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Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours (part review of TA86)

Assessment Report

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Systematic review of the clinical and cost-effectiveness of imatinib at escalated doses of 600 mg/day or 800 mg/day for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours which have progressed on treatment at a dose of 400 mg/day

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1 LIST OF ABBREVIATIONS

AGITG	Australasian Gastrointestinal Trials Group
ATP	Adenosine triphosphate
BNF	British National Formulary
BSC	Best supportive care
CEA	Cost effective analysis
CI	Confidence interval
c-KIT	Cytokine- tyrosine kinase receptor
CT	Computer tomography
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D	EuroQol-5D
ESMO	European Society for Medical Oncology
FDG-PET	Fluorodeoxy glucose - positron emission tomography
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumours
HR	Hazard ratio
HRQOL	Health related quality of life
ICC	Interstitial cells of Cajal
ICER	Incremental cost effective ratio
ICUR	Incremental cost utility ratio
IM	Imatinib
IQR	Interquartile range
ISG	Italian Sarcoma Group
KIT	Tyrosine kinase
LYG	Life year gain
LYS	Life year saved
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
OS	Overall survival
PD	Progressive disease
PDGFRA	Platelet-derived growth factor receptor alpha
PFM	Progression free month
PFS	Progression free survival
PR	Partial response

QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
REBIP	Review Body of Interventional Procedures
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Relative risk
SCF	Stem cell factor
SD	Stable disease
SMC	Scottish Medicine Consortium
VEGFR	Vascular endothelial growth factor receptor
WHO	World Health Organization
WMD	Weighted mean difference

2 EXECUTIVE SUMMARY

Background

Less than 1% of all cancers in the gastrointestinal (GI) tract are gastrointestinal stromal tumours (GISTs). The median age of patients at diagnosis is between 50 and 60 years old and diagnosis typically depends upon morphological and clinical features being consistent with positive KIT/CD117 protein expression. Surgical resection is potentially curative but some patients will have unresectable and/or metastatic disease. Conventional chemotherapy and radiotherapy are ineffective in the management of unresectable and/or metastatic GIST and symptom control through best supportive care was the main treatment available. Imatinib (Glivec®) at a dose of 400 mg/day was recommended in NICE's 2004 guidance as first line management for those with KIT (CD117)-positive unresectable and/or metastatic GIST. Dose escalation upon disease progression after initially responding at the 400 mg/day dose was not recommended, although other recent guidelines have recommended dose escalation to a maximum dose of 800 mg/day, particularly for those patients with unresectable and/or metastatic GIST who also have specific exon mutations in the KIT gene. Since the 2004 guidance sunitinib malate (SUTENT), another tyrosine kinase inhibitor, has been licensed for the treatment of people with unresectable and/or metastatic GIST. NICE guidance recommends sunitinib as a treatment option for people with unresectable and/or metastatic malignant GISTs if imatinib treatment has failed because of resistance or intolerance, and the drug cost of sunitinib for the first treatment cycle is met by the manufacturer.

Objectives

The aim was to assess the effectiveness and cost-effectiveness of imatinib at escalated doses of 600 mg/day and 800 mg/day following progression of disease at a dose of 400 mg/day, with sunitinib, or the provision of best supportive care only for patients with unresectable and/or metastatic GISTs. Particular subgroups of interest were patients with specific KIT mutations.

Methods

Electronic searches were undertaken to identify published and ongoing randomised controlled trials (RCTs), non-randomised comparative studies and case series. Participants were adult patients with unresectable and/or metastatic GISTs whose disease had progressed on an imatinib dose of 400mg/day. The interventions considered were imatinib at a dose of 600 mg/day and 800 mg/day, sunitinib, or best supportive care only. Outcomes considered included overall response, overall survival, disease-free survival, progression-free survival, time to treatment failure, health related quality of life, and adverse effects.

The titles and abstracts of all identified reports were screened and full text reports of potentially relevant studies assessed. Data were extracted from included studies, including details of study design, participants, interventions, comparators and outcomes. These studies were quality assessed using a checklist developed for non-randomised studies and case series, adapted from several sources, including the Centre for Reviews and Dissemination's guidance for those carrying out or commissioning reviews, Verhagen and colleagues, Downs and Black, and the Generic Appraisal Tool for Epidemiology (GATE). The Cochrane Collaboration's risk of bias tool, was also used to evaluate the quality of sequence generation and allocation concealment of RCTs. Data analysis was confined to a comparison of data extracted from published Kaplan-Meier curves, and a narrative synthesis of results was presented.

For the review of economic evaluations, electronic searches were undertaken to identify cost or cost-effectiveness analyses relevant to the study question. Selection of relevant papers used similar methods to the review of clinical effectiveness. For included studies, data were extracted and critically appraised according to the guidelines produced by the Centre of Reviews and Dissemination for the critical appraisal of economic evaluations, and guidelines relevant to modelling studies. A Markov model was developed to compare the cost-effectiveness of seven clinically plausible alternative care pathways. The data used to populate the model were derived from the review of clinical effectiveness as well as the review of economic studies. Within the model people were assumed to move to the next therapy specified for a care pathway unless they had responded to treatment. All pathways ended with best supportive care, which patients would enter if they had exhausted all other treatments in a pathway. Both deterministic and probabilistic sensitivity analysiswere conducted. The latter was restricted to considering distributions for the probability of death and non-response to focus attention on uncertainty in these data.

Results

Clinical effectiveness

Five studies (n = 2032) met the inclusion criteria, with four (n = 318) reporting outcomes for patients who received escalated doses of imatinib and one (n = 351) reported outcomes for patients who received sunitinib. No studies meeting our inclusion criteria were identified for best supportive care. The included studies were essentially observational in nature and subject to the biases associated with such data, consisting mostly of reporting of subgroups of patients who had been enrolled in RCTs that were not designed to assess the effects of dose escalation

on patients with advanced and/or metastatic GIST whose disease had progressed on the 400 mg/day dose. Therefore the selection of patients was neither randomised nor consecutive.

At an escalated dose of 600 mg/day between 26% and 42% of patients showed either a partial response or stable disease. Median time to progression was 1.7 months (range 0.7 to 24.9 months). No data on other outcomes were available.

At an escalated dose of 800 mg/day between 29% and 33% of patients showed either a partial response or stable disease. The median overall survival was 19 months (95% CI 13 to 23 months). Progression-free survival ranged from 81 days to 5 months (95% CI 2 to 10 months). The median duration of response was 153 days (range 37 to 574 days). Treatment progression led to 88% discontinuations but between 16% and 31% of patients required a dose reduction, and 23% required a dose delay. There was a statistically significant increase in the severity of fatigue ($p<0.001$) and anaemia ($p=0.015$) following dose escalation.

For sunitinib, median overall survival was 90 weeks (95% CI 73 to 106 weeks). No data were available for other outcomes.

Insufficient data were available on the subgroup population of interest with KIT mutations, and these were not considered in the economic analysis.

Cost-effectiveness

Although seven economic studies were identified only one full-text study and one abstract, comparing imatinib at an escalated dose, sunitinib and best supportive care were identified. Neither were based on a UK context. The definition of best supportive care was not consistent across the studies, and the pattern of resources (including drugs for treatment) and measures of effectiveness also varied.

Within the model, Path – 1, best supportive care, (which was assumed to include continuing medication to prevent tumour flare) was the least costly and least effective. It would be the care pathway most likely to be cost-effective when the cost per QALY threshold was less than £25,000. Path – 4, imatinib at 600 mg/day was most likely to be cost-effective at a threshold between £25,000 and £45,000. Imatinib at 600 mg/day followed by further escalation, followed by sunitinib was most likely to be cost-effective at a threshold over £45,000.

Sensitivity analysis

The results did not greatly alter under the majority of the sensitivity analyses conducted. However, all the economic data were based upon point estimates for mortality and response rates that were in turn based upon sparse and potentially biased data.

It was also not possible, due to lack of data, to make alternative assumptions about probabilities of death and response change over time, or reductions in utility associated with adverse effects of treatment. Further assumptions that were required to be made in the model were that patients who move on to best supportive care would remain on treatment with imatinib at 400 mg/day to prevent tumour flare, but that this would have no impact on effectiveness.

Discussion

Relatively little relevant data were identified for this review and what data were available are essentially observational and non-comparative. Such data are potentially biased, with both the magnitude and direction of the bias being uncertain. Therefore, all results should be interpreted with caution.

Approximately one third of unresectable and/or metastatic GIST patients who receive dose escalated imatinib show either response or stable disease, which can be maintained over several months. However, few data were available for imatinib at 600 mg/day and median overall survival for imatinib at 800 mg/day and sunitinib was less than 24 months. Few data were available on adverse events but up to one third of patients may need a dose reduction or a dose delay. Patients may see a significant worsening of anaemia and/or fatigue upon dose escalation.

The results of the economics model showed that pathways involving dose escalation would be cost-effective should the cost per QALY threshold be £30,000 or above. Treatment with sunitinib after progressing on imatinib at 400mg/day was not likely to be cost-effective. However, this result was based on limited non-comparative data for this treatment and is probably unreliable.

There are a number of remaining uncertainties, including:

- The results are suggestive of a benefit from dose escalation but the non-randomised, non-comparative data available for review are potentially biased. This limits the usefulness of both the review of effectiveness and the economic model.

- There was a lack of evidence on quality of life outcomes, which would have informed the economic model, but would also be of importance to patients.
- There was little evidence on response and survival on escalated doses of imatinib, specifically for those with different mutations in the KIT gene.
- There is uncertainty surrounding the effects of dose modifications and potential differential effects of sunitinib for both the population being given this drug because of intolerance to imatinib and those receiving sunitinib after failure on imatinib.
- There is also uncertainty surrounding the nature and severity of adverse events and their impact on quality and quantity of life and costs.

Conclusions

Implications for service provision

- There was very limited evidence available from very few studies on the effects of escalated doses of imatinib or treatment with sunitinib for the target population. The evidence that was available was essentially observational in nature and subject to the biases associated with such data, consisting mostly of reporting of subgroups of patients in RCTs that were not designed to assess the effects of dose escalation.
- The limited evidence base suggests that around one third of patients with unresectable and/or metastatic GIST who have failed on a dose of 400 mg/day, may show response or stable disease with escalated doses of imatinib, and those who do respond may have a reasonable chance of maintaining this response over a longer period of time than would otherwise have been the case.
- For all patients receiving either dose escalated imatinib, or sunitinib, median overall survival, where reported, was less than two years.
- Although the results should be interpreted with caution due to the limitations of the evidence base, should society's threshold for willingness to pay be less than £25,000 per QALY a pathway of best supportive care only has the highest probability of being cost-effective. Between a threshold of £25,000 and £45,000 provision of an escalated dose of imatinib would be most likely to be cost-effective. Above a threshold of £45,000 a threshold a pathway of escalated doses of imatinib followed by sunitinib, if necessary would most likely to be cost-effective.

Recommendations for research

Suggested priorities for further research are made:

- An RCT involving patients who progress on 400 mg/day imatinib where patients are randomised to pathways describing alternative combinations of dose escalation with imatinib and the use of sunitinib should be performed. The pathways most likely to be cost-effective at thresholds society might be willing to pay and hence potentially the most useful to assess were: dose escalation with imatinib and dose escalation with imatinib followed by sunitinib if necessary. A trial should include an economic evaluation and measurement of health state utilities and have sufficiently long enough follow-up to capture all outcomes of interest.
- Where possible further studies should also report outcomes for subgroups of patients with specific KIT mutations.
- In any prospective comparative study a wider perspective on the consideration of costs might also be informative (e.g. costs that fall on personal social services, which would be relevant for NICE to consider, and costs for patients and their families, which goes beyond NICE's reference case).

3 BACKGROUND

3.1 Description of health problem

3.1.1 Introduction

Gastrointestinal stromal tumours (GISTs) are tumours of mesenchymal origin that arise in the gastrointestinal tract (GI tract). Historically and based upon morphological appearance alone, GISTs were considered to be of smooth muscle origin and regarded as leiomyomas or leiomyosarcomas. Subsequently, electron microscopic and molecular analysis has demonstrated that GISTs are a distinct tumour type arising from the interstitial cells of Cajal (ICC), and characterised by the expression of receptor tyrosine kinase KIT (CD117) protein demonstrated by immunohistochemistry.[1] CD117/KIT immunoreactivity now provides the diagnostic criteria for GISTs, although there is recognition that a small proportion of GISTs (4%) are KIT immunoreactive negative.[2,3]

3.1.2 Aetiology, pathology, and prognosis

Recent investigation has provided clinically significant insights into the molecular pathogenesis of GISTs. This has allowed the rational development of systemic therapies (including imatinib and sunitinib); provided robust diagnostic criteria for GISTs; and demonstrated the ability of certain pathogenic gene mutations to predict clinical behaviour and response to therapy in GISTs which therefore have potential application as predictive biomarkers.

Activating mutations in the *KIT* proto-oncogene are an early and key event in the pathogenesis of GISTs, and present in up to 95% of cases.[4-10] The protein product is a member of the receptor tyrosine kinase family and a transmembrane receptor for stem cell factor (SCF).[11] Extracellular binding of SCF to the receptor results in dimerisation of KIT and subsequent activation of the intracellular KIT kinase domain[9] leading to activation of intracellular signaling cascades controlling cell proliferation, adhesion, and differentiation. *KIT* mutation is necessary but not sufficient for GISTs pathogenesis, other mutations are essential, and KIT mutation is absent in a minority of cases (<5%).[12,13] In the majority of KIT mutation negative cases, mutational activation of the closely related tyrosine kinase Platelet Derived Growth Factor Receptor Alpha (PDGFRA) is the pathogenic event and KIT and PDGFRA activation have similar biological effects.[12,13]

It has been demonstrated that KIT and PDGFRA gene mutations are mutually exclusive[7,8,10,14] and GISTs with no *KIT* mutations have either PDGFRA-activating mutations or no identified kinase mutations.[13] GISTs that lack *KIT* mutations may still have high KIT kinase activity

and so may have *KIT* mutations that are not detected by conventional screening methods. Alternatively, KIT kinase activation may be due to non-mutational mechanisms.[6]

Diagnosis of GIST is made when morphological and clinical features of the tumour are consistent and the tumour has positive KIT/CD117 protein expression.[15] However, as noted above, approximately 4% of GISTs have clinical and morphological features of GIST but have negative KIT immunoreactivity.[2] These KIT negative GISTs are more likely to contain PDGFRA mutations.[2] It is important in these cases, when KIT/CD117 staining is negative, that other markers are investigated to confirm GIST diagnosis. Recent studies have shown that a novel protein DOG1, is highly expressed in both *KIT* and *PDGFRA* mutant GISTs [16,17] and immunostaining for DOG1 can be used in conjunction with CD117 staining, and diagnosis of GIST made on the basis of KIT and/or DOG1 immunoreactivity.[15] PDGRFA immunohistochemistry should also be performed and positivity can assist with diagnosis. Mutational analysis also plays a role in the diagnosis of KIT/CD117 negative suspected GISTs, as with consistent morphological and clinical features, positive mutation analysis for either KIT or PDGFRA is diagnostic.[15]

Without treatment GISTs are progressive and will eventually metastasise to distant organs and so are invariably fatal without any intervention. GISTs are resistant to 'conventional' oncology treatments of cytotoxic chemotherapy and radiotherapy. Prognosis is highly dependent on the resectability of the tumour, however only 50% of GIST patients have resectable disease at first presentation.[18,19] Ten year survival for resectable/non-metastatic tumours is 30-50%, and at least 50% will relapse within 5 years of surgery, but for unresectable tumours, prognosis is very poor with survival generally less than 2 years without further treatment.[18,19]

3.1.3 Epidemiology and incidence

While GISTs are the most common mesenchymal tumour of the GI tract, overall they are a rare cancer accounting for less than 1% of all cancers of the GI tract.[20] GISTs can occur anywhere in the GI tract from the oesophagus to the rectum, but most arise in the stomach or small intestine.[21] They are rare before the age of 40 years and very rare in children with a median age at diagnosis of 50-60 years.[22,23] Some data show a slight male predominance but this is not a consistent finding.[22,24,25]

Retrospective studies carried out using KIT immunoreactivity as a diagnostic criterion have shown that GISTs have been under-diagnosed in the past.[26,27] These retrospective population-

based reclassification studies provide the most reliable and accurate current estimate of an annual incidence of 15 cases per million, which would equate to 900 cases in the UK. [15]

3.1.4 Impact of health problem

The symptoms of GISTs depend on the size and location of the primary tumour and any metastatic deposits. While one third of cases are asymptomatic and discovered incidentally during investigations or surgical procedures for unrelated disease, severe and debilitating symptoms occur in many patients and are invariable in those patients who have (or develop) metastatic disease.[28]

GISTs less than 2 cm in size with no metastatic disease are usually asymptomatic. Larger primary tumours and those of patients with metastatic disease are usually symptomatic and the most common symptom is GI tract bleeding, which occurs in 50% of patients, 25% of these patients presenting as emergencies with acute GI haemorrhage, either into the intestine or peritoneum.[29] Abdominal discomfort is a feature of larger tumours.[30] Oesophageal GISTs typically present with dysphagia, which represents the main symptomatic problem in these cases and colorectal GISTs may cause bowel obstruction. In metastatic disease debilitating systemic symptoms such as fever, night sweats, and weight loss are common.

3.2 Current service provision

3.2.1 Management of disease

There is wide consensus that the management of GISTs should be undertaken in the context of discussion of individual cases by a multidisciplinary team.[15,31]

3.2.1.1 Management of resectable disease

Surgical resection is the primary treatment for GISTs and offers the only possibility of cure. Surgical resection is undertaken with the aim of achieving a complete microscopic resection (R0 resection). Evaluation of the suitability and possibility of a complete microscopic resection of a GIST is made after appropriate pre-operative assessment to determine stage and also the fitness of the patient for the procedure required. Preoperative assessment for staging includes (as a minimum) a CT scan of the chest, abdomen and pelvis, and in specific circumstances there is a role for endoscopic ultrasound, laparoscopy and angiography.

After resection patients are followed up with protocols involving clinical examination and/or surveillance imaging, based upon relapse risk stratification by means of histopathological criteria of the resected tumour.[15,32] Preliminary results from one randomised, placebo-controlled phase III trial suggest that adjuvant therapy with imatinib (400mg/day for one year)

increases recurrence-free survival following resection, and it is therefore suggested that adjuvant imatinib may have an important role to play in the prevention of recurrence of GISTs after resection.[33] The results of other similar adjuvant trials are awaited.[15] At present UK guidelines recommend adjuvant imatinib (400mg/day) in patients considered to be of moderate or high-risk of relapse, according to histopathological criteria.[15] However it is acknowledged that, until more data are available from ongoing adjuvant studies, there is still uncertainty regarding the optimal duration of treatment, and also the sub-groups of patients who may or may not benefit from adjuvant therapy. The use of imatinib as an adjuvant therapy may have implications, for example with regard to the development of drug resistance, for the subsequent systemic treatment of GISTs upon recurrence.[34]

Studies are ongoing to determine the role of imatinib as preoperative therapy in resectable tumours.[35] Nevertheless, the use of imatinib preoperatively to downstage tumours from unresectable to resectable is considered safe and clinically worthwhile.[15] Similarly, preoperative imatinib has also been recommended to limit the extent and (accordingly) morbidity of resection in specific circumstances, for example to facilitate sphincter sparing resection in rectal GISTs.

