submitted in accordance with the 3rd December 2009 deadline set by NICE. Following receipt of the submission, members of the Aberdeen TAR Team will critically appraise sections of the report according to each member's own area of expertise. Studies reported in the manufacturer's submission that meet the inclusion criteria for the review will be data extracted and quality assessed in accordance with the procedures outlined in this protocol, and included in the data analysis.

Any economic evaluations included in the company submission, provided they comply with NICE's guidance on presentation, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model, again using the methods outlined in this protocol. Strengths and weaknesses in terms of methodology adopted, reporting of results and conclusions will be described. The default position of the TAR team is that further modelling work will be necessary and if the TAR team judge that the existing economic evidence is not robust then further work will be undertaken, either by adapting what already exists or developing de-novo modelling (as described in Section 6.2). The conclusions derived from the company submission may then be compared with those provided by the review of the other existing evidence and any model we develop so that differences in results can be highlighted. If the model we may develop differs substantively from that submitted by any company, we shall justify any assumptions made.

Any 'commercial in confidence' data taken from a company submission will be reported in accordance with NICE guidelines.

8. Competing interests of authors

None

Reference list

1 *Gastro-intestinal stromal tumours (GIST) - imatinib : guidance TA86 [document on the Internet].* London: National Institute for Health and Clinical Excellence; 2004 [accessed August 2009]. Available from: URL: http://guidance.nice.org.uk/TA86/Guidance/pdf/English.

2 Wilson J, Connock M, Song F, Yao G, Fry-Smith A, Raftery J et al. Imatinib for the treatment of patients with unresectable and/or metastatic gastrointestinal stromal tumours: systematic review and economic evaluation. *Health Technol Assess* 2005;9:1-142.

3 *TA86 Gastro-intestinal stromal tumours (GIST) - imatinib: quick reference guide [document on the Internet].* London: National Institute for Health and Clinical Excellence; 2004 [accessed August 2009]. Available from: URL: http://guidance.nice.org.uk/TA86/QuickRefGuide/pdf/English.

4 King DM. The radiology of gastrointestinal stromal tumours (GIST).]. *Cancer Imaging* 2005;5:150-6.

5 Judson I, Leahy M, Whelan J, Lorigan P, Verrill M, Grimer R. A guideline for the management of gastrointestinal stromal tumour (GIST). *Sarcoma* 2002;6:83-7.

6 DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. *Ann Surg* 2000;231:51-8.

7 Corless CL, Fletcher JA, Heinrich MC. Biology of gastrointestinal stromal tumors. *J Clin Oncol* 2004;22:3813-25.

8 Heinrich MC, Corless CL, Duensing A, McGreevey L, Chen C-J, Joseph N et al. PDGFRA activating mutations in gastrointestinal stromal tumors. *Science* 2003;299:708-10.

9 Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. *Archiv Pathol Lab Med* 2006;130:1466-78.

10 Hamilton SR. *World Health Organization Classification of Tumours: Pathology and genetics of tumours of the digestive system.* Geneva: IARC Press; 2000.

11 Casali PG, Jost L, Reichardt P, Schlemmer M, Blay JY, ESMO Guidelines Working Group. Gastrointestinal stromal tumours: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 1920;20:64-7.

12 *Gastrointestinal stromal tumours - sunitinib: final appraisal determination [document on the Internet].* London: National Institute for Health and Clinical Excellence; 2009 [accessed August 2009]. Available from: URL: http://www.nice.org.uk/guidance/index.jsp?action=download&o=45125.

13 *Single Technology Appraisal of Sunitinib for the treatment of gastrointestinal stromal tumours [document on the Internet].* Sandwich, Kent: Pfizer Ltd; 2008 [accessed August 2009]. Available from: URL: http://www.nice.org.uk/guidance/index.jsp?action=download&o=43440.

14 Ahmed N, Ahmedzai S, Vora V, Hillam S, Paz. Supportive care for patients with gastrointestinal cancer. *Cochrane Database of Systematic Reviews* 2004;Art. No.: CD003445. DOI: 10.1002/14651858.CD003445.pub2.

15 Blanke CD, Demetri GD, Von Mehren M, Heinrich MC, Eisenberg B, Fletcher JA et al. Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. *J Clin Oncol* 2008;26:620-5.