3.2.1.2 Management of unresectable and metastatic disease

Conventional cytotoxic chemotherapy and radiotherapy are ineffective in the treatment of advanced GISTs. Similarly, initial debulking surgery is not recommended unless there is an immediate clinical need, such as to remove an obstructing tumour.

Imatinib (Glivec®) is a rationally-designed small molecule inhibitor of several tyrosine kinases including KIT and PDGFRA and has provided the first clinically effective systemic therapy for GISTs. The European license for imatinib was based on a phase II study of 147 patients who were randomised to receive either imatinib at 400 mg or 600 mg orally taken once daily.[36] The treatment was well tolerated, objective response rate was the primary efficacy outcome and an overall partial response rate of 67% was demonstrated with no difference between treatment arms. Long-term results revealed median survival of 57 months for all patients.[37] A concurrent study investigated dose escalation and established 800 mg daily as the maximum tolerated dose.[38] Phase III trials performed both in Europe and Australasia (EORTC 62005 study), and in North America (S0033 Intergroup study) confirmed the efficacy of imatinib in a larger patient population, and established the starting dose of 400mg orally per day.[39,40]

Primary resistance to imatinib is uncommon, but acquired resistance is inevitable, and manifest clinically by the observation of disease progression.[39-43] Guidelines suggest that patients should have a CT scan every three months while on therapy.[15] Measurement of response by conventional criteria such as Response Evaluation Criteria in Solid Tumors (RECIST), based on objectively measured changes in tumour size, may not occur, or may only happen after many months of treatment. This means that definitive evidence of patient response, and therefore clinical benefit, can be difficult to ascertain (at least initially). This has been addressed by the development of alternate methods of GIST response assessment, such as the 'Choi criteria' based upon tumour density as well as tumour size.[44,45] Similarly, FDG-PET has demonstrated some efficacy in predicting early response to imatinib therapy.[46]

In addition, the assessment of progression of GISTs may be problematic, based on RECIST based tumour size criteria as tumour liquefaction (cystic degeneration) can occur which may give the appearance of progressive disease although the tumour is actually responding.[45] Accordingly, it is recognised that experienced radiologists should assess CTs before confirming progression.

It has been demonstrated that interruption of treatment results in rapid disease progression in many patients with advanced GISTs.[43] This includes patients with disease progression where a symptomatic worsening or 'flare' has been described.[47] Therefore continuation of imatinib in these patients has been common practice despite progression, as part of best supportive care.

Several studies have reported further disease control after progression on an initial imatinib dose of 400 mg orally per day, with dose escalation of imatinib to 800 mg orally per day and this has also become common practice.[37,42] However, it should be noted that current NICE guidelines for imatinib do not actually recommend dose escalation for unresectable and/or metastatic GIST patients who progress on an initial dose of 400 mg/day.[48]

Recently, additional molecular-based treatments for GIST have become available, including sunitinib (Sutent®), which has been approved by NICE for patients with unresectable and/or metastatic GIST who have progressed on treatment imatinib.[49] The NICE advice follows a randomised, double-blind, placebo-controlled, multicentre phase II trial in which 312 patients who were resistant or intolerant to imatinib, received either sunitinib (50 mg starting dose in 6 week cycles; 4 weeks on and 2 weeks off treatment) or placebo,[50] was unblinded early when interim analysis showed a significantly longer time to tumour progression (the primary endpoint) with sunitinib.

To date, no randomised trial has been conducted comparing imatinib and sunitinib. One had been planned but was stopped due to poor recruitment.[51] As new options for management of patients with unresectable and/or metastatic GIST have developed since the initial 2004 publication of NICE guidance for GIST treatment with imatinib, a review of the evidence available on treatments currently used in clinical practice is required.

3.2.2 Current service cost and anticipated costs associated with the intervention

As GIST affects mostly the middle aged and older age population, the loss of productivity from the middle age population suffering from GIST is of concern. The median age of the GIST patients was found to be between 50-60 years,[22,23] and incidence of GIST was found to increase with increase in age.[52] The cost of different treatment strategies needs thorough investigation in a robust economic evaluation.

Treatment with imatinib per patient within an NHS setting has been estimated at £18,896 and £24,368 for patients on 400 mg/day and 600 mg/day respectively[53] Other associated annual costs of treatment (including the treatment of adverse events) were estimated at £2730 (price year not stated). Estimates from previous disease models suggest that in two years it would cost the NHS approximately £31,160 to treat a patient with imatinib, and for ten years this figure would be £56,146 (2002 price year).[52,53] It has also been suggested that the total cost of treatment with imatinib in the NHS (England and Wales), would be between £5.6 million and £11.2 million.[53] Costs would differ when patients who fail to respond to imatinib are provided with higher doses, or alternative treatments (e.g. sunitinib).[48]

The costs of treating unresecetable and/or metastatic GIST using imatinib were estimated at between £1557 and £3115 per month per patient, resulting in a cost to NHS (England and Wales) of between approximately £5.6 million and £11.2 million per year (2002 price year).[53] NICE estimates suggest the number of new cases of unresectable and/or metastatic GISTs to be around 240 people per year. Another study estimates that the total costs over ten years for managing GIST patients with molecularly-targeted treatment would be between £47,521 and £56,146 per patient compared with a cost of between £4047 and £4230 per patient with best supportive care (price year not stated).[52]

3.2.3 Variation in service and uncertainty about best practice

The treatment of GISTs after progression on imatinib is generally decided on a case by case basis by multidisciplinary teams, and the alternatives are; dose escalation of imatinib; sunitinib 50mg/day (4 weeks out of 6), or alternatively best supportive care only (although due to the 'symptomatic flare' already mentioned this may include continuation of imatinib at

400mg/day). Many clinicians advocate initial dose escalation of imatinib and then consider sunitinb on subsequent progression, but there will be variation in clinical practice depending on the specific needs of individual patients.

3.2.4 Relevant national guidelines

UK guidelines recommend the dose escalation of imatinib, and/or sunitinib following imatinib failure,[15,54] but also suggest clinical decisions are made on an individual case by case basis, reflecting uncertainty regarding optimal practice.

3.3 Description of technology under assessment

3.3.1 Summary of intervention

3.3.1.1 Imatinib

Imatinib (Glivec®) is a rationally designed small molecule inhibitor of several oncogenic tyrosine kinases - c-Abl, ARG, PDGFR, and the KIT tyrosine kinases. Its therapeutic activity in GISTs relates to inhibition of KIT, although in cases with no KIT mutation, inhibition of PDGFRA is likely to be of therapeutic importance[2] Imatinib is a derivative of 2-phenylaminopyrimidine, and a competitive antagonist of ATP binding which blocks the ability of KIT to transfer phosphate groups from ATP to tyrosine residues on substrate proteins. This interrupts KIT-mediated signal transduction which is the key pathogenic driver for many GISTs. The inhibitory activity of imatinib on KIT is highly selective, and minimal inhibition of other kinases that are important in normal cell function occurs, thereby affording a good toxicity and safety profile.

Imatinib is licensed and approved for use in the NHS in KIT immunoreactive positive advanced/unresectable GISTs.[48,55]

3.3.1.2 Sunitinib

Sunitinib malate (SUTENT), is a tyrosine kinase inhibitor targeting KIT, PDGFRA, all three isoforms of vascular endothelial growth factor receptor (VEGFR), FMS-like tyrosine kinase 3 (FLT3) colony-stimulating factor 1 receptor (CSF-1R) and glial cell line-derived neurotrophic factor receptor.[56] Sunitinib activity in GISTs may predominantly relate to inhibition of KIT and/or PDGFRA, and ex-vivo investigation has shown that sunitinib can inhibit the kinase activity of KIT molecules harbouring secondary mutations conferring imatinib resistance.[57] However the potent anti-angiogenic activity of suntinib as a consequence of strong VEGFR inhibition may also be important for clinical activity in GISTs.

3.3.1.3 Best supportive care

Best supportive care is not well defined or standardised, and can also be referred to as "supportive care" or "active symptom control".[53] It usually involves interventions to manage pain; treat fever, anaemia (due to GI haemorrhage) and GI obstruction[48] and can include palliative measures.[58] A Cochrane review of supportive care for gastrointestinal cancer patients defined supportive care as "the multi-professional attention to the individual's overall physical, psychosocial, spiritual and cultural needs".[59] It was argued that this type of care should ethically be made available to all treatment groups, meaning that in clinical practice for GIST patients, treatment with imatinib or sunitinib could not be provided without concomitant 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.

3.3.2 Identification of important subgroups

The differential benefit from imatinib and sunitinib in subgroups of GIST patients whose tumours have different primary and secondary KIT mutations has suggested possible benefits in personalising first and second line therapy.

Primary KIT mutations are those that are pathogenic and present before any systemic treatment, while secondary mutations are those that have been identified after imatinib treatment and confer resistance to imatinib. Identification of secondary mutations requires rebiopsy of tumours, and studies have suggested that the emergence of secondary (or acquired) imatinib resistance is polyclonal, so GIST patients may acquire more than one secondary KIT mutation.[60]

A meta-analysis of 1640 patients revealed that patients with *KIT* exon 9 primary mutations have a better outcome if treated at the escalated dose of 800 mg daily.[61] Similarly, objective response rates to imatinib 400mg/day are higher in patients with exon 11 primary mutations compared to those with exon 9 mutations, or those with no detectable KIT or PDGFR mutation.[14,39] Therefore, advanced GIST patients with exon 9 mutations may benefit from immediate dose escalation of imatinib, and the benefit of dose escalation on progression may be more significant in this subgroup of patients and thereby have implications for therapeutic alternatives and choices on progression in different groups of patients defined by KIT mutations.

Secondary mutations in KIT exons 13, 14, 17 and 18 are associated with acquired resistance to imatinib.[41] Sunitinib activity after progression on imatinib has been demonstrated in GIST patients with imatinib resistance conferring secondary KIT mutations.[60] However, both the

primary KIT mutation genotype and secondary KIT mutations may influence the clinical benefit effect of sunitinib in GIST patients who have progressed on imatinib.[60] Interestingly, in contrast to imatinib, greater benefit from sunitinib (after imatinib failure) is seen in patients with primary exon 9 mutations or wild-type KIT as opposed to primary exon 11 mutations.[60] However it is not clear how dose escalated imatinib (800mg/day) compares to sunitinib in patients with primary exon 9 KIT mutation. While the polyclonal emergence of resistance is an investigational and clinical challenge, it appears that GIST patients with secondary *KIT* mutations associated with acquired imatinib resistance in exons 13 or 14 (which involve the KIT-adenosine triphosphate binding pocket) appear to gain greater clinical benefit from sunitinib after imatinib failure, than those patients with exon 17 or 18 imatinib resistance secondary mutations (which involve the KIT activation loop).[60]

Changes in FDG (F-2-fluoro-deoxy-D-glucose) avidity of GISTs measured by FDG-PET occur earlier than anatomical changes in GISTs and so may also have a role as a predictive biomarker for imatinib response, and also for detecting early disease progression.[47]

3.3.3 Current usage in the NHS

Current practice is to commence patients at imatinib 400mg/day, and on confirmed disease progression the options are dose escalation of imatinib up to 800mg/day or sunitinib, or best supportive care only. Practice is variable, and decided on a case-by-case basis. Some clinicians proceed with dose escalation of imatinib initially and then on further progression, use sunitinib. Some guidelines and clinicians advocate returning to imatinib for symptomatic benefit, when there are no other therapeutic options, and the cessation of imatinib in the absence of alternative treatment options is not recommended due to the tumour flare phenomenon, with rapid deterioration in symptoms observed in some patients.

4 DEFINITION OF THE DECISION PROBLEM

4.1 Decision problem

Specific information on the population, interventions, comparators and relevant outcomes considered for this review are discussed in detail in Section 6.1.1

Until the licensing of imatinib, the prognosis for people with unresectable and/or metastatic GISTs was poor.[19] Since 2002, the clinical effectiveness of treatment for GIST with imatinib at a dose of 400 mg/day has been well documented.[48,53] There is also clinical trial evidence showing that patients with unresectable and/or metastatic GIST can also respond to higher doses of imatinib, up to a maximum tolerated dose of 800 mg/day,[38] and that patients with different exon mutations in the KIT gene may differ in their response to imatinib at both standard and escalated doses.[14]

NICE guidance does not currently recommend the prescription of escalated doses of imatinib upon progression on the standard 400 mg/day dose,[48] although it is common in clinical practice.[15,32] Most of the evidence relating to dose-escalated imatinib comes from randomised trials where participants were randomised to doses greater that 400 mg/day, as opposed to receiving these higher doses upon disease progression on the 400 mg/day dose. However evidence suggests that tolerability of higher doses may depend on the extent of prior exposure to the drug,[62] and if in clinical practice, escalated doses are prescribed upon progression, these trial data may not provide reliable estimates of response, progression-free and overall survival, quality of life effects or the extent of adverse event occurrence. In addition, if patients with unresectable and/or metastatic GIST are likely to attain different levels of clinical benefit from different imatinib doses, clinicians' decision-making on appropriate dosages for individual patients should be informed by the best available evidence.

The development of imatinib has represented a paradigm shift in the treatment of unresectable and/or metastatic GIST, as prior to its introduction onto the market, the only available treatment remaining for this population group was best supportive care, which, given the severity of this disease, represents essentially palliative intervention. Since the introduction of imatinib, other new treatments for unresectable and/or metastatic GIST have become available, including sunitinib, which has been recommended by NICE as the second line treatment for the population of interest, after failure on treatment with imatinib.[49] As there are now various options available for treating unresectable and/or metastatic GIST, and it is therefore necessary to review the available evidence on imatinib at escalated doses, when

compared with sunitinib, for patients with unresectable and/or metastatic GIST whose disease has progressed on the standard imatinib dose of 400 mg/day.

4.2 Overall aims and objectives

The aim of this review was to assess the clinical and cost-effectiveness of imatinib at escalated doses (i.e. 600 mg/day or 800 mg/day) within its licensed indication,[63] for the treatment of patients with unresectable and/or metastatic GISTs, who have progressed on imatinib at a dose of 400 mg/day.

The objectives of this review will help facilitate decision-making on the most appropriate treatment(s) for patients with unresectable and/or metastatic GIST who have progressed on imatinib at a dose of 400 mg/day, by:

- Conducting a systematic review of the evidence available on the clinical effectiveness of imatinib at dosages of 600 mg/day, or 800 mg/day compared with sunitinib and/or best supportive care
- Conducting a systematic review of the cost-effectiveness of imatinib at dosages of 600 mg/day or 800 mg/day compared with sunitinib and/or best supportive care
- Analysing available outcome data for particular sub-groups of interest (e.g. patients with different KIT mutations) in order to establish any differences in clinical effectiveness for specific groups
- Develop an economic model to compare the cost-effectiveness and cost-utility of using imatinib at a dose of 600 mg/day or 800 mg/day, with sunitinib (within its recommended dose range) or best supportive care only

5 CRITIQUE OF THE MANUFACTURER SUBMISSION

The manufacturer of imatinib (Novartis) did not provide an economic analysis in their submission, stating that due to the limited amount of data available from the key clinical studies and the dearth of data comparing imatinib dose escalation with sunitinib and best supportive care, they were unable to submit a sufficiently robust economic analysis which met the scope for the appraisal. However, they did provide a summary of clinical evidence and implications for the economic analysis. With the exception of the Executive Summary section, and most of the References section, a large proportion of the submission document was highlighted as commercial in confidence. Electronic copies of all the papers cited in the References section, including two labelled as commercial in confidence by the manufacturer, were provided. Apart from both of the commercial in confidence documents, these studies had already been retrieved by our searching process and are discussed in Chapter 6.

Of the two commercial in confidence reports provided, one [redacted] was a report on the randomised, phase II, B2222 trial comparing imatinib at doses of 400 mg/day and 600 mg/day. Patient data from this trial that is relevant to this review has since been published by Blanke and colleagues in the Journal of Clinical Oncology.[37] The remaining commercial in confidence report [redacted] provided a meta-analysis of data from the randomised, phase III, intergroup S0033 trial comparing imatinib at doses of 400 mg/day and 800 mg/day, and the randomised, phase III, EORTC-ISG-AGITG trial also comparing imatinib at these doses. Crossover data from the S0033 trial have been published separately,[39,64] as have crossover data from the EORTC-ISG-AGITG trial.[42] [redacted]

All relevant results pertaining to the population of interest for this review have been provided in Chapter 6 (Assessment of Clinical Effectiveness). [redacted] but as more recent results for the study population of interest has been published, only study characteristics information was used in Chapter 6 (Assessment of Clinical Effectiveness) of this review.

The key points made in the manufacturer submission were as follows:

- The limited amount of data available from the key clinical studies and the paucity of data comparing imatinib dose escalation with sunitinib and best supportive care prevent, in the opinion of the manufacturer, the submission of a sufficiently robust economic analysis which meets the scope of the appraisal.
- There are currently no head-to-head trial data comparing imatinib with sunitinib.
- Sunitinib represents a third line treatment, rather than second line as per the scope of the evaluation, making it difficult, if not impossible, to conduct a robust and plausible indirect comparison of the two technologies. UK National GIST Guidelines recommend that changing treatment to sunitinib should only be considered after patients have shown progression on imatinib dose escalation.
- Since the publication of TA86 clinical practice has evolved to consider dose escalation to a daily dose of 600 mg or 800 mg, when patients progress on the standard daily dose of 400 mg, and this change in clinical practice is reflected within UK National GIST Guidelines.[54]

[redacted]

6 ASSESSMENT OF CLINICAL EFFECTIVENESS

6.1 Methods for reviewing effectiveness

6.1.1 Identification of studies

Extensive sensitive electronic searches were conducted to identify reports of published and ongoing studies on the clinical effectiveness of imatinib. The searches were also designed to retrieve clinical effectiveness studies of the comparator treatments (sunitinib and best supportive care). In addition, reference lists of retrieved papers and submissions from industry and other consultees were scrutinised to identify additional potentially relevant studies.

The databases searched were: Medline (1966 - September Wk 3 2009), Medline In-Process (25th September 2009), Embase (1980 – Week 39 2009), CINAHL (September 2009), Science Citation Index (2000 - 26th September 2009), Biosis (2000 - 24th September 2009), Health Management Information Consortium (September 2009), and the Cochrane Controlled Trials Register for primary research and the Database of Abstracts of Reviews of Effects (DARE) (October 2009), the Cochrane Database of Systematic Reviews (CDSR) (Issue 3 2009) and the HTA database for relevant evidence syntheses (October 2009).

Ongoing and recently completed trials were searched in the following 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. Recent conference proceedings of key oncology and gastrointestinal organisations, including the American Society for Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO) and the European Cancer Organisation. Websites of the GIST Support International, and the drug manufacturers Pfizer and Novartis were also scrutinised.

Full details of the search strategies used are reproduced in Appendix 1.

6.1.2 Inclusion and exclusion criteria

Types of studies

An initial scoping search suggested that there would be few studies looking specifically at either of the named interventions (imatinib 600 mg/day or 800 mg/day). Therefore we considered all of the following types of studies for the assessment of clinical effectiveness:

1. RCTs;
2. Non-randomised comparative studies; and
3. Case series.

If the number of studies meeting our inclusion criteria was sufficiently large, consideration was to be given to limiting them by type of study design, and also possibly other factors (e.g. sample size). Additionally, it was planned to exclude non-English language papers, and/or reports published as meeting abstracts if the evidence base of English language and/or full text reports was sufficiently large.

- ***Types of participants***

Participants considered were people with KIT (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST), whose disease had progressed on treatment with imatinib at a dose of 400 mg/day. If sufficient evidence was available, sub-group analysis was to be undertaken for those patients with different mutations of CD117, as there is some evidence to suggest this may affect their response to escalated doses of imatinib[14,39,61]- see background section 3.3.2. In addition, sub-group analysis was also to be undertaken on methods used to identify response or resistance (e.g. FDG-PET or CT scanning) and the use of imatinib in a neoadjuvant or adjuvant setting for patients with previously resectable GIST, where sufficient data were available.

- ***Types of intervention and comparators***

The interventions considered were imatinib at escalated doses of 600 mg/day and 800 mg/day respectively, being prescribed with best supportive care. The comparators considered were sunitinib, prescribed within its recommended dose range of 27-75 mg and provided with best supportive care, and best supportive care only. As previously stated, best supportive care is defined as "the multi-professional attention to the individual's overall physical, psychosocial, spiritual and cultural needs".[59]

- ***Types of outcomes***

For the assessment of clinical effectiveness, the following outcomes were considered:

- Overall response
- Overall survival
- Disease-free survival
- Progression-free survival
- Time to treatment failure
- Health-related quality of life (e.g. EQ-5D scores)
- Adverse effects of treatment (e.g. number of discontinuations due to adverse events)

- ***Exclusion criteria***

We excluded studies of animal models, preclinical and biological studies, reviews, editorials, opinions, case reports, and reports investigating technical aspects of the interventions.

6.1.3 Data extraction strategy

The titles and abstracts (where available) of all records identified by the search strategy were screened by two reviewers independently. Full-text copies of all potentially relevant reports were retrieved. The full-text reports were assessed against the inclusion and exclusion criteria by two reviewers independently. Full-text papers and conference abstracts were assessed using a screening form that was developed and piloted for this purpose. Any disagreements were resolved by consensus or arbitration by a third party. A copy of the screening form used can be found in Appendix 2.

A data extraction form was developed and piloted (Appendix 3). One reviewer extracted details of the study design, participants, intervention, comparator and outcomes and a second reviewer checked the data extraction for accuracy. Any disagreements were resolved by consensus or arbitration by a third party.

6.1.4 Quality assessment strategy

Two reviewers independently assessed the methodological quality of the included full-text studies. Non–randomised comparative studies were assessed using an 18-question checklist, with the same checklist minus four questions used to assess the methodological 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,[65] Verhagen and colleagues,[66] Downs and Black,[67] 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.

We planned to assess the quality of RCTs using the Cochrane Collaboration's tool for assessing risk of bias.[68] The tool addresses six specific domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other issues. Each quality assessment item had three possible responses; "Yes", "No" or "Unclear", with space

for additional comments. Disagreements between reviewers over study quality were to be resolved by consensus and if necessary, arbitration by a third party. Abstracts were not quality assessed because they were considered unlikely to provide sufficient methodological information to enable an accurate assessment of study quality. Methodological quality did not form part of the criteria for the inclusion or exclusion of studies. A copy of the quality assessment tool can be found in Appendix 4.

6.1.5 Data analysis

The type of data analysis considered was dependent on the number of studies meeting the specified inclusion criteria, and study design. Where a quantitative synthesis was considered inappropriate or not feasible, it was planned that a narrative synthesis of results would be provided instead.

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

The pooled weighted ratio of median survival was to 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 would be extracted directly from the trial publications, but if not reported it would be extracted if possible from other available summary statistics or from data extracted from published Kaplan-Meier curves using methods described by Parmar and colleagues.[69] A pooled HR from available RCTs could then 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.[70] A weighted average of survival duration across studies was to be calculated. The chi square test for heterogeneity was to be used to test for statistical heterogeneity between studies.

Where no RCT data were available, but non-randomised studies had reported relevant data for survival outcomes, assessment of the risk of bias and heterogeneity was to be undertaken using meta-regression analysis.

It was expected that few studies, if any would report direct comparisons of the intervention and comparators, so (depending on feasibility, and appropriateness) it was decided that where non-randomised evidence was available, meta-analysis models would be used to model survival rates for interventions and comparators. A "cross design" approach was to be adopted to allow non-randomised evidence to be included, whilst avoiding the strong assumption of the equivalence of studies. Evidence suggests that this approach would allow data from RCTs, non-randomised comparative studies and case-series to be included.[71] Differences between treatments for survival outcomes were to be assessed via the corresponding odds ratio and 95% credible intervals. These results are "unadjusted odds ratios", but meta-analysis models adjusting for study type were also to be used. The results from these models produce "adjusted" odds ratios.[72] WinBUGS software was to be used for the analysis.

Any reported data on adverse effects of treatment and quality of life (QoL) that were collected were to be combined, using standardised mean difference, where appropriate.

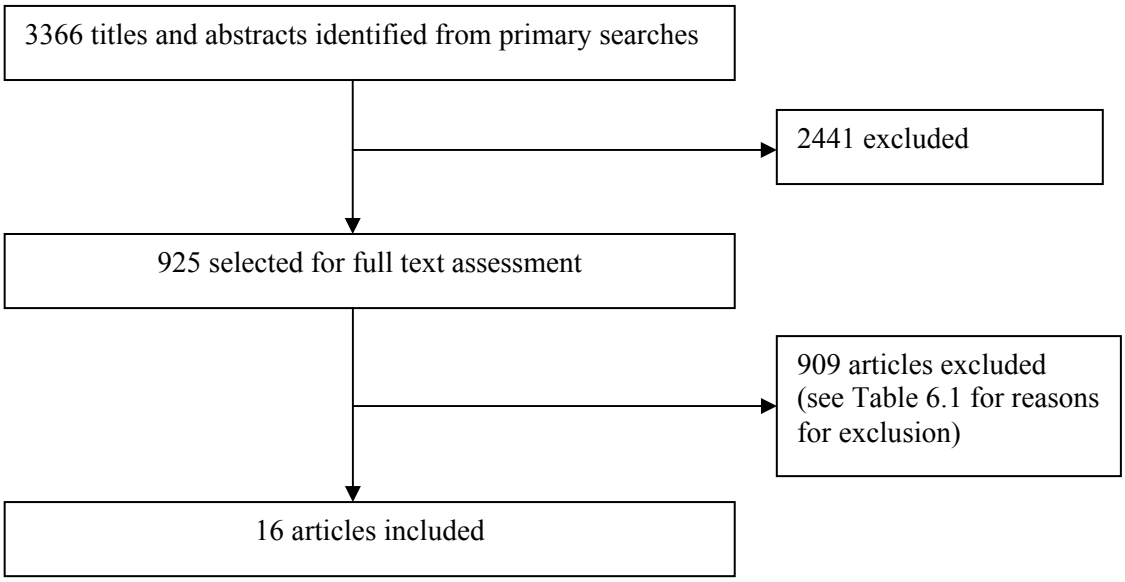
In addition, and taking into account the type of evidence, the feasibility of using a mixed treatment comparison model for indirect comparisons was to be considered.

6.2 Results

6.2.1 Number of studies identified

We identified 3366 records from the primary searches for the review of clinical effectiveness. After title and abstract screening, 2441 articles were considered not to be relevant for this review and were excluded. The full text papers of 925 records were obtained and screened. One hundred and twenty-three of these full-text papers were non-English language publications. In total, six full-text papers and ten abstracts reporting four separate clinical trials and one additional retrospective cohort, met our inclusion criteria. An additional 49 papers were retained for background information. The reasons for exclusion of assessed full-text papers are given in Table 1. A flow diagram of the screening process is outlined in Figure 1 below. Information on the reasons for excluding individual studies is provided in Appendix 5.

Figure 1 Flow diagram outlining the screening process for the review of clinical effectiveness



6.2.2 Included studies

See Appendix 6 for a list of studies that were included in the review of clinical effectiveness. We did not identify any RCTs, or non-randomised comparative studies comparing the effectiveness of escalated doses of imatinib (600 mg/day or 800 mg/day) with sunitinib or best supportive care, that met our inclusion criteria. One on-going trial was identified comparing imatinib and sunitinib. However, this study was stopped due to poor recruitment. We identified five full-text reports of three randomised trials of imatinib that contained relevant data for this review.[14,36,37,39,42] The studies by Zalcberg and colleagues,[42] Blanke and colleagues (S0033)[39] and Blanke and colleagues (B2222)[37] were designated as the primary reports for the EORTC-ISG-AGITG (62005) trial, the S0033 trial and the B2222 trial respectively. The study by Debiec-Rychter and colleagues[14] met our inclusion criteria and provided additional information from the EORTC-ISG-AGITG (62005) study on response following crossover, whilst the study by Demetri and colleagues[50] met our inclusion criteria and provided interim data from the B2222 trial on response following crossover.

An additional three abstracts were identified, with two[64,74] reporting interim data for the S0033 trial, and one reporting interim data for the EORTC-ISG-AGITG 62005 trial.[75]

All of these included studies contained a treatment arm of 400 mg/day, and reported data separately for participants who received an escalated dose of imatinib upon progression at this randomised dose. One additional full-text paper detailing the results of a non-randomised retrospective study by Park and colleagues[73] was also included. This study met our inclusion

criteria as it also provided separate outcome data for metastatic or unresectable GIST patients who received escalated doses of imatinib on progression at an initial dose of 400 mg/day.

For the comparator treatment of sunitinib, we identified seven abstract reports meeting our inclusion criteria. All were interim results of an on-going, open-label sunitinib trial reporting information on participants recruited to the trial following failure at different doses of imatinib, including doses of ≤400 mg/day.[76-82] We designated the abstract by Seddon and colleagues[82] to be the primary report for this trial, as it was thought to contain its most recent results.

For the comparator treatment of best supportive care, no randomised, non-randomised or case series studies were identified that compared either of the interventions (imatinib at a dose of 600 mg/day or imatinib at 800 mg/day) with best supportive care, or provided data on relevant outcomes for the population of interest for best supportive care only. It should be noted that studies published on the clinical effectiveness of best supportive care prior to the licensing of imatinib[18,19] were not eligible for this review as our population of interest was those who had failed on imatinib at 400 mg/day, therefore all studies published prior to the availability of imatinib automatically failed to meet our inclusion criteria because best supportive care at that time could not possibly have been provided following failure of treatment with imatinib at a dose of 400 mg/day.

Corresponding authors for each of the included trials were contacted in order to determine whether any additional data could be provided specifically for the population of interest (i.e. those participants failing on an imatinib dose of 400 mg/day and receiving either an escalated dose of imatinib 600 mg/day or 800 mg/day, or alternatively, sunitinib). For the ongoing, open-label sunitinib study, the corresponding author replied that no further information could be provided as the study was an official, ongoing trial by the manufacturer (Pfizer). For the imatinib trials, in the case of both studies by Blanke and colleagues[37,39] our requests for information were forwarded to the statistics team involved in the trials. The requested data for the S0033 trial were provided on the 17th February 2010. For the study by Zalcberg and colleagues, a response to our request was received, explaining that an official data request form must be completed. This has been submitted and we are presently awaiting a response.

Two additional reports [redacted] to the ones identified through our search strategy were provided for this review by the manufacturer and have been

discussed in Chapter 5, and are also discussed below. Both of these reports were marked as commercial in confidence.

6.2.3 Excluded studies

A list of 340 studies, originally identified as potentially relevant but subsequently failing to meet our inclusion criteria is provided in Appendix 5. The studies were excluded because they failed to meet one or more of the inclusion criteria in terms of the type of study, participants, intervention, comparator, or outcomes reported. In addition, the types of participants were limited to an adult population; therefore studies involving paediatric GIST patients were excluded. However, it should be noted that the age range provided in the baseline data for the included study by Seddon and colleagues[82] indicates that at least one child was recruited onto this trial, but as the median age reported indicates that the majority of patients in this trial were adults, the study was not excluded.

Studies with a relevant population of fewer than ten patients were also excluded. Changes to our original protocol were reported to NIHR in a progress report submitted on the 9th of December 2009.

In addition to the included studies identified above, nine studies (reported in 14 papers) reported sufficient information with regard to our inclusion criteria to be considered for potential inclusion in this review, subject to clarification from the study authors regarding specific aspects of the study. Corresponding authors for each of the nine studies were therefore contacted. Responses were received from four corresponding authors [personal communication, GD Demetri, YK Kang, P Rutkowski, and P Wolter]. In the cases of two responses, this resulted in the exclusion of the studies (five papers in total) from the review.[personal communication, P Rutkowski and P Wolter] In the remaining two studies (four papers), the responses did not result in clarification, as the authors requested that we wait for a further response from them or their colleagues.[personal communication, GD Demetri and YK Kang]. In the case of correspondance with YK Kang, it was decided that the study by Park and colleagues[73] could be included in the review without further clarification from the corresponding author.

Of the correspondences that did not result in responses, one email could not be sent successfully[83] and the remaining four authors did not respond.[84-87]

Table 1 Reasons for exclusion of studies

Reason for exclusion	Number of studies excluded
Patient had resectable GIST	24
Outcomes not reported separately for GIST patients	11
<10 patients in relevant study population	46
Imatinib dose is 400 mg/day	13
No/insufficient data reported for escalated dose patients	66
No imatinib dose reported	83
No relevant interventions	15
Treatment not evaluated	11
No outcomes of relevance	10
Other reason	61
	340
Retained for background information	49
Review articles	169
Letter/editorial/correspondence/symposium articles/meeting reports/expert views/comments	117
Case study/ case series<10 patients	64
Non-English language exclusions	123
Not obtained	47
Total	***909***

6.2.4 Characteristics of the included studies

Study characteristics data were available for the four full-text included imatinib studies[37,39,42,73] and the primary report of the included sunitinib trial.[82] However, of these studies, only the studies by Zalcberg and colleagues, and Park and colleagues gave specific baseline information for the crossover subgroup of interest. Therefore, Table 2 provides details of all characteristics information provided for each crossover group, whilst Table 3 provides details of the same characteristics for all patients in the treatment arms of interest (initial randomisation to a dose of 400 mg/day). In the case of the EORTC-ISG-AGITG trial reported by Zalcberg and colleagues, relevant study characteristic data for participants initially randomised to the 400 mg/day dose were not available. However, these data were reported in a paper by Verweij and colleagues,[40] for the same trial. The paper by Verweij and colleagues failed to meet the inclusion criteria for this review as it did not provide any outcome data for patients receiving an escalated dose of 800 mg/day imatinib upon

progression at a 400 mg/day dose, but as it provides information on the characteristics of all randomised patients (of whom a proportion went on to receive an escalated dose of 800 mg/day and formed the study population of the included study by Zalcberg and colleagues), it was felt that the baseline data from this excluded study could still be used.

Table 2 Characteristics of the included studies for the population of interest

	Zalcberg 2005[42]	Blanke S0033[39]	Blanke B2222[37]	Park 2009[73]	Seddon 2008[82]
Drug assessed:	Imatinib	Imatinib	Imatinib	Imatinib	Sunitinib
Doses given:	400 mg/day 800 mg/day	400 mg/day 800 mg/day	400 mg/day 600 mg/day	600mg/day 800mg/day	Cycle of 50 mg/day for 4 weeks, then 0 mg/day for 2 weeks
Start Date:	[redacted]	Dec 2000	July 2000	June 2001	Unspecified
End Date:	April 2004	[redacted]	May 2006	June 2006	Dec 2007
Study countries:	Australia, Belgium, Denmark, France, Germany, Italy, The Netherlands, New Zealand, Poland, Singapore, Spain, Switzerland, UK	Canada, US	Finland, US	Seoul, South Korea	Unspecified but "worldwide" and "multicenter"
Number of institutions involved (number of countries involved)	[redacted]	148 (2)	4 (2)	1 (1)	96 (33)
Length of follow up at time of analysis:	median of 25 months (max. of 35 months)	median of 4.5 years	Median of 63 months (max of 71 months)	median of 8 months (range 1.4 to 22.3)	median of 51 weeks (range 0.1 to 159)
Number receiving escalated dose of imatinib after failure of imatinib at 400 mg/day, out of all those randomised to receive 400 mg/day	133/473 (28.1%)	118/345 (34.2%)	43/73 (58.9%)	24/24 (100.0%)	N/A
Number receiving sunitinib after failure of imatinib at ≤400 mg/day, out of all those receiving sunitinib	N/A	N/A	N/A	N/A	351/1117

Four of the included trials reported data for imatinib,[37,39,42,73] whilst the remaining trial reported data for sunitinib.[82] Two of the imatinib trials randomised patients to imatinib doses of either 400 mg/day or 800 mg/day[39,42], one randomised patients to imatinib doses of either 400 mg/day or 600 mg/day.[37] and the other was a retrospective study looking only at GIST patients who had received escalated doses of imatinib at either 600 mg/day or 800 mg/day on progression at a dose of 400 mg/day.[73] The sunitinib trial is an ongoing, non-randomised, open-label study and participants are provided with a six-week cycle of sunitinib, at a dose of 50 mg/day for four weeks followed by two weeks without the drug.[82]

The study start date was reported for three out of the four included imatinib trials[37,39,73] and was made available for the study by Zalcberg and colleagues by the manufacturer [redacted] From this it can be seen that the earliest study start date is that of the study [redacted][37] [redacted]. The included sunitinib abstract did not report a start date.

Three out of the four included imatinib studies reported an end date,[37,42,73] or in the case of the study by Seddon and colleagues, a date for the most recent analysis.[82] The manufacturer also made this information available for the study by Blanke and colleagues [redacted]. The on-going sunitinib trial has the most recent update, whilst the study by Zalcberg and colleagues was completed first, in April 2004.[42]

With the exception of the study by Park and colleagues,[73] which involved one centre in one country, all trials were international and multicentre.[37,39,42,82] with the sunitinib trial involving the most countries[81] and the S0033 trial involving the most institutions.[39] The B2222 trial involved the fewest countries and fewest institutions.[37]

The longest length of follow up occurred in the B2222 trial reported by Blanke and colleagues[37] where patients were followed up for a median of 63 months, whilst the shortest length of follow up was found in the study by Park and colleagues[73] which gave a median follow up for the study population of 8 months.