16 *Systematic reviews: CRD's guidance for undertaking systematic reviews in health care [document on the Internet].* University of York: Centre for Reviews and Dissemination; 2009 [accessed March 2009]. Available from: URL: http://www.york.ac.uk/inst/crd/SysRev/!SSL!/WebHelp/SysRev3.htm.

17 Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:332-9.

18 The Cochrane Collaboration's tool for assessing risk of bias [webpage of the Internet] In: The *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.1. The Cochrane Collaboration, 2008. [accessed August 2009] Available from: URL: http://www.cochrane-handbook.org/

19 Verhagen AP, de Vet HC, de Bie RA, Kessels AG, Boers M, Bouter LM et al. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *J Clin Epidemiol* 1998;51:1235-41.

20 Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998;52:377-84.

21 Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med* 1998;17:2815-34.

22 Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis* 1985;27:335-71.

23 Sutton AJ, Abrams KR. Bayesian methods in meta-analysis and evidence synthesis. *Stat Methods Med Res* 2001;10:277-303.

24 Lunn DG, Thomas A, Best N, Spiegelhalter D. WinBUGS -- a Bayesian modelling framework: concepts, structure, and extensibility. *Stat Comput* 2000;10:325-37.

25 Reddy P, Boci K, Charbonneau C. The epidemiologic, health-related quality of life, and economic burden of gastrointestinal stromal tumours. *J Clin Pharm Therapeut* 2007;32:557-65.

26 National Institute for Health and Clinical ExcellenceNational Institute for Health and Clinical Excellence. *Guide to the methods of technology appraisal [document on the Internet].* London: National Institute for Health and Clinical Excellence; 2008 [accessed September 2008]. Available from: http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf.

27 Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technol Assess* 2004;8:1-158.

28 Contreras-Hernandez I, Mould-Quevedo JF, Silva A, Salinas-Escudero G, Villasis-Keever MA, Granados-Garcia V et al. A pharmaco-economic analysis of second-line treatment with imatinib or sunitinib in patients with advanced gastrointestinal stromal tumours. *Br J Cancer* 2008;98:1762-8.

9. Appendices

9.1 Search strategy

- Preliminary Medline strategy for Clinical Effectiveness Studies

1 Gastrointestinal Stromal Tumors/
2 gastrointestinal neoplasms/
3 gist.tw
4 (gastro$ adj3 stromal).tw
5 or/1-4
6 imatinib.tw,rn
7 gleevec.tw,rn.
8 glivec.tw,rn.
9 (sti571 or sti 571).tw,rn.
10 or/6-9
11 sunitinib.tw,rn
12 sutent.tw,rn.
13 (su11248 or su 11248).tw,rn.
14 or/11-13
15 dt.fs.
16 15 and (1 or 3 or 4)
17 16 not (10 or 14)
18 Palliative Care/ (
19 ((palliative or support$) adj3 (care or treatment)).tw.
20 or/17-19
21 5 and 10
22 5 and 14
23 5 and 20
24 or/21-23
25 exp clinical trial/
26 randomized controlled trial.pt.
27 controlled clinical trial.pt.
28 randomi?ed.ab.
29 placebo.ab.
30 drug therapy.fs.
31 randomly.ab.
32 trial.ab.)
33 groups.ab.
34 comparative study/
35 follow-up studies/
36 time factors/
38 (chang$ or evaluat$ or reviewed or baseline).tw.
39 (prospective$ or retrospective$).tw.
40 (cohort$ or case series).tw.
41 or/25-40
42 24 and 41
43 humans/
44 42 and 43
45 limit 44 to yr="2000 - 2009"