Among the imatinib trials, 133/473 (28.1%), 118/345 (34.2%), and 43/73 (58.9%) of those initially randomised to imatinib at 400 mg/day progressed and were given an escalated dose.[37,39,42] In the imatinib study by Park and colleagues,[73] the study population comprised only those who were given escalated doses of imatinib so 24/24 (100%) received an escalated dose. In the sunitinib study by Seddon and colleagues, 351/1117 (31.4%) of those who failed on imatinib and were entered into the trial, had failed on a dose of 400 mg/day or less.

Therefore the study with the largest relevant population was the sunitinib trial,[82] whilst the study by Park and colleagues had the smallest study population.[73]

Table 3 Characteristics of the included studies for all participants randomised

	EORTC-ISG-AGITG*[40]	Blanke S0033[39]	Blanke B2222[37]	Park 2009[73]	Seddon 2008[82]
Included in this analysis	**All those randomised to 400 mg/day**	**All those randomised to 400 mg/day**	**All those randomised to 400 mg/day**	**All those who received escalated doses of imatinib on progression at a dose of 400 mg/day†**	**All those receiving sunitinib**
Number included	473	345	73	24	1117
Age in years – median (range)	59 (49-67)	61.9 (18-87)		52 (31-73)	59 (10-92)
Sex (M/F)	283/190	187/158		18/6	665/451
ECOG/WHO Performance Status Score					
0	217			4	420
1	191			18	515
2	48			2	134
≤2	(456)	332			(1069)
>2	17	13			38
Missing					10
Race/ethnicity (N)	Not reported			Not reported	Not reported
White		273			
Black		37			
Asian		25			
Other/Unknown		10			
Number had previous chemotherapy	156 (32.9%)	Not reported		3 (12.5%)	225 (26.8%)
Number having previous radiotherapy	26 (5.5%)	Not reported		Not reported	78 (7.9%)
Number having prior surgery	410 (86.7%)			20 (83.3%)	Not reported

* Baseline data for only the crossover patients from this treatment arm were available and are reported in Appendix 8 (Characteristics of Included Studies)
† Participants in this study were part of a retrospective cohort. Treatment was not randomised. The population of interest received escalated imatinib doses

The Park study[73] had the youngest population, whilst the S0033 trial,[39] had the oldest study population. In [redacted] studies, the number of male patients was higher than the number of female patients, which concurs with the epidemiological trends in gender associated with this disease.

[redacted] studies reported data on the performance status score of participants although the study by Blanke and colleagues for the S0033 trial[39] had combined the ECOG performance status categories 0 to 2. Doing the same for the remaining studies shows that the vast majority of participants, 456/473 (96.4%), 332/345 (96.2%), [redacted], 24/24 (100%) and 1069/1107 (96.6%) in the EORTC-ISG-AGITG trial,[40] S0033 trial[39] B2222 trial, [redacted] Park study[73] and the sunitinib trial[82] respectively, had a performance status score of ≤ 2.

[redacted]

In terms of prior treatment, [redacted] two reported the number having previous radiotherapy,[40,82] [redacted] For the imatinib studies, 3/24 (12.5%), 156/473 (32.9%) and [redacted] of participants had undergone previous chemotherapy in the study by Park and colleagues[73] the EORTC-ISG-AGITG trial and the B2222 trial[40] [redacted] respectively, whilst 26.8% (225/1117) patients had received prior chemotherapy in the study by Seddon and colleagues.[82] With regard to radiotherapy, 26/473 (5.5%) of patients in the EORTC-ISG-AGITG trial[40] and 78/1117 (7.9%) of patients in the sunitinib trial[82] had received prior radiotherapy. [redacted] of participants involved in the B2222 trial reportedly had received prior surgery, [redacted] whilst this figure was 86.7% (410/473) for participants in the EORTC-ISG-AGITG trial,[40] and 83.3% (20/24) in the study by Park and colleagues.[73]

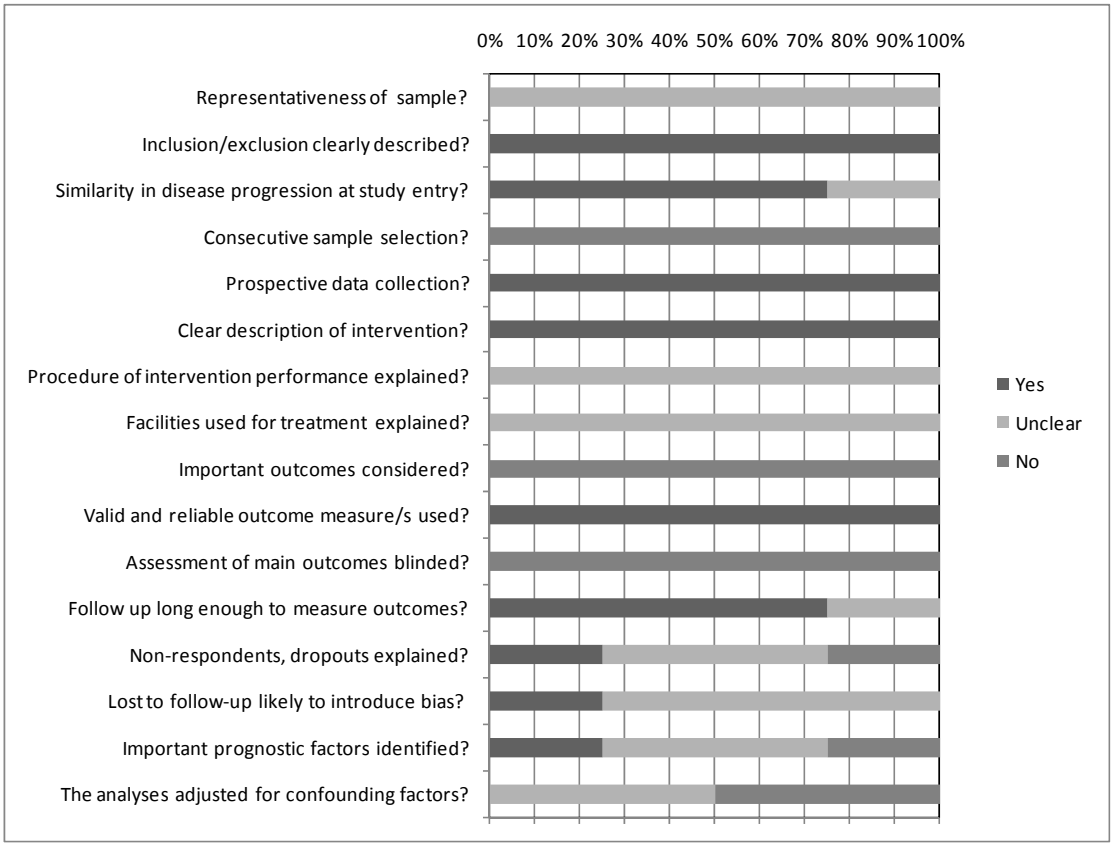
6.2.5 Quality of the included studies

Results of the quality assessment for all four included full-text papers, are summarised in Figure 2. No third party arbitration for quality assessment was required. The results of the quality assessment for each individual study are provided in Appendix 9. Three full-text studies assessed for quality assessment were included in the review because they provided crossover data on a subset of patients who were originally randomised to a dose of 400 mg/day, but progressed and received an escalated dose of either 600 mg/day[37] or 800 mg/day.[39,42] The fourth study[73] was assessed for quality because it included a retrospective analysis of a subgroup of a cohort of patients given treatment with imatinib at 400 mg/day. The subgroup were patients who received escalated doses of 600 mg/day and/or 800 mg/day after progression on the 400 mg/day dose.

As the study populations of interest were not the original randomised populations, but the crossover sub-group in three studies,[37,39,42] and a subgroup of consecutively treated patients in the remaining study,[73] quality was assessed using the checklist for non-randomised studies (detailed in the methods section above). Questions within this checklist which were specific to non-randomised comparative groups (i.e. Q6 and Q16) were not considered applicable to the crossover subset population included in our review, and were therefore not summarised.

However, two specific domains were assessed using the Cochrane Collaboration‘s tool for assessing risk of bias, namely sequence generation and allocation concealment, as these would check for selection bias at trial level.

Figure 2 Quality assessment results summary



Sample definition and selection

In three studies[37,39,42] the included subgroups of participants were randomised at trial level, but crossover patients were not randomly selected, and so it is unclear the extent to which this group can be considered representative of the relevant patient population (Q1). The other study provided inadequate information to allow judgement of the representativeness of sample of the relevant population.[73] With regard to the randomisation process at trial level, the studies by Blanke and colleagues[39] and Zalcberg and colleagues[42] used methods that adequately generated the allocation sequence to avoid influence of confounding factors whilst Blanke and colleagues[37] did not report sufficient data on the randomisation process. In the study by Zalcberg and colleagues,[42] allocation to treatment was not concealed. Both the B2222 and S0033 studies by Blanke and colleagues reported inadequate information on allocation concealment. All four studies adequately described inclusion and exclusion criteria (Q2). We considered the inclusion of only those participants who progressed on 400 mg imatinib with performance status of the disease to be at a similar point in their disease progression at the time of study entry. Three of the studies[37,39,73] involved participants whose performance status at the time of study entry was similar, while the study by Zalcberg and colleagues[42] included participants with different performance status at study entry (Q3), although most of the participants in all populations had an performance status of less than

two, meaning they were ambulatory and awake for at least 50% of their waking hours. None of the studies undertook consecutive selection of patients (Q4). Data were collected prospectively in all of the four studies (Q5).

Description of the intervention

The intervention was adequately defined by all studies (Q7). However, no study provided sufficient data describing supervision of the intervention (Q8) and no information was provided describing the types of staff involved, or the facilities used (Q9).

Outcome assessment

The quality of all four studies was similar in terms of outcome assessment (Q10). None of the studies had considered all the outcomes of interest, but all reported the objective response of escalated imatinib dosing in GIST patients while one[39] reported overall survival and two [39,42] measured progression-free survival. The study by Park and colleagues[73] reported time to progression, and the study by Zalcberg and colleagues was the only study which also reported adverse events for those on an escalated dose of imatinib. No study reported outcomes related to quality of life.

All four studies used valid and reliable outcome measures (Q11), such as Response Evaluation Criteria in Solid Tumors (RECIST) to assess objective response, or Kaplan-Meier methods to estimate survival curves minimising detection bias. Assessment of main outcomes was not blinded in any of the studies (Q12).

Follow up and attrition bias

Follow up was considered long enough to detect important effects on outcomes of interest in all but one study where follow up information was not provided and so this was unclear[73](Q13). Information on those lost to follow up was either not provided [37] or was not provided at a sufficient level of detail[39,42,73] to judge whether those lost to follow up would be likely to introduce bias (Q14 and Q15).

Performance of the analysis

For both studies by Blanke and colleagues, important prognostic factors such as sex, performance status, neutrophils counts etc were investigated and multivariate analyses was performed at trial level but this was not done for the subset of patient who crossed over.[37,39] Similarly, Park and colleagues[73] identified possible prognostic factors (but did not adjust for confounding factors during analysis). The study by Zalcberg and colleagues[42] also did not identify any prognostic factors, their effect on analyses, or adjust for confounding factors

(Q17 and Q18). Hence we considered the quality of reporting ambiguous in terms of the performance of the analyses.

6.2.6 Assessment of effectiveness

Response

For imatinib at an escalated dose of 600 mg/day following progression at a dose of 400 mg/day, response is reported in the B2222 study by Blanke and colleagues, [37] and the study by Park and colleagues.[73] In the study by Blanke and colleagues, the median follow-up at this time was 63 months (maximum 71 months), and at that time, 43 patients had crossed over from 400 mg/day to 600 mg/day. Of these 43 patients, 11 (25.6%) showed either partial response or stable disease[i]. Some of the 43 patients who crossed over would have had an initial response to 400 mg/day before progression, as only 11 patients in the 400 mg/day arm showed a best response of progressive disease.[37] Interim data for this study population are provided in the study by Demetri and colleagues,[36] where, after a median follow up of 288 days (maximum nine months), nine patients had crossed over, with one showing partial response at that point, and two with stable disease.[36]

In the study by Park and colleagues,[73] median follow up was eight months (range 1.4 to 22.3 months) and of the 12 patients who received an escalated dose of of 600 mg/day of imatinib, five (41.7%) showed either partial response or stable disease.

With regard to response data provided by the manufacturer,

[redacted]

[redacted]. As a result, these data from the manufacturer's submission were not used in our review.

For imatinib at a dose of 800 mg/day following progression at a dose of 400 mg/day response data is available from the S0033 study by Blanke and colleagues,[39], the EORTC-ITG-AGITG trial by Zalcberg and colleagues,[42] and the study by Park and colleagues.[73] Of the crossover populations in S0033 and EORTC trials (117 and 133 patients respectively), three patients in each trial (i.e. six in total) had a partial response, whilst 33 patients in the S0033 trial and 36 patients in the EORTC-ISG-AGITG trial had stable disease as a best response. This means that out of a total of 250 patients, 75 (30%) had a response after escalation from 400 mg to 800 mg/day.

Response information from the study by Park and colleagues did not provide separate data for those with stable disease and those achieving partial responses. However, it did state that four out of the 12 patients (33.3%) receiving an escalated imatinib dose of 800 mg/day upon progression at the 400 mg/day dose, achieved either partial response or stable disease.[73]

Some of the patients receiving dose escalated imatinib to 800 mg/day would have had an initial response to the 400 mg/day dose, because only 42/345 patients (12.2%) in the S0033 trial 400mg arm had a best/only response of progressive disease (or "early death"),[39] and in the study by Zalcberg and colleagues this figure was 61/473 (12.9%).[40]

Interim data for the EORTC-ISG-AGITG trial was provided for a data cut-off point of 7th December 2003, at which point there were 2/97 (2.1%) patients showing a partial response, 30/97 (30.9%) patients with stable disease, and 65/97 (67.0%) patients with progressive disease.[75] Interim data for the S0033 trial, also from December 2003, showed that there were 5/68 (7.4%) patients with partial response, and 20/68 (29.4%) patients with stable disease, during crossover treatment with 800 mg/day of imatinib, following failure of treatment at 400 mg/day.[64]

In addition, secondary analysis for the EORTC-ISG-AGITG trial in the study by Debiec-Rychter and colleagues[14] indicated, without stating the number of patients involved, that response following crossover was significantly more likely to occur in patients with wild-type

[i] One patient only showed response after further escalation from 600 to 800mg

GIST than KIT exon 11 mutation (p=0.0012), and response following crossover was also significantly more likely to occur in patients with KIT exon nine mutation compared with exon 11 mutation (p=0.0017).[14]

No response data were provided for treatment with sunitinib at a dose of 50 mg/day (as part of a four weeks on treatment, two weeks off treatment, six week cycle), following progression on an imatinib dose of 400 mg/day.

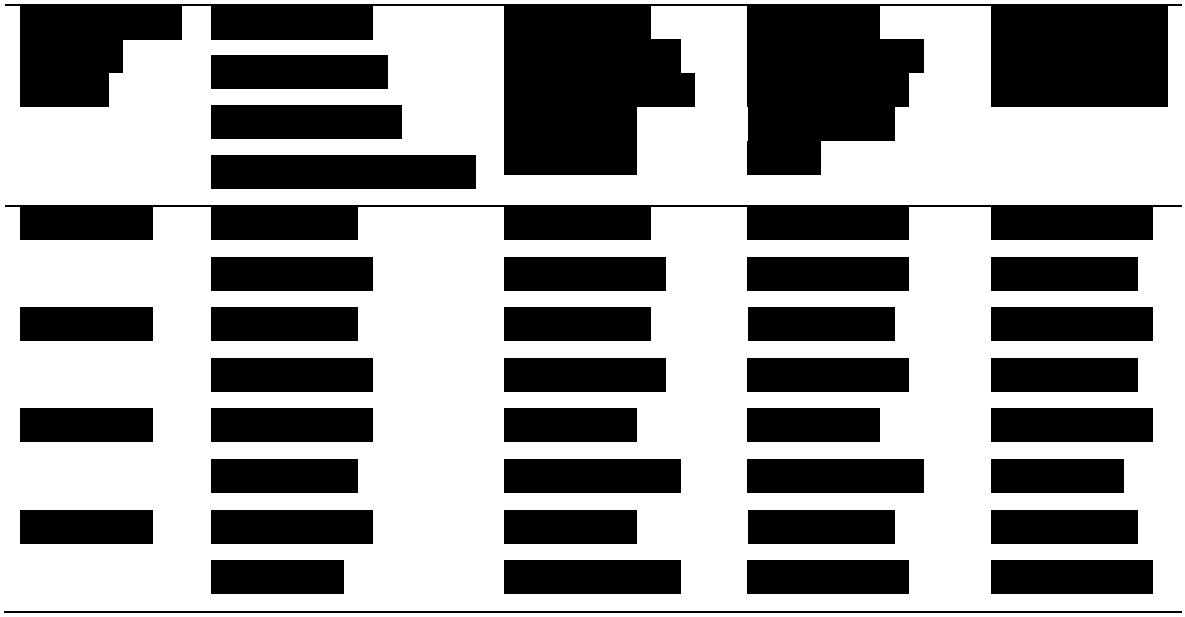
Overall survival

For imatinib at an escalated dose of 600 mg/day following progression at a dose of 400 mg/day, overall survival data were not reported by Blanke and colleagues[37] [redacted] for the B2222 trial.

For imatinib at a dose of 800 mg/day following progression at a dose of 400 mg/day, the EORTC-ISG-AGITG trial by Zalcberg and colleagues,[42] did not report overall survival outcomes. However, the S0033 trial by Blanke and colleagues,[39] reported relevant outcome data, and at the time of the analysis (median follow up of 4.5 years) noted that, 76/118 (64.4%) of patients had died.[39] Median overall survival was 19 months (95% CI 13 to 23 months) starting from the commencement of crossover. Interim data for the S0033 trial was also provided in the study by Rankin and colleagues,[64] which stated median overall survival at December 2003 was 19 months.[64]

[redacted]

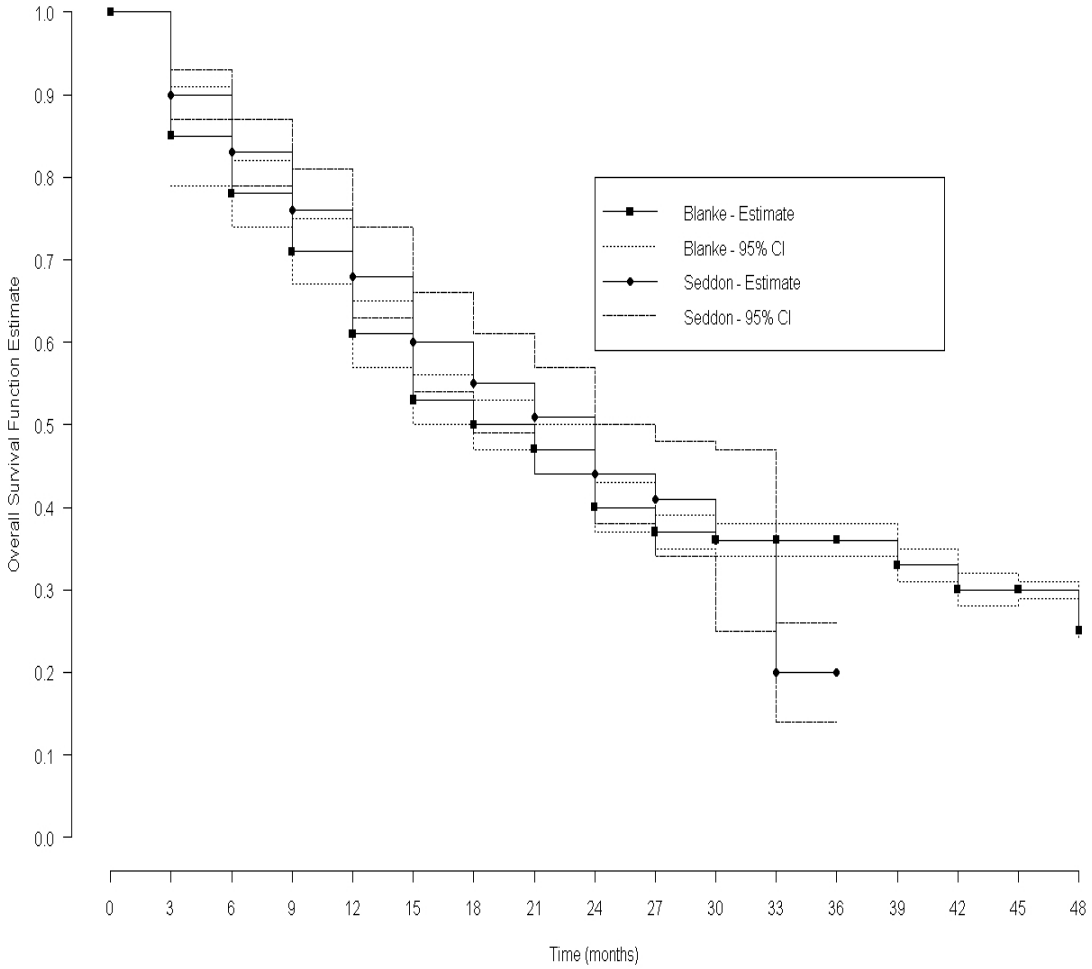
[redacted]



For sunitinib, overall survival data were available for those on 50 mg/day of sunitinib who failed on a prior imatinib dose of ≤400 mg/day, from two abstracts of the same trial, taken at different follow-up periods.[78,82] The data from the study by Reichardt and colleagues were analysed after a median of 4 cycles.[80] Median survival at this point was 93 weeks (95% CI 72-100 weeks) and 231/339 (68.1%) of patients were still alive.[78] The data from the report by Seddon and colleagues were analysed after a median of 51 weeks (range 0.1 to 159 weeks). Median survival at that time was 90 weeks (95% CI 73 to 106 weeks) and 193/351 (55%) were still alive.[82] It should also be noted that further interim overall survival data were provided in another study by Seddon and colleagues,[81] but although the date of analysis is the same month as that reported by the studies by Reichardt and colleagues[78] and Rutkowski and colleagues[79] the median overall survival reported differed, at 80.4 weeks (95% CI 60.3 to N/A weeks), whilst the population who had failed on doses of imatinib of ≤400 mg/day was also less (307 patients).[81]

It was possible to compare overall survival with an escalated dose of 800 mg/day, from the S0033 trial reported by Blanke and colleagues,[39] with sunitinib at a dose of 50 mg/day (provided in four weeks on/two weeks off cycles of six weeks), for patients who had progressed on imatinib at a dose of 400 mg/day. Quarterly overall survival estimates for the sunitinib participants reported in a Kaplan-Meier chart by Seddon and colleagues[82] were obtained using the method proposed by Parmar and colleagues[69] and compared with overall survival estimates for the S0033 trial provided by the authors. The results are provided in Figure 3.

Figure 3 Comparison of overall survival estimates for imatinib at 800 mg/day and sunitinib at 50 mg/day



The study by Zalcberg and colleagues did not report information on overall survival and was therefore not included in the comparison in Figure 3. However, data are available from the [redacted], and data from the study by Seddon and colleagues on treatment with sunitinib, are provided in Table 6.[redacted]

Table 6 Comparison of overall survival estimates for imatinib at 800 mg/day and sunitinib at 50 mg/day

	Seddon (N=351)			[redacted]		
Number of years elapsed	**Survival estimate**	**95% C.I.**		[redacted]		
1	0.684	0.626	0.741	[redacted]	[redacted]	[redacted]
2	0.441	0.379	0.503	[redacted]	[redacted]	[redacted]
3	0.200	0.140	0.261	[redacted]	[redacted]	[redacted]
4	Not reported			[redacted]	[redacted]	[redacted]

Disease-free survival

No data were reported for this outcome on account of no patient in any of the included studies having a complete response.

Progression-free survival

For imatinib at an escalated dose of 600 mg/day following progression at a dose of 400 mg/day, progression-free survival data were not reported by Blanke and colleagues[37] [redacted] for the B2222 trial.

For imatinib at an escalated dose of 800 mg/day following progression at a dose of 400 mg/day, data were reported for the S0033 trial by Blanke and colleagues,[39] and for the EORTC-ISG-AGITG trial by Zalcberg and colleagues.[42]

For the S0033 trial, at the time of the analysis, median follow up of four and a half years (54 months), 99/118 (83.9%) of the crossover cohort for whom data were available, had progressed.[39] Median progression-free survival was estimated to be five months (95% CI 2 to 10 months). Of the 99 patients who had progressive disease or had died at the time of the analysis, 23/99 (23.2%) had progressed but were still alive. Interim data from this trial, at a data cut-off point of December 2003, gave median progression-free survival to be four months following crossover, for 68[iv] patients.[64]

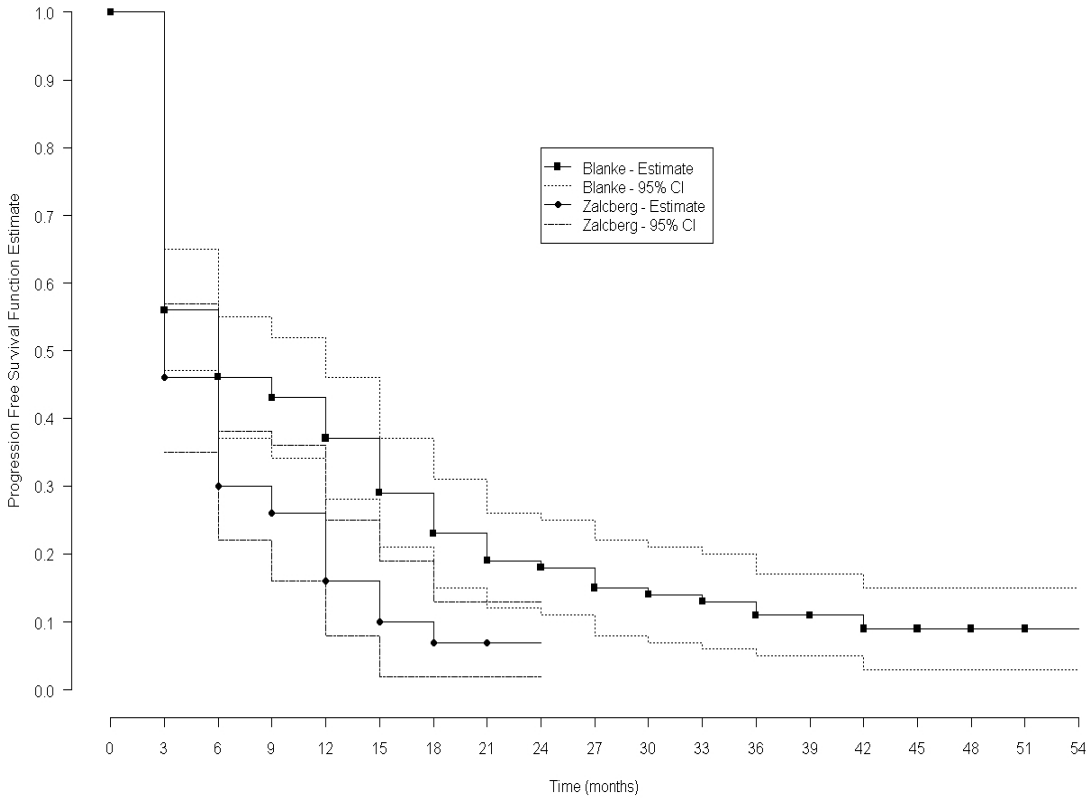
For the EORTC-ISG-AGITG trial, median follow up was 25 months (maximum follow-up was 35 months), and at that time, 108/133 (81.2%) of the cross-over cohort with data available had progressed. Median progression-free survival was 81 days. Sixty-seven patients (50.4%) had progressed or died within three months (Kaplan-Meier survival estimate 0.467). At one year, the Kaplan Meier survival estimate was 0.181.[42]

[redacted]

The estimates of progression-free survival provided at three month intervals by the authors of the S0033 study, and available as a Kaplan-Meier chart in the published paper of this study by Blanke and colleagues[39] were compared with progression-free survival estimates at three

month intervals that were measured from an enlarged copy of the plot of the Kaplan-Meier survival function estimate given in the paper by Zalcberg and colleagues.[42] The number of events in each time period was then calculated using the method proposed by Parmar and colleagues,[69] corrected to ensure that the total number of patients censored was consistent with the number reported in the published paper.[42] For both trials the standard error of the survival function estimates was estimated from the quarterly numbers for events and patients at risk using Greenwood's formula. Figure 4 shows the survival functions from each trial, together with 95% confidence intervals for each.

Figure 4 Kaplan-Meier plot for progression free survival with 800 mg/day imatinib



A meta-analysis of these two survival curves was attempted, using the methods described in Arends and colleagues.[88] However, no valid results could be achieved, due to the lack of data.

For sunitinib at a dose of 50 mg/day for a six week cycle, no progression data were available specifically for trial participants who had failed on a prior dose of imatinib at ≤400 mg/day.

Time to treatment failure

Data on the duration of response/time to treatment failure were available from the study by Park and colleagues[73] which showed that of the 12 patients who had their dose escalated to 600 mg/day following progression at the 400 mg/day dose, one patient died of a cause unrelated to both their disease and imatinib treatment, whilst the remaining 11 patients eventually progressed on imatinib treatment at the escalated dose after a median of 1.7 months (range 0.7 to 24.9 months).

For those receiving an escalated dose of 800 mg/day of imatinib following progression at an initial dose of 400 mg/day, data were available from the EORTC-ISG-AGITG trial showing that, of those who achieved partial response or stable disease after crossover, the median duration of "stabilisation" (i.e. partial response or stable disease after crossover) was 153 days

(range 37-574 days).[42] Interim data from this trial, (7th December 2003 data cut-off) gave a median time to progression of 78 days.[75]

For the sunitinib trial, the specific median treatment duration for those given sunitinib after failure on imatinib at a dose of ≤400 mg/day was not provided, but interim median treatment duration for the whole cohort was reported at 126 days (range 1-618), and at that time point (median follow up not stated) it was noted that median treatment duration "did not significantly differ based on the dose of prior imatinib therapy (≤400 vs > 400 mg/day).[76]

Health-related quality of life

No data were reported for this outcome by any of the included studies.

Adverse events

Data on adverse events were not reported for participants receiving an escalated dose of 600 mg/day of imatinib following progression at an initial dose of 400 mg/day.

For those receiving an escalated dose of 800 mg/day of imatinib following progression at an initial dose of 400 mg/day, data were available from the EORTC-ISG trial reported by Zalcberg and colleagues,[42] and there was some information on dose reductions in the S0033 trial report by Dileo and colleagues.[74]

The number of discontinuations due to adverse events is not explicitly stated for the EORTC-ISG-AGITG trial reported in the study by Zalcberg and colleagues, but they did report that the vast majority of discontinuations (88.4%, i.e. approximately 86/97 withdrawals) were due to disease progression, suggesting the maximum possible adverse event withdrawals possible would be 11.6% of all 97 withdrawals, i.e. 11 patients.[42] Interim data for this trial at a December 2003 data cut-off point showed that there were two toxicity withdrawals at that time.[75]

Data from this trial on specific adverse events following crossover is shown in Table 7 for those patients with 60 days follow up data.

Table 7 Adverse event data from the study by Zalcberg and colleagues[42]

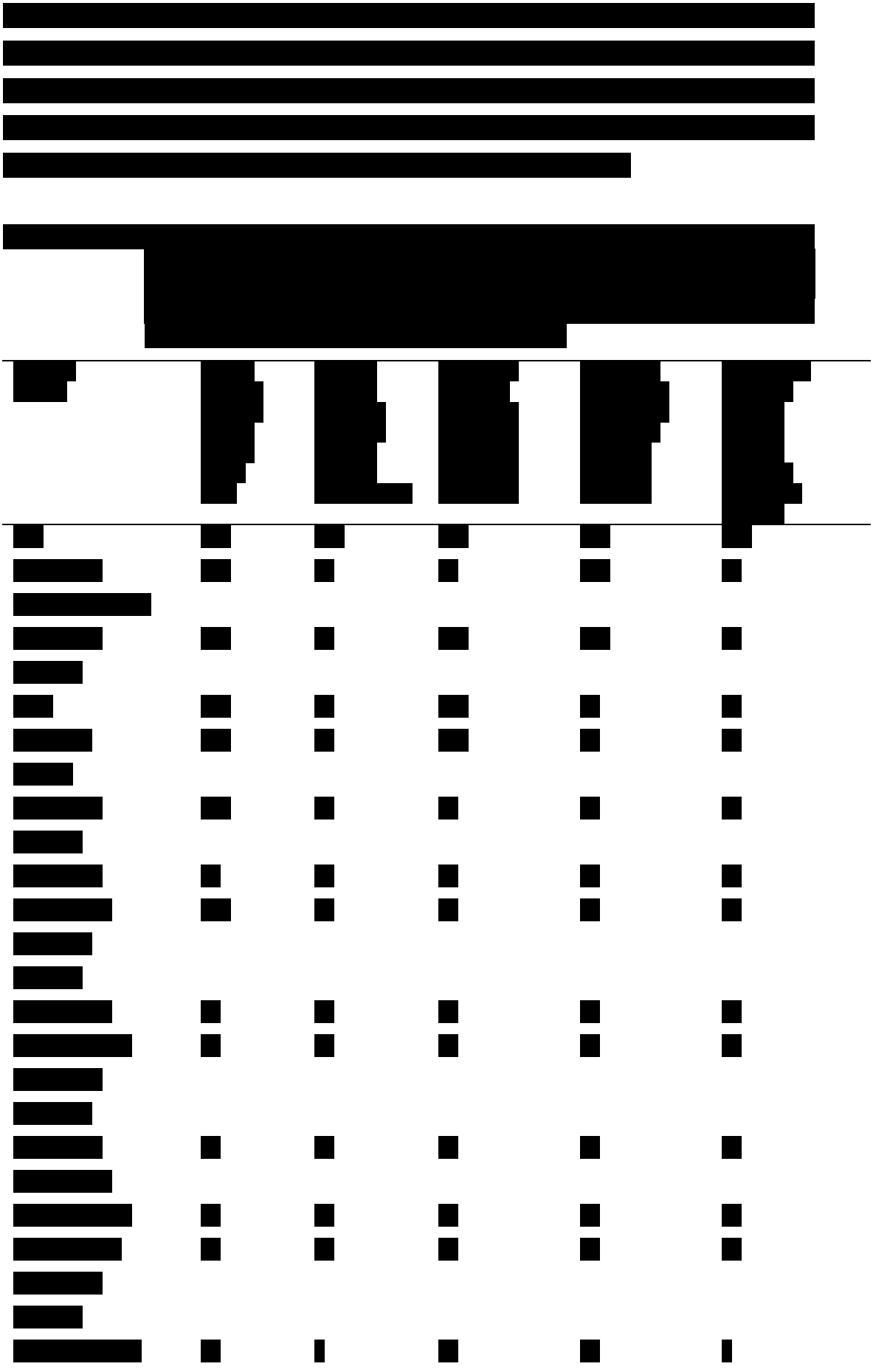
Adverse event	Number with adverse event	Less severe after crossover	More severe after crossover	Number achieving new grade 3-4 level adverse event
Oedema	99	25/99 (25.3%)	33/99 (33.3%)	7
Skin rash	45	23/45 (51.1%)	19/45 (42.2%)	2
Fatigue	102	21/102 (20.6%)	47/102 (46.1%)	10 (p<0.001)
Dyspnoea	30	8/30 (26.7%)	14/30 (46.7%)	1
Infection	20	9/20 (45.0%)	9/20 (45.0%)	1
Nausea	82	38/82 (46.3%)	26/82 (31.7%)	3
Leucopenia	56	25/56 (44.6%)	16/56(28.6%)	0
Neutropenia	49	30/49 (61.2%)	13/49 (26.5%)	0 (p=0.002)
Thrombocytopenia	7	4/7 (57.1%)	2/7 (28.6%)	0
Anaemia	119	15/119 (12.6%)	51/119 (42.9%)	17 (p=0.015)

A higher proportion of those with skin rash, nausea, leucopenia, neutropenia and thrombocytopenia had reduced severity from these effects following crossover to the 800 mg/day dose of imatinib, compared with the proportion who had increased severity from these effects following crossover, (though with the exception of neutropenia these differences were not significant at the 0.05 level). The same proportion of people with infection had increased and decreased severity from this following crossover. For all other adverse events, a higher proportion of sufferers had increased severity from these effects than improvement, and in the case of anaemia and fatigue, the increase in severity following crossover was significant at the 0.05 level.[42]

Interim data reported by Zalcberg and colleagues for this trial show that 31% of patients (exact number not calculable) required a dose reduction (NB: stated as "cumulative incidence").[75] No information was provided on the dose given following dose reduction.

Interim data for the S0033 trial reported by Dileo and colleagues,[74] show that of the 77 patients who had crossed over from an imatinib dose of 400 mg/day to 800 mg/day at that time, 18 (23.3%) had at least one dose delay, and 12 (15.6%) had at least one dose reduction, due to oedema and rash. No information was provided on the dose given following dose reduction.

[redacted]



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For sunitinib at a dose of 50 mg/day for a six week cycle, no progression data were available specifically for trial participants who had failed on a prior dose of imatinib at ≤400 mg/day.
A summary of the results for all outcomes with the exception of adverse events, is provided in Table 10.