- Preliminary Medline Strategy for Cost-Effectiveness Studies

1 Gastrointestinal Stromal Tumors/
2 gastrointestinal neoplasms/
3 gist.tw.

4 (gastro$ adj3 stromal).tw.
5 or/1-4
6 imatinib.tw,rn.
7 gleevec.tw,rn.
8 glivec.tw,rn.
9 (sti571 or sti 571).tw,rn.
10 or/6-9
11 sunitinib.tw,rn.
12 sutent.tw,rn
13 (su11248 or su 11248).tw,rn
14 or/11-13
15 dt.fs.
16 15 and (1 or 3 or 4)
17 16 not (10 or 14)
18 Palliative Care/
19 ((palliative or support$) adj3 (care or treatment)).tw.
20 or/17-19
21 5 and 10
22 5 and 14
23 5 and 20
24 or/21-23
25 exp "costs and cost analysis"/
26 economics/
27 exp economics,hospital/
28 exp economics,medical/
29 economics,pharmaceutical/
30 exp budgets/
31 exp models, economic/
32 exp decision theory/
33 ec.fs. use mesz
34 monte carlo method/
35 markov chains/
36 exp health status indicators/
37 quality of life/
38 quality adjusted life year/
39 "Value of Life"/
40 cost$.ti.
41 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimis$)).ab
42 economics model$.tw.
43 (economics$ or pharmacoeconomic$ or pharmo-economic$).ti.
44 (price$ or pricing$).tw.
45 (financial or finance or finances or financed).tw.
46 (value adj2 (money or monetary)).tw.
47 markov$.tw.
48 monte carlo.tw.
49 (decision$ adj2 (tree? or analy$ or model$)).tw.
50 (standard adj1 gamble).tw
51 trade off.tw.
52 (quality adj1 life).tw.
53 quality adjusted life.tw.
54 . (qaly? or qald? or qale? or qtime? or daly?).tw.
55 (euroqol or euro qol or eq5d or eq 5d).tw.
56 or/25-55
57 24 and 56
58 limit 57 to yr="2000 -Current"

9.2 Data extraction form

GIST Review – Draft Data Extraction Form

Reviewer ID: **Date:**

Administration Details for Study	
Study ID: (Surname of 1st Author and Year of Publication) **Possibly related studies in this review:** **Multicentre Study:** ☐ Yes. Number of centres _____ ☐ No. **Country/countries:** **Funding Details:** Government Private Manufacturer Other (specify)**:** **Additional Info**:	**Study Design:** ☐ - RCT ☐ - Crossover study ☐ - Non-randomised comparative study ☐ - Prospective case series ☐ - Registry-based study **Duration of Study:** **Study start/end dates:** **Length of follow up:**
Aim of Study	
Interventions investigated	
Interventions: ☐ - Imatinib at 600 mg per day ☐ - Imatinib at 800mg per day	**Comparators:** ☐ - Sunitinib (specify dose): ☐ - Best supportive care, defined as:

Outcomes Reported	
Outcome:	**Tool Used in Assessment/Outcome defined as:**
☐ - Overall response	
☐ - Overall survival	
☐ - Disease free survival	
☐ - Progression-free survival	
☐ - Time to treatment failure	
☐ - Health-related quality of life	
☐ - Adverse effects of treatment	
Inclusion Criteria	
Exclusion Criteria	

Characteristics of Participants				
Characteristic	**Intervention 1**	**Comparator 1**	**Comparator 2**	**All**
Enrolled				
Randomised				
Analysed				
Number lost to follow up				
Age (mean/median, SD/IQR/range)				
Sex:	**F:** **M:**	**F:** **M:**	**F:** **M:**	**F:** **M:**
Stage of disease: ☐ - Unresectable ☐ - Metastatic ☐ - Recurrent	No (%) at stage:	No (%) at stage:	No (%) at stage:	No (%) at stage:
Mutations of c-KIT present: ☐ - exon 9 ☐ - exon 11 ☐ - exon 13 ☐ - exon 17	No (%) with mutation	No (%) with mutation	No (%) with mutation	No (%) with mutation
Previous imatinib use: mg/day mg/day mg/day	No (%) on this dose	No (%) on this dose	No (%) on this dose	No (%) on this dose
Used imatinib at mg/day as: ☐ - neoadjuvant treatment ☐ - adjuvant treatment	No (%) affected	No (%) affected	No (%) affected	No (%) affected

Number/proportion of KIT positive patients (if not 100%):

Method of GIST diagnosis (if specified):

Method used to determine progression/response:
☐ - CT scan
☐ - FDG – PET scan

Additional Information on Participants				
Interventions				
Description of intervention (e.g. dose, number of times taken per day, care provided etc)	**Intervention 1**	**Comparator 1**	**Comparator 2**	**All**
Results				
Outcome:	**Intervention 1**	**Comparator 1**	**Comparator 2**	**All**
Overall Response				
Overall Survival				
Disease-free survival				
Progression-free survival				
Time to treatment failure				
Health-related QoL				

Adverse Events				
General Information on Adverse Events:				
Adverse Events Reported	**Intervention 1**	**Comparator 1**	**Comparator 2**	**All**
Additional Study Information				