Table 10 Summary of results

Drug/dose	Median follow-up (range)	N (%) with partial response or stable disease	Duration of response/time to treatment failure	Median overall survival (95% CI)	N (%) still alive	Median progression - free survival (95%CI)	N (%) progression - free	Reference source
Sunitinib at 50mg/day	4.5 months (0 to 22.1 months)		median treatment duration did not differ based on prior imatinib dose					Kang 2007[76]
Sunitinib at 50mg/day	<6 months?			20.1 months (15.1 to N/A months)	?/307			Seddon 2007[81]
Sunitinib at 50mg/day	6 months			23.3 months (18 to 25 months)	231/339 (68.1%)			Reichardt 2008[78]
Imatinib at 600 mg/day	8 months	5/12 (41.6%)	1.7 months (range 0.7 to 24.9 months)					Park 2009[73]
Imatinib at 800 mg/day	8 months	4/12 (33.3%)						Park 2009[73]
Imatinib at 600mg/day	9.5 months (? to 9 months)	3/9 (33.3%)						Demetri 2002[36]
Sunitinib at 50mg/day	12 months (0 to 39.8 months)			22.5 months (18.3 to 26.5 months)	193/351 (55%)			Seddon 2008[82]
Imatinib at 800 mg/day	<25 months (<? to <35months)	32/65 (49.2%)	2.8 months					Zalcberg 2004[75]
Imatinib at 800 mg/day	25 months (? to 35 months)	39/133 (29.3%)	5.5 months (1.3 to 20.5 months)			2.9 months	25/133 (18.8%)	Zalcberg 2005[42]
Imatinib at 800 mg/day	<54 months	25/68 (36.8%)		19 months (not stated)				Rankin 2004[64]
Imatinib at 800 mg/day	54 months	36/117 (30.8%)		19 months (13 to 23 months)	42/118 (35.6%)	5 months (2 to 10 months)	19/118 (16.1%)	Blanke S0033[39]
Imatinib at 600mg/day	63 months (? to 71 months)	11/43 (25.6%)						Blanke B2222[37]
Imatinib at 800 mg/day		significantly more likely to occur in patients with wild-type and exon 9 mutations than exon 11						Debiec Rychter 2006[14]

NB: All units of measurement for time have been converted into months by dividing by 4 for weeks, dividing by 28 for days, and multiplying by 12 for years. All figures that were originally in units of measurement other than months are therefore approximate

7 ASSESSMENT OF COST-EFFECTIVENESS

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

The specific objectives are:

a) To determine, by undertaking a systematic review of the literature, the cost-effectiveness of using imatinib at an escalated dose of 600 mg/day or 800 mg/day to treat patients with unresectable and/or metastatic GISTs (whose disease has progressed with imatinib at a dose of 400 mg/day), compared with treatment with sunitinib (within its recommended dose range) or best supportive care.

b) To develop an economic model to compare the cost-effectiveness and cost-utility of imatinib at a dose of 600 mg/day or 800 mg/day; the use of sunitinib (within its recommended dose range); or best supportive care only, for people with KIT (CD117) positive unresectable and/or metastatic GISTs whose disease has progressed on treatment with imatinib at a dose of 400 mg/day or those whose treatment with imatinib has failed due to intolerance.

7.1 Systematic review of existing cost-effectiveness evidence

The purpose of the review of economic evaluation studies was to identify published studies and assess their quality and usefulness for comparisons of treatments 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).

7.1.1 Methods

Search strategy for identification of published reports

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

The search strategy used is provided in Appendix 10. The abstracts of ISPOR conferences from 2006 were also searched and in addition, websites of key professional organisations, GIST Support International and the drug manufacturers Pfizer and Novartis were scrutinised.

The reference lists of all identified studies and evidence syntheses, as well as submissions from industry and other consultees were also checked for additional potentially relevant references. The methods for how the industry submissions were to be handled is described below, although as noted in Chapter 5 no industry submission was reviewed for this Technology Assessment Review. The full texts of potentially relevant reports were obtained and assessed in terms of their relevance to the economic evaluation or cost-analysis.

Quality assessment

Included studies were assessed using the guidelines of the Centre for Reviews and Dissemination.[65] Modelling studies were assessed against the Phillips checklist.[89]

Inclusion and exclusion criteria

To be included, studies had to include a cost-analysis, or a cost-effectiveness analysis of alternative treatments for GISTs. Non-English language studies were excluded.

Data extraction

Information and relevant data were extracted by an economist according to the guidelines produced by the Centre for Reviews and Dissemination for the critical appraisal of economic evaluations. Where an economic evaluation has been based on a modelling exercise, additional data extraction criteria developed by Phillips and colleagues were applied.[89,90]

Handling industry submissions

Information from the manufacturer was to be considered if it was submitted in accordance with the 3rd December 2009 deadline set by NICE. Any economic evaluations included in the company submission, provided they complied with NICE's guidance on presentation, would be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model, using the methods outlined above. The strengths and weaknesses in terms of the methodology adopted, and reporting of results and conclusions, would be described. The conclusions derived from the company submissions were then to be compared with those provided by the review of the other existing evidence and the model reported in Section 7.2, highlighting any differences in results. Any 'commercial in confidence' data taken from a company submission were to be reported in accordance with NICE guidelines.[90]

Synthesising evidence

Data from the included studies on economic analysis and economic evaluation were summarised in order to identify common results, and to summarise the variations and differences between studies. The studies that used economic modelling were critically reviewed with regard to, for example, model structure use, and how these models dealt with uncertainties whilst predicting results.

7.1.2 Results

Results of literature search

In total there were 250 papers identified from the initial search (Table 11). Of these, 18 were selected as potentially relevant abstracts, and 13 were included for further screening. From these papers, nine were selected for the review. Appendix 11 summarises the included studies.

Table 11 Search results

Database	**Number retrieved**
Medline (2000 - Oct Wk 4 2009) Embase (2000 - Wk 44 2009) Medline In Process (3rd Nov 2009) (after de-duplication in Ovid)	227
Science Citation Index* (2000 to 3rd Nov 2009)	16
Health Management Information Consortium* (Sep 2009)	0
NHS Economic Evaluation Database* (Oct 2009) HTA Database (Oct 2009)	0
ISPOR conference abstracts 2006-2009	7
Total	**250**

* Numbers retrieved after de-duplication against Medline and Embase search

As already noted no submission was received from industry reporting relevant evidence.

Characteristics of included studies

Out of the nine studies, seven[53,91-96] reported a full economic evaluation which assessed both the costs and cost-effectiveness of the alternatives compared. Of the remaining two studies, the study by Reddy and colleagues[52] is a review reporting information related to costs and health outcomes reported in other studies and did not undertake an economic evaluation. The other study[97] which is also a review of the management of GIST with sunitinib, reports on,

amongst other things, the cost of treatment with sunitinib. Details of these two studies are reported in the main background section.

Five studies[53,91,92,95,96] conducted a modelling exercise rather than incorporating data from actual patient follow-up. Two studies[92,94] used non-randomised, or non-trial patient data (from retrospective cohorts) to inform their economic evaluations.

One study[53] reported an economic evaluation in a UK context, which was based on an industry submission to NICE for a previous TAR. Two studies[91,94] reported a Canadian context, and one study was from a US context.[93] The remaining three studies were conducted in the context of Mexico,[92] Spain[95] and Brazil[96] respectively. Table 12 summarises the main features of the included studies.

Comparative studies:

- *Imatinib vs. best supportive care*

Three studies[53,93,94] compared imatinib with best supportive care. The study by Wilson and colleagues[53] used the manufacturer submissions (Novartis model) and compared imatinib and best supportive care, but in the imatinib group allowed for escalation of doses from 400 mg/day to 600 mg/day for those who failed to response or were intolerant to imatinib at the 400 mg/day dose. The study by Mabasa and colleagues[94] noted that patients included from retrospective cohorts in their analysis were given imatinib 400 mg/day until disease progression, and later were allowed escalated doses of between 600-800 mg/day. Six out of fifty-six patients in the imatinib groups of patient considered in this economic evaluation were then allowed to switch to sunitinib therapy. The economic evaluation by Huse and colleagues[93] considered imatinib at 400 mg/day (Table 12).

Table 12 Characteristics of included cost-effectiveness analysis studies

Study	Country, Currency , Price Year	Perspectives	Comparisons					Patient failed on imatinib?	Outcomes Reported											Modelling
			Imatinib 400 mg/day	Imatinib 600 mg/day	Imatinib 800 mg/day	Best Supportive Care	Sunitinib		Overall Survival	Median Overall Survival	Survival Rate	Progression Free Survival	Progression Free Life Years	Time to Progression	PFM	Life Years Gain	QALY	Cost Effectiveness Ratio	ICER	
Chabot et al (2008)[91]	Canada Canadian $, 2005	Provincial Health Authority				✓	✓	Yes	✓			✓				✓	✓		✓	Markov Model
Contreras-Hernandez et al (2008)[92]	Mexico US $, 2006[2]	Health Insurance System			✓	✓	✓	Yes							✓	✓			✓	Markov model
Mabasa et al (2008)[94]	Canada Canadian $, 2006	British Columbia Cancer Agency (BCCA)	✓			✓		No	✓	✓		✓				✓			✓	CEA using cost effectiveness ratios and ICERs
Paz-Ares, L (2008) [95]	Spain €, 2007	Health Care System				✓	✓	Yes					✓		✓	✓	✓		✓	Markov Model
Huse et al (2007)[93]	USA US $, 2005	Societal perspective (Payers for Health Care)	✓			✓		N/A									✓	✓		CEA
Teich et al (2009)[96]	Brazil Brazilian R$, 2005 [3]	Health Care system			✓	✓	✓	Yes					✓			✓			✓	Markov Model
Wilson et al (2005)[53]	UK GB £, (2004?)	Health Care System	✓	✓		✓		Yes			✓						✓		✓	Markov Model

[2] 1 US$=11 Mexican pesos
[3] And US$ at PPP, 1US$=1.4 R$

Imatinib, sunitinib, and best supportive care

Two studies[92,96] compared sunitinib, escalated doses of imatinib, and best supportive or palliative care as comparators for their economic evaluations. The Contreras-Hernandez and colleagues[92] study compared treatment with imatinib, sunitinib and palliative care. Both treatments (sunitinib and imatinib) were compared with the same best supportive care in a model based analysis. The doses for both the treatments were clearly specified (imatinib at 800 mg/day and sunitinib at 50 mg/day) as the study was based on primary data collected from hospital records. The study did not include dose escalation with imatinib at a 600 mg/day dose. Teich and colleagues[96] compared sunitinib, imatinib at 800 mg/day and best supportive care (Table 12).

Sunitinib and best supportive care

The studies by Chabot and colleagues[91] and Paz-Ares and colleagues[95] compared treatment with sunitinib and best supportive care for GIST patients who were imatinib resistant or intolerant. Chabot and colleagues did not specify the dose of sunitinib used, or mention whether patients who were imatinib resistant or intolerant were initially treated with 400 mg/day and then with escalated imatinib doses (e.g. 600 or 800 mg/day). Paz-Ares and colleagues[95] specified a dose of 50 mg/day for the patients in the sunitinib group. The patients in the sunitinib group were provided with best supportive care. Therefore, this study compared sunitinib plus best supportive care with best supportive care alone. Best supportive care in this study included diagnostic tests and routine palliative treatment.[95]

The definition of best supportive care in the economic evaluation studies was not the same across the studies. Chabot and colleagues[91] did not clearly define what best supportive care included, while Contreras-Hernandez and colleagues[92] defined clearly that best supportive care included treatment with imatinib. Paz-Ares and colleagues[95] defined best supportive care as essentially consisting of diagnostic tests and routine palliative care. In the other three studies,[53,93,94] the control group of patients which are considered as effectively being treated with best supportive care were not provided with treatment with imatinib. As a full-text paper of the study by Teich and colleagues[96] was not available, information on how this study defined best supportive care was not available.

Escalated doses of imatinib at 600 or 800 mg/day, sunitinib and best supportive care

We did not find any studies that conducted an economic evaluation of all of the alternative treatments (e.g. escalated doses of imatinib 600 mg/day, imatinib 800 mg/day, sunitinib and BSC) for patients who failed or were intolerant to imatinib at a dose of 400 mg/day.

Study design

Among the seven studies that conducted a full economic evaluation, five used Markov modelling.[53,91,92,95,96] Huse and colleagues[93] used a very simple modelling framework and Mabasa and colleagues[94] also used patient level data and had 46 and 47 patients in their imatinib and best supportive care (historical group) groups respectively. Contreras-Hernandez and colleagues[92] also used patient level data (for 21 patients) collected at the *Hospital de Oncologia,* to estimate the costs of care associated with imatinib, best supportive care and other procedures, and used these costs in their model.

Perspective

Three studies[53,95,96] adopted the perspective of a National Health Care system. The study by Contreras-Hernandez and colleagues[92] was from Mexico's Health Insurance Systems' perspective. The study by Huse and colleagues did not specifically mention whether it was from a health insurance system perspective, however it mentioned that it had been conducted from a US societal perspective. The studies by Chabot and colleagues[91] and Mabasa and colleagues[94] considered a provincial health authority and a specialised agency (British Columbia Cancer Agency) perspective respectively for their economic evaluations. None of the seven studies[53,91-96] that conducted full economic evaluations reported indirect non-medical resource use, or indirect costs to society in terms of productivity loss, costs to carers, and other indirect costs associated with GIST.

Health outcome measures

The major outcome measures used in the seven studies reporting full economic evaluations were: progression free survival (PFS)[91,92,94-96] overall survival (OS)[91,94] life years gained[91,92,94-96] and quality adjusted life years (QALYs).[53,91,93,95] Four studies[53,91,93,95] reported the incremental cost per QALY gained. The remaining three studies [92,94,96] used incremental cost per life year gained, and incremental cost per progression-free life year gained.

Data sources

Most of the studies[91,92,95] which are based on modelling exercises used effectiveness or health outcome data from major trials[36,50,98-100] and adapted them for their specific contexts. The source of cost data were mainly from relevant patients' records, and health care cost databases. Wilson and colleagues[53] used data from an industry submission (Novartis Trial). Table 13 summarises the data sources used for the studies. A full paper of the study by Teich and colleagues[96] was not available and so information on the data sources used was unknown.

Table 13 Data sources

Study	Unit Costs	Resource Use for Treatment	Effective/Health Outcomes
Chabot et al (2008)[91]	Published literature and Canadian government benefit schedule and medical oncologist	Published literature and Canadian government benefit schedule and medical oncologist	Phase III trial NCT00075218 [50]
Contreras-Hernandez et al (2008)[92]	Hospital records (Hospital de Oncologia,) for 21 patients in Mexico, IMSS pricing and reimbursement procedure, and cost of sunitinib from Pfizer Laboratories	Patients medical charts, associated information from IMSS (Mexican Insurance system)	Phase III trial[50,100]
Mabasa et al (2008)[94]	British Columbia Cancer Agency (BCCA)	BCCA registry	Patients data in two arms (imatinib groups and 46 non-imatinib group) was compared with Demetri et al (2002[36]) and Verweij et al (2003) [98]
Paz-Ares, L (2008) [95]	Health costs database eSalud (for administration, radiotherapy, nephectomy and monitoring costs). General Council of Pharmacists Official Colleges for drug costs. Ojeda *et al* (2003) unit costs of adverse events	Data reported by expert panel on number of visits to oncology clinic, laboratory tests, CT scans, nurse visits, and visits to palliative units, and analgesic drugs	Demetri et al (2006) [50] Adverse events[101]
Huse et al (2007)[93]	Drug acquisition costs: Published average wholesale price, (Red Book: Pharmacy's Fundamental Reference 2005, Montvale (NJ): Thomson PDR, 2005 and Physicians' Desk References 2005. Montvale (NJ): Thomson PDR, 2005)	Based on the resources used by patients with pancreatic cancer (not advanced in US context) to determine the resources used for medical management in the absence of data on resource used by GIST patients	Demetri et al (2002)[36]Phase II and Blanke (2006)[99]
Wilson et al (2005)[53]	Industry submission: Novartis Model – Novartis Submission to NICE 2003	Novartis Model – Novartis Submission to NICE 2003	Quality of life based on ECOG data from B2222 trial[37], and Goss and colleagues study (data academic in confidence)

Time horizon

The studies that used models in their economic evaluations used different time horizons and treatment cycle lengths for the Markov model. The two studies[91,95] which had sunitinib and BSC as comparator treatments used a time horizon of six years and a treatment cycle length of six weeks in the modelling exercise. Of the other studies the study by Contreras-Hernandez and colleagues[92] which has sunitinib as a comparator along with imatinib and best supportive care, used a lifetime time horizon and also a six-week cycle of treatment (to be consistent with the sunitinib treatment cycle of six weeks). Huse and colleagues[93] used a ten year time horizon for the analysis, whilst Teich and colleagues[96] used a six year time horizon, and a six-week treatment cycle.

Discount rate

A 5% discount rate for cost and health outcomes was used in two studies.[91,92] Wilson and colleagues[53] in their model, discounted costs by 6% and QALYs by 1.5%, as per NICE methods guidance at the time the work was conducted. Paz-Ares and colleagues[95] and Huse and colleagues[93] used 3% and 3.5% respectively. Mabasa and colleagues [94] used 3% for discounting costs and outcomes. The abstract by Teich and colleagues[96] did not report the discount rate used in their modelling exercise.

Findings on costs and cost effectiveness

The cost of treatment and cost per different health outcome under different alternatives are presented in Table 14. As regards to cost in relation to the health outcomes, the incremental cost-effectiveness ratios from the studies are noted in the table with respect to the main outcomes, i.e. life year saved, progression free survival and QALYs. Although the Contreras-Hernandez and colleagues study[92] considered three alternative treatments (sunitinib, imatinib, and best supportive care), it did not report an ICER for imatinib versus best supportive care.

Table 14 Summary of cost of treatment from studies reviewed

Study	Comparator	Mean Cost of Treatment per patient	ICER1	ICER2
Chabot et al 2008[91]. *Costs in Can $ at 2005 prices*.	Sunitinib	Can $46,125	Sun vs. BSC Can$ 49,826 per Life Year Saved	Sun vs. BSC Can $79,884 per QALY
	BSC	Can $11,632		
Contreras-Hernandez et al (2008)[92] *Costs in US $ at 2006 prices*	Sunitinib	US $17,806 sd US $695 CI US $15377 to $19816	.	Sun vs. BSC $15,734 per patient treated with sunitinib and $56,612 per year of progression free survival, and $46,108 per life year gained
	Imatinib	US $35,057, sd US $1253 CI US $31,381 to 38,705		
	BSC	US $2071, sd 473 CI US $ 1543 to 2869		
Mabasa et al 2008[94] *Costs in Can $ at 2006 prices*	Imatinib	Can $79,839	Imatinib vs. BSC(control) Can$ 15,882 per life year	
	BSC	Can $1743		
Paz-Ares, L (2008)[95] *Costs in Euros at 2007 prices*	Sunitinib	€ 23,259	Sun. vs. BSC €30,242 per life year.	Sun. vs. BSC €4,090 per progression free month €49,090 per QALY gained.
	BSC	€1622		
Huse et al 2007[93] Cost in US $ at 2005. price	Imatinib	US $416,255		
	BSC	US$ 341,886		
Wilson et al 2005[53] *Cost in £ at.2004. prices*	Imatinib	£18,896 (400 mg/day) £24,368 (600 mg/day) Other cost of treatment £1,136		Cost per QALY £70,206 (yr 2), £51,514 (yr 3), £36,479 (yr 5), and £25,859 in yr 10
	BSC	£562		

BSC = best supportive care; Sun = sunitinib

Higher doses of imatinib versus best supportive care

The Contreras- Hernandez and colleagues[92] study suggested that a higher dose of imatinib (800 mg/day) may be cost-effective compared to best supportive care (where best supportive care includes treatment with imatinib at a lower dose). Wilson and colleagues[53] using the modified Novartis model in a UK context and from an NHS perspective estimated the incremental cost per QALY gained at £51,515 to £98,889 at two years, and £27,331 to £44,236 at five years compared with best supportive care.

Sunitinib versus higher dose of imatinib versus best supportive care

Sunitinib treatment was associated with an estimated gain of 0.7 years and 0.4 QALYs compared with best supportive care.[91] Sunitinib treatment also resulted in a higher number of progression free months than both the imatinib and best supportive care therapies. The mean progression free months was found to be 5.64 months for sunitinib while it was 5.28 and 2.58 months respectively for imatinib and best supportive care. The incremental effectiveness of sunitinib therapy compared with best supportive care was 3.1 progression free months and 0.3 progression free months compared with a high dose of imatinib. Over the five year treatment horizon, Contreras-Hernandez and colleagues[92] found that patients with sunitinib had a mean life year gain of 1.4 compared with 1.31 and 1.08 for imatinib and best supportive care respectively. The study also suggests that patients taking imatinib at a dose of 800 mg/day had the highest mean costs of treatment. Teich and colleagues[96] reported that sunitinib was cost-effective compared with imatinib at a dose of 800 mg/day for a six year time horizon. Their study suggested that sunitinib increases life years and progression free life years by 0.3 and 0.26 respectively, with an incremental cost of Brazil $86,756 (US $61,968 Purchasing Power Parity 2005) in comparison with best supportive care. They found that sunitinib was both more effective showing a gain in life years of 0.02 and progression free life years of 0.47, and less costly than imatinib over six years.

Assessment of uncertainty

All six full-text studies[53,91-95] used some form of sensitivity analysis. Chabot and colleagues[91] varied the most influential model parameters, i.e. utility of progression and no progression, overall survival (hazard ratio), progression free survival, positron-emission tomography (PET) at initiation of sunitinib treatment, the cost of palliative care and the cost of PET. The model assumed the acquisition cost of sunitinib was certain and did not vary this in the sensitivity analysis. The sensitivity analysis suggested that results of the economic evaluation were most sensitive to health-state utility value and rate of overall survival and progression free survival. The sensitivity analysis also suggested that the results were robust. Contreras-

Hernandez and colleagues[92] conducted probabilistic sensitivity analysis with data obtained from the Markov model. An acceptability curve was derived and reported the cost-effectiveness ratios for sunitinib in comparison with palliative care. In the absence of any threshold for cancer therapy in Mexico, they used three hypothetical re-imbursement cut points equivalent to US$27,723, US$36,364, and US$45,455 to derive acceptability curves. These hypothetical values were based on taking 5%, 14% and 40% of the upper threshold that NICE reimburses for imatinib as first-line treatment. Mabasa and colleagues[94] varied the median overall survival rate, the rate of progression free survival and years of life expectancy, and conducted univariate sensitivity analysis. They found that the model used for the analysis remained robust. The ICER for each median life year gained was found to be within the range of Can $0 to Can $550, and for each median progression free year it ranged from Can $0 to Can $75,505. Paz-Ares and colleagues[95] also conducted univariate sensitivity analysis. Their model results were calculated in a probabilistic analysis considering the impact of uncertainty on the values of each variable included in the model, by assuming different distributions of these variables. The study conducted sensitivity analysis of the results by adding the cost of imatinib to the best supportive care group by assuming all patients in the palliative care group would be given imatinib 400mg/day. The most sensitive variables affecting the results were efficacy of treatment, and the unit cost of sunitinib. The study by Huse and colleagues[93] also used univariate sensitivity analysis and examined the impact of considering the upper and lower values of the cost of the drugs, the cost of treatment, the utilities of successful treatment and progressive disease, the time horizon, and the annual rate of discount, in their analysis. They used imatinib at a 600 mg/day dose to examine the impact of results variation as an alternative scenario for the sensitivity analysis. The study by Wilson and colleagues[53] fitted a Weibull curve to estimate progression and death due to GIST, in their sensitivity analysis, and found that the ICER based on a Weibull curve was £26,427 and with an exponential fitting was £21,707.

7.1.3 Summary of the review

We found that most of the economic evaluation studies reviewed used modelling exercise However, only two studies[92,96] compared both imatinib and sunitinib with best supportive care for patients who had failed or become resistant to imatinib 400 mg/day. The full paper for only one of these[92] was available. Among the five studies[53,91,92,95,96] which used modelling exercises, Contreras-Hernandez and colleagues[92] and Teich and colleagues[96] did not use QALYs as health outcome measures. Although Contreras-Hernandez and colleagues[92] used patient level data as the basis of their cost estimates, they used survival and progression free survival as effectiveness measures in their model, which was based on the studies by Motzer and colleagues[100] and Demetri and colleagues.[50]

The two studies[91,95] which used modelling exercises to compare the cost-effectiveness of sunitinib only with best supportive care used the same trial data (A6181004).[50] Their utility data were based on responses to the EQ-5D instrument provided by participants in this trial.

In our review we did not identify any published economic evaluation studies in a UK context comparing all the relevant interventions. The study that included an economic evaluation of higher dose imatinib in a UK context[53] did not actually have as a comparator those who failed with imatinib 400 mg/day, rather the model allowed patients who failed on 400 mg to cross over to a higher dose of imatinib 600 mg/day rather than 800 mg/day.

The definition of best supportive care in the economic evaluation studies reviewed was not the same across the studies and cost-effectiveness of treatments compared with best supportive care cannot be easily compared. In addition, the pattern of resources including the drugs for treatment was reported in different ways in different studies.

For a comprehensive economic evaluation of the alternative treatment of GIST patients who failed on or became resistant to imatinib 400 mg/day, further evidence is needed to fill in gaps in the evidence base. The challenge is to obtain appropriate and sufficient information on survival rates and responses to treatments with escalated doses of imatinib, and sunitinib. The economic evaluations which were identified based on modelling exercises have limitations. For example, all extrapolated clinical trial data from a short time horizon, to predict cost-effectiveness results for a longer period. There is a need for empirical patient-level data for future economic evaluations. The outcome measures for disease severity can be considered as important surrogate endpoints. In cases where the patients in placebo groups or in best supportive care arms of trials are allowed to cross over to an experimental group (either escalated doses of imatinib or sunitinib) it could be argued that an intention to treat analysis would result in an underestimation of the survival benefit of patients randomised in the treatment groups, and the cost of the treatment for these patients who were assigned to placebo/best supportive care groups is often not accounted for in economic evaluations.

There has been no consideration of the patients' and society's costs/ resource use in the studies reviewed. A wider perspective might be informative but to consider this costs and resource use falling outside the NHS (e.g. on personal social services and patients and their families) would be helpful.

7.2 Economic modelling

7.2.1 Model structure

The structure of the model was 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 have also drawn upon advice from health care professionals within the research team in this regard.

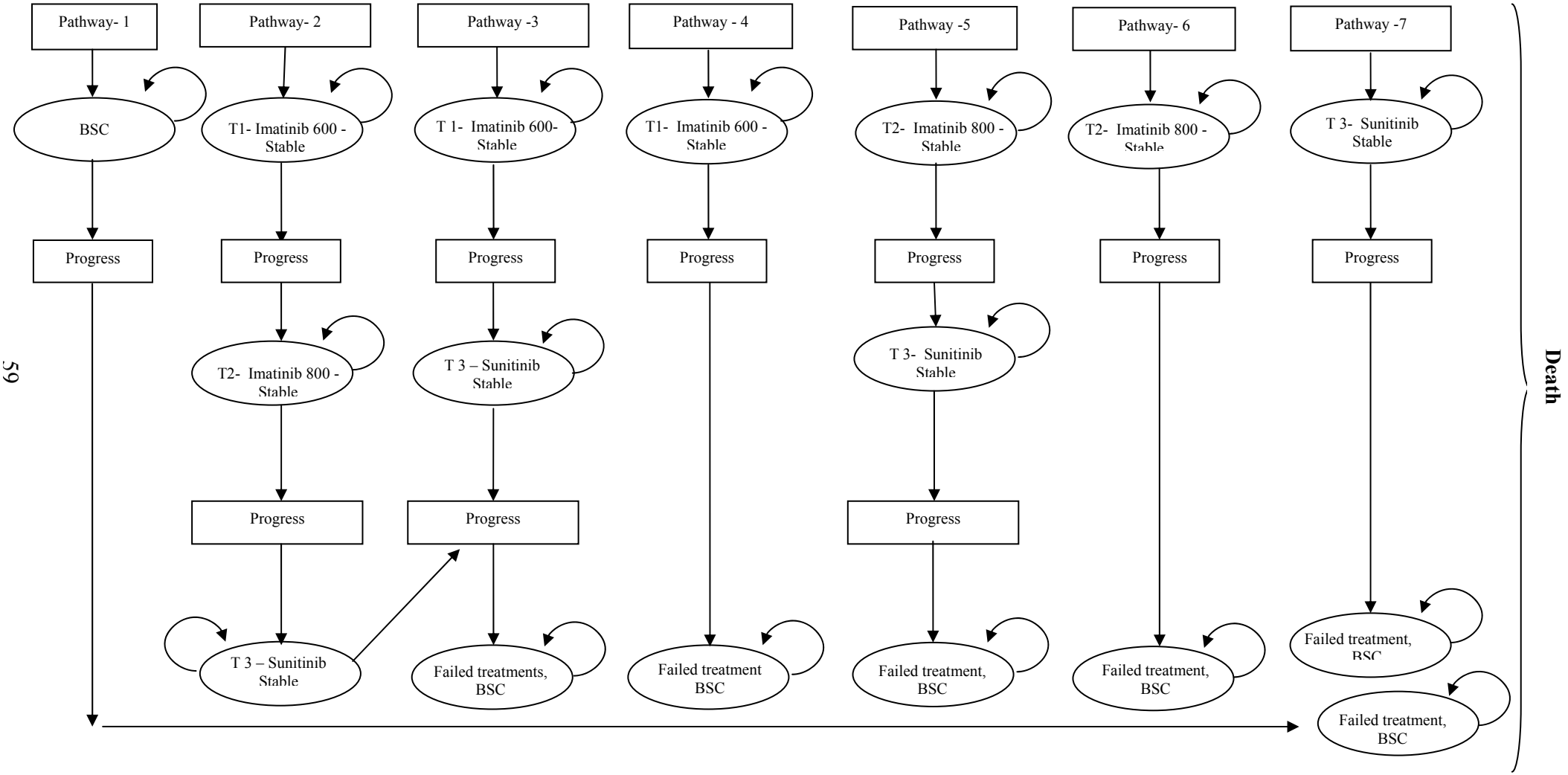
The model is developed to compare the alternative treatment strategies for people with KIT (CD117) positive unresectable and/or metastatic gastrointestinal stromal tumours (GISTs) whose disease has progressed on treatment with imatinib at a dose of 400 mg/day or those whose treatment with imatinib has failed due to intolerance. According to the scope for the review the treatment strategies to be compared in the models were:

i) Treatment with an escalated dose of 600 mg/day, regulating symptoms with best supportive care
ii) Treatment with an escalated dose of 800 mg/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 assumed pathway of the model

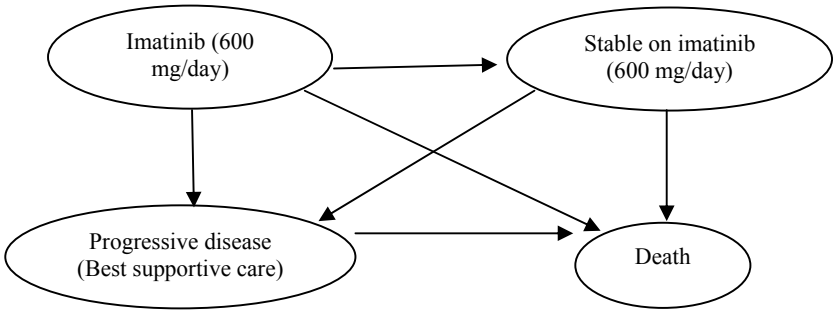
We considered a range of different alternative pathways for patients who progressed on imatinib at a dose of 400 mg/day, which led to the creation of nine alternative pathways and following advice from our clinical advisers, we determined seven clinically plausible pathways (Figure 5). The model is based on these seven clinically plausible care pathways. Circles represent health states that individuals may return to, rectangles represent health states during which treatment is administered, and the arrows show the possible directions in which individuals could move at the end of each cycle, depending on the transition probabilities. The states considered in the model were those thought to reflect care pathways for people with GIST. Patients entering the pathways are those who failed on imatinib 400 mg/day. The alternative treatments considered dose T1= imatinib 600 mg/day, T2 = imatinib 800 mg/day, T3 = sunitinib (with recommended dose 50 mg/day), BSC = Best Supportive Care.

Figure 5 **Markov model for GIST patients who have failed with imatinib 400 mg per day.**



A Markov model was developed to model these care pathways using Tree Age Pro 2009.[102] In this model, patients whose disease has progressed on treatment with imatinib at a dose of 400 mg/day or those whose treatment with imatinib has failed due to intolerance, enter one of the seven care pathways. Figure 6 is an illustrative example of the model structure for pathway 4 where patients are treated with imatinib, 600 mg/day and if the disease progresses on this treatment the patients are treated with best supportive care. Appendix 12 illustrates the model for all the seven pathways of alternative treatments.

Figure 6 Example of model structure for care pathway 4 (imatinib 600 mg/day – best supportive care)



Pathway 1, shows the patients with the BSC treatment. It is assumed that the patients with best supportive care are still treated with imatinib and palliative care. Pathway 2 represents treatment options where escalated doses of imatinib (600 and 800 mg/day) and treatment with sunitinib are provided to the cohort of patients. All patients start the treatment with imatinib 600 mg/day. If they survive and respond to imatinib 600 mg/day, then they will continue with the dose until they move to a state of stable condition with complete response or partial response (CR/Stable IM 600). From this point, a proportion of patients will survive and continue to respond to treatment. Dose is escalated to imatinib 800 mg/day if they failed to respond. Those who stop responding to imatinib 600 mg/day move to a state where they receive imatinib 800 mg/day (PD at IM 800). A proportion of patients will remain with the escalated doses of imatinib 800 mg daily (CR/Stable IM 800). If patients fail to respond on imatinib 800 mg daily, they are switched to treatment with sunitinib (PD with sunitinib). If they respond to sunitinib then they will continue with the treatment and move to a state of stable condition with complete response or partial response (CR/Stable with sunitinib). From this point, a proportion of patients might continue to respond to the treatment and remain stable, or they may stop responding to sunitinib and now receive best supportive care for the remainder of their life.

Pathway 3 represents treatment options where an escalated dose of imatinib (imatinib 600 mg/day only) and treatment with sunitinib are provided. In this pathway, all patients also start the treatment with imatinib 600 mg/day (PD initial treatment IM600). If they respond to imatinib 600 mg/day, then they will continue with the dose and move to a state of stable condition with complete response or partial response (CR/Stable IM 600). If a patient treated with imatinib 600 mg/day fails to respond or ceases to respond then instead of trying further dose escalation with imatinib, they are switched to treatment with sunitinib (PD with sunitinib). If they respond to sunitinib they will continue with the treatment and move to a state of stable condition with complete response or partial response (CR/Stable with sunitinib). Should they fail to respond to sunitinib or if at some point they cease to respond they continue with best supportive care for the remainder of their life.

In pathway 4 all patients start the treatment with imatinib 600 mg/day and no switching to other treatment is considered. If they respond to imatinib 600 mg/day then they continue with this treatment until the GIST progresses or they die (CR/Stable IM 600). If at any point they do not respond to imatinib 600 mg/day they continue with best supportive care for the remainder of their life.

The remaining care pathways are variants of earlier pathways. Pathway 5 is similar to pathway 3 with respect of combination of escalated dose of imatinib and sunitinib. The main difference being in this case is that the escalated dose is imatinib 800 mg/day. Apart from this difference the pathways are identical. Pathway 6 is similar to pathway 4. However, in this pathway the escalated dose is imatinib 800 mg/day instead of imatinib 600 mg/day. Pathway 7 is similar to pathway 4. In this pathway however instead of being treated with imatinib 600 mg/day patients receive sunitinib. Apart from this change the care pathways are identical (see Appendix 12).

Key assumptions of the modelling exercise

The key assumptions of the model are:

a. The time horizon of the model is 10 years over which time all patients are expected to die and the cycle length is for weeks.
b. The model assumes that patients entering a pathway will remain in that treatment for one cycle only if they do not respond and survive in the treatment arm. In these cases they are

either considered to move to the escalated doses or to another alternative (if allowed by a treatment pathway) or continue with best supportive care for the remainder time horizon of the model.

c. The model assumed that the probabilities of progressing and dying did not change over time. This assumption was made because of the limited data available.

d. The utility of the health outcome from the treatment with imatinib 600 mg/day, imatinib 800 mg/day, and sunitinib are assumed to be the same.

e. All patients failing or not responding to the treatment in any of the treatment arms of the model continue with best supportive care for the remainder of the model time horizon or until they die and are assumed to derive the same utility from the health state of progression.

7.2.2 Data requirements and model inputs

For our model, data on the clinical effectiveness of interventions was based upon the systematic review of clinical effectiveness described earlier. These data were combined within the model with health state utilities data to provide estimates of QALYs for the alternative treatment strategies for GIST patients.

With respect to clinical effectiveness, data were required for the model on the probability of death per cycle and the probability of not responding to treatment per cycle.

Probability of death

As described in the systematic review of effectiveness few data were available for any of the treatments, little of which was based on direct comparisons. Therefore, the data available are imprecise and potentially biased. The direction and magnitude of any bias is unknown. As a consequence the data used to derive probabilities of death for each therapy under medication should be treated cautiously.

- ***Probability of death for best supportive care***

  The data for best supportive care were taken from the three studies[103-105] and pooled weighted estimates suggest that 88.4% (50 out of 58) died during the observation period of 60 months. A monthly rate was derived using an exponential function which assumes the probability of death per month is constant over time. The same value was used in circumstances where patients moved on to best supportive care after previously being treated with imatinib at an

escalated dose or with sunitinib. Alternative data for this parameter were available and these are outlined in Appendix 13, however these data would provide similar, imprecise and potentially biased estimates for this probability.

- ***Probability of death for imatinib for 600mg/day and 800mg/day***

  The data on mortality for the imatinib 600 mg/day treatment groups were taken from the available trial data[37] and 45% (5 out of 11) of those who crossed over to imatinib 600 per day died over the trial period of 60 months. The data on the mortality for 800 mg/day were taken from Blanke and colleagues[39] (where the data suggest that 64.41 % (66 out of 118) died in the Imatinib 800 mg/day group. Again monthly rate was derived as an exponential rate.

- ***Probability of death for sunitinib***

  The mortality data for those treated with sunitinib came from Schutte and colleagues.[80] In this study 193 out of 351 patients receiving sunitinib were still alive after a median survival period of 11.76 months. Monthly mortality rate was derived from this survival rate assuming an exponential rate. In the analysis it has been assumed that the mortality rate for those receiving sunitinib is the same regardless of any prior treatment.

Response rate to the treatment

For our model, response to treatment was also taken to include partial response, complete response and those reported to be in a stable condition.

The response rate to imatinib 600 mg/day was based upon data from the B222[2] trial data.[37] This study reported that 25.5% of patients had responded and remained stable during a median follow-up of 63 months. The same study was also used to provide evidence on the response rate to imatinib 800 mg/day. This study reported that 75 out of 250 patients responded to the treatment with imatinib 800 mg/day and showed partial response or stable condition after a median follow-up of 54 months. For sunitinib the response rate was estimated from the weighted average response rate from two studies.[36,106] In these two studies in total 266 out of 382 patients responded, and simple weighted mean was used to derive the pooled response rate. This response rate was assumed to be unaffected by prior treatment received. The non-response data for each treatment were converted into monthly transition probabilities by assuming an exponential function.

Cost data

Resources used by the selected treatment strategies were identified from relevant sources (e.g. NHS reference costs, the BNF, etc) and the review of economic evaluations. Costs have been considered from a NHS perspective only.

Cost of drugs

We included the costs of drugs, i.e. costs of imatinib 400 mg/day, 600 mg/day, 800 mg/day, and sunitinib 50 mg/day. As the sunitinib treatment process involved taking medications for four weeks and then no medication for the following two weeks, we estimated the yearly medication costs of this drug and then equally proportioned this cost to each month within that year. Data on cost of drugs were obtained from BNF 58.[107] It has been assumed that patients on best supportive care still receive medications and it has been assumed that the cost of these is equivalent to the cost of imatinib at 400 mg/day.

Cost of other resources

Resource use in the treatments were based on the study by Wilson and colleagues[53] which suggested that there are GP visits (£40 per year), outpatient visits including tests (£440 per year), and CT scans (£656 per year) and cost of management of adverse events (£159 per year). These cost estimates for these services used by Wilson and colleagues[53] at 2003 prices were used for our model after adjusting for inflation with HCHS (Hospital and Community Health Services) Index for pay and prices inflator for the year 2008/09.[108] Based on these estimates, the total monthly cost for management with imatinib treatment is £128.16. In the absence of better data these costs have been used for both Imatinib 600 mg/day and 800 mg/day.

For the sunitinib group we have used the resources based on the Pfizer single technology assessment submission[58] for patient monitoring, outpatient and GP visits (£799.73 per year), CT imaging (£336 per year) and management of adverse events (£159 per year). These costs are at 2008 prices and were adjusted to 2009 prices using the same methods as described above. Based on these data the estimated total monthly cost of this care used within the model is £185. For best supportive care, data from the Pfizer submission were again used,[58] the suggested costs in 2008 prices for patient monitoring, outpatient and GP visits was £249 per year, and £105 per year for CT imaging. These costs were inflated to 2009 prices using the same methods described above.

Utility data

There were few data relating to health state utilities. Our model has used data where the health state valuations are derived from the EQ-5D and the values used were taken from Wilson and colleagues[53] and Chabot and colleagues.[91] The utility associated with progression free survival for those responding to imatinib (regardless of dose) was 0.935.[53] The utility for those receiving best supportive care was taken from Chabot and colleagues and was taken to be 0.577.[91] In the absence of alternative data it has been assumed that the utility for those who have not progressed on sunitinib is the same as that assumed for imatinib i.e. 0.935.

Table 15 describes the parameter inputs used within the model. It also describes the sources of data, alternative valuation and data used to inform the probabilistic sensitivity analysis (described in more detail below).

In a sensitivity analysis, the high value of the costs of drugs (imatinib and sunitinib) have been assumed to be similar to the value based on BNF price[107] which we used in our model for the base case analysis. For the lower value, we have taken an average of the price of the higher and lower doses assuming that there may be need to lower the dose in the treatment pathways assumed in our model. For sunitinib, during the sensitivity analysis the price of the lower dose is assumed.

Table 15 Model parameters, values and data sources

Parameters	Description	Value	Low	High	Distribution	Values	Data Source and assumptions
Cost parameters			**For Sensitivity Analysis**				
cImat600	Cost of drugs : imatinib 600	£2406	£2005	£2406			BNF54 (March 2010) Low value is average of imatinib 400 and 600mg.
cImat800	Cost of drugs: imatinib 800	£3208	£2807	£3208			BNF54 (March 2010) Low value is average of imatinib 600 and 800mg
CNott	Cost of Best Supportive Care	£1604	£1283	1604			Include cost of imatinib 400mg (BNF54 March 2010)
CSunb	Cost of drugs: sunitinib	£31398.8	£2092.5	£3138.8			BNF54 (March 2010) Low value is average of reduced dose of sunitinib
OthCostBSC	Other cost and management of treatment in BSC	£50.61					Resource use in the treatment were based on the study by Wilson and colleagues.[53]
OthCostIm	Other cost and management of treatment in imatinib treatment	£128.16					Resource use in the treatment were based on the study by Wilson and colleagues[53] Assumed to be same fro imatinib 600 and imatinib 800
OthCostSun	Other cost and management of treatment in sunitinib treatment	£185.11					Resource use in the treatment were based on the study by Wilson and colleagues[53] and STA Pfizer[58]
Mortality and response to treatment							
deathBSC	Probability of death in the BSC treatment arm	0.014627			Beta	α = 0.8448898 β = 57.775	Pooled weighted rate [103-105]
dth600	Probability of death in imatinib 600 treatment	0.007472			Beta	α = 0.08162 β =10.91838	B2222 study[39]
dth800	Probability of death in imatinib 800 treatment	0.011857			Beta	α = 1.39948 β =116.600	S0033 study[39]
Dthsun	Death due to GIST: sunitinib	0.026706			Beta	α = 9.3284 β =341.62	Schutte 2008[80]
nonrespIm600	Transition Probability of Non response to imatinib 600	0.011743			Beta	α = 0.504949 β =42.495051	B2222 study[39]
nonrespIm800	Transition Probability of Non response to imatinib 800	0.012879			Beta	α = 3.21875 β =246.780	S0033 study [39] and Zalcberg et al 2005

Table 15 Model parameters, values and data sources (cont)

nonrespSun	Transition Probability of Non response to sunitinib	0.080959			Beta	$\alpha = 12.30$ $\beta = 139.6945$	Weighted average response rate [50,106]
uImat600	Utility with imatinib 600	0.935	0.712	0.939			Wilson et al 2005[53]
uImat800	Utility with imatinib 800	0.935	0.712	0.939			Wilson et al 2005[53]
uProg	Utility for Progression Disease	0.577	0.52	0.712			Wilson et al 2005[53]
uSun	Utility with sunitinib treatment	0.935	0.712	0.939			Chabot *et al* 2008[91]
Structural and methodological parameters							
Cycle length	Time period that utilities, costs and probabilities relate to	1month					Assumption
Length of run	Number of cycles model is run for	120 (10 yrs)	72 (6 yrs)	144 (12 yrs)			Assumption
DR	Discount rate	0.002917	0	0.005			NICE guideline

7.2.3 Time horizon for the model

The model looked at the costs and consequences directly attributable to GIST. As reported earlier the typical survival of such patients is relatively short and hence the time horizon of the model was limited to 10 years. The cycle length was one month to reflect the natural history of the condition.

7.2.4 Analysis methods

The results of the model are presented in terms of the incremental cost per QALY. The costs and outcomes were discounted at 3.5% in accordance with NICE. As described below both deterministic and probabilistic sensitivity analyses were conducted with a net benefit framework being used to compare the different treatment strategies.

7.2.5 Sensitivity analysis

Probabilistic sensitivity analyses

Probabilistic analysis of the base case scenario was conducted by assuming a beta distribution of the probability of death and non-response to treatment in the different treatment strategies. The values used to define these distributions are reported in Table 15 and are derived from the data reported in Section 7.2.2.

The beta distribution as defined above might arguably be considered to be too precise and not truly reflect the degree of uncertainty that exists. To examine the uncertainties around the distribution assumed for the base scenario, sensitivity analysis was conducted by assigning a uniform distribution to these parameters, where the low and high value of probability of death and non-response rate were assumed 90% more than and 90% lower than the mean value used in our model. The justification for this distribution was that comparisons of interventions that are based on non-randomised and non-comparative data are potentially biased and that both the magnitude and direction of that bias are uncertain.

Deterministic sensitivity analyses

Sensitivity analysis was conducted with respect to methodological and structural assumptions. First the discount rate for cost and effectiveness was changed to 0% and 6% in the sensitivity analysis. The time horizon was also varied between six and 12 years (data are presented in the results for a six years, and 12 years time horizon).

Sensitivity analysis was also conducted to examine the uncertainties around the values used for the cost of drugs (which are major components of the cost of treatment for different

treatment strategies) and the utility values for the different health states of the model. The values used in the sensitivity analysis are reported in Table 15 above.

A further area of uncertainty relates to the very limited data available for imatinib 600 mg/day. In the base case analysis the effectiveness (in terms of survival and response rates) is better for imatinib 600 mg/day compared with imatinib at 800 mg/day. As this was based on non-randomised, non-comparative data the relative difference is potentially biased. Therefore, in this sensitivity analysis a more conservative assumption was taken that the survival rate and the response rate to the treatment of imatinib 800 mg/day also applied to imatinib 600 mg/day.

7.2.6 Results

Base case analysis

Table 16 shows the mean estimates of cost and effectiveness of the six alternative treatment strategies modelled. As this table shows, effectiveness has been reported in two ways: life years, and QALYs. Path – 4, treatment was imatinib 600 mg/day, has an incremental cost per QALY that was less than £30,000 compared with Path-1: best supportive care. The only other non-dominated or non-extendedly dominated strategy was Path-2 (imatinib 600 mg/day to imatinib 800 mg/day to sunitinib). However, in this case the incremental cost per QALY (compared to the next most costly option (of Path – 4: imatinib 600 mg/day) is in excess of £40,000.

Of note is that in the base case analysis treatment with sunitinib for those who failed with imatinib 400 mg (Path-7) was estimated to have a lower life-expectancy than best supportive care but greater QALYs. The reason for this was that the estimates of survival for sunitinib were based upon limited non-randomised and non-comparative data (as was the case for all the other comparators). Hence, any comparison should be treated cautiously.

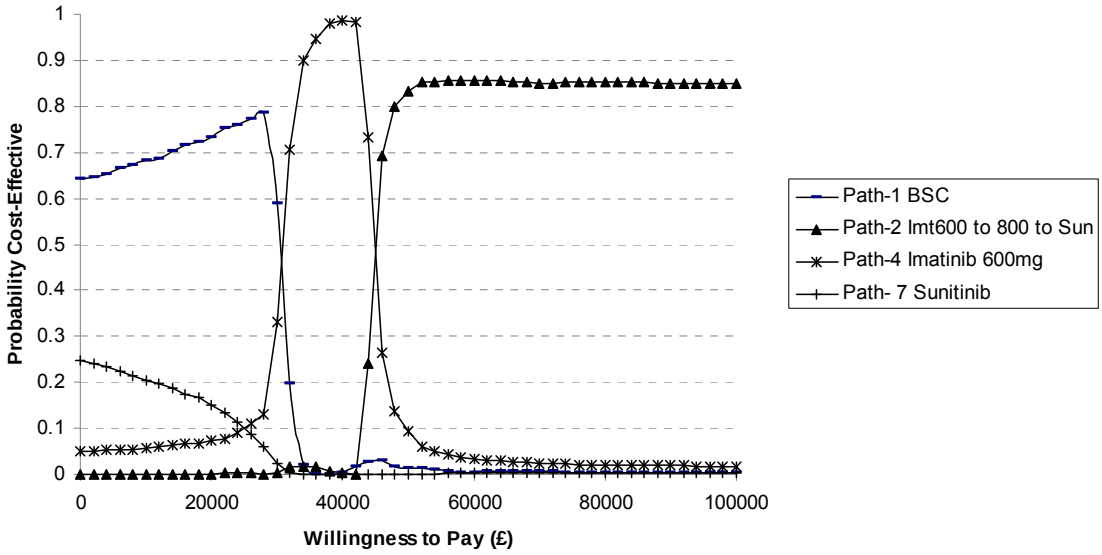
The finding that sunitinib was dominated by best supportive care when effectiveness was measured in life years but not dominated when effectiveness was measured in QALYs illustrates the importance of the utility estimates used within the model. Again such data were sparse and particularly for sunitinib, do not reflect the potentially worse side effect profile. Other things remaining unchanged the inclusion of side effects would have reduced the QALYs obtained from pathways containing sunitinib and potentially led to Path - 7 being dominated by best supportive care (at the very least the incremental cost per QALY would have increased from the £272,365 reported in Table 16).

Table 16 Base case analysis and incremental cost-utility of the alternative treatment pathways

Strategies	Cost	Incremental cost	Life years	Incremental life years	QALYS	Incremental QALYs	Incremental cost per QALY
Path-1 Best supportive care	£92,811		4.154		2.397		
Path-7 Sunitinib	£96,688	£3877	3.716	(Dominated)	2.411	0.014	£272,365
Path-4 Imatinib 600mg	£147,060	£50,372	5.211	1.057	4.256	1.845	£27,304
Path-3 Imatinib 600mg to Sunitinib	£149,200	£2,139	5.032	Dominated	4.286	0.030	£71,723
Path 6 Imatinib 800mg	£153,901	£4702	4.506	Dominated	3.635	-0.651	Dominated
Path-5 Imatinib 800mg to Sunitinib	£155,828	£6628	4.336	Dominated	3.659	-0.627	Dominated
Path-2 Imatinib 600 mg to 800 mg to Sunitinib	£172,152	£22,953	5.278	0.067	4.803	0.517	£44,359
With dominated and extendedly dominated options removed							
Path-1 Best supportive care	£92,812		4.154		2.397		
Path-4 Imatinib 600mg	£189,484	£54,249	5.211	1.057	4.256	1.859	£29,181
Path-2 Imatinib 600 mg to 800 mg to Sunitinib	£212,595	£25,092	5.278	0.067	4.803	0.547	£45,850

The results reported in Table 16 are surrounded by considerable imprecision. One of the main sources of the imprecision in the analysis surrounds the clinical effectiveness data. Therefore, a partial probabilistic sensitivity analysis was conducted, with the imprecision surrounding response rates and mortality rates being characterised by Beta distributions. Figure 7 shows the cost-effectiveness acceptability curve and illustrates that the pathway with the highest likelihood of being considered cost-effective when society's willingness to pay for a QALY is less than approximately £25,000 is Path – 1, best supportive care. When society's willingness to pay for a QALY is between approximately £25,000 and £45,000 Path – 4, imatinib 600 mg/day is most likely to be considered cost-effective. Beyond a threshold of approximately £45,000 Path – 2, imatinib 600 mg/day to imatinib 800 mg/day to sunitinib, is most likely to be cost-effective.

Figure 7 Cost-effectiveness acceptability curve for alternative treatments over the ten year time horizon*



* Pathways with a low probability of being cost-effective over the range of willingness to pay for a QALY values considered have not been shown

Sensitivity Analysis

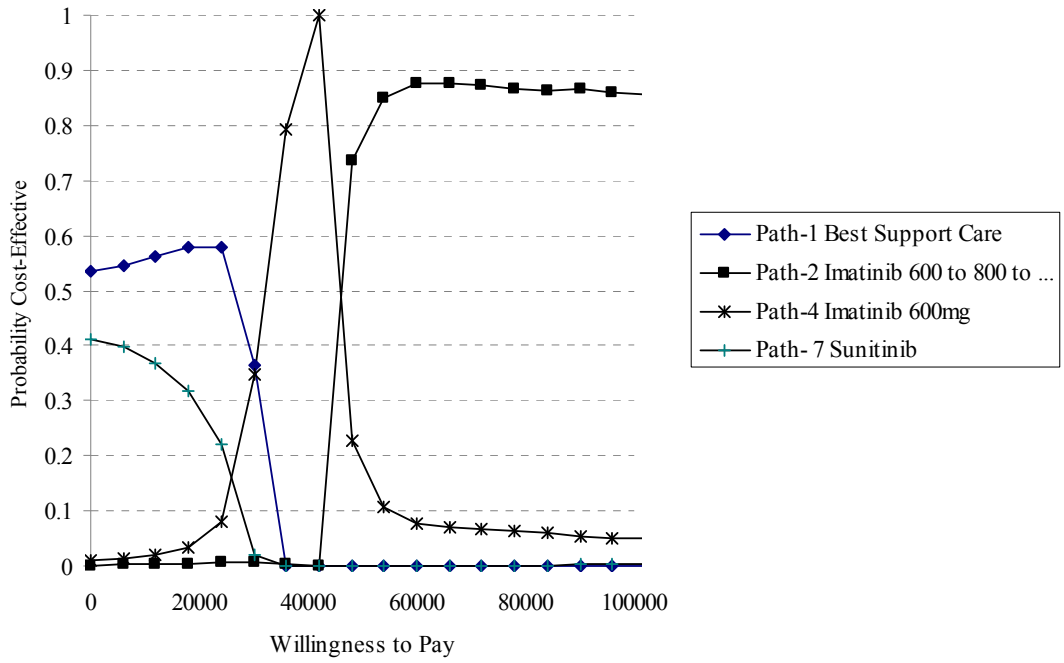
Uncertainty around the distributions used for mortality and response rates

The Beta distributions used to generate Figure 7 above potentially do not fully characterise the extent of the uncertainty surrounding the estimates of mortality and response used within the model. As noted in the methods section this is because the data used come are essentially used as if they came from non-randomised, non-comparative sources, and hence any comparisons drawn may be highly biased. For this reason in this sensitivity analysis uniform distributions were substituted for the beta distributions (Figure 8). It should be noted that these uniform distributions were assumed to be symmetrical around the point estimates used in the base case analysis.

As Figure 8 illustrates, the basic pattern of the cost-effectiveness acceptability curve is the same as that depicted in Figure 7. At low threshold values for the willingness to pay for a QALY Path -1, best supportive care is still the most likely to be considered cost-effective. However, Path – 7 sunitinib is more likely to cost-effective at low thresholds. It should be noted that even though the distributions surrounding mortality weights are very wide in this analysis sunitinib is still associated with a trend toward a slightly higher mortality rate than best supportive care. As previously noted this trend is based upon sparse and potentially unreliable data on the performance of sunitinib. At a threshold value of approximately £36,000 Path – 3 Imatinib 600 mg daily to sunitinib has a similar probability of being

considered as cost-effective as Path – 1, best supportive care and Path – 4, imatinib 600 mg/day. Between a threshold of £36,000 and £48,000 Path – 4, imatinib 600 mg/day is most likely to be cost-effective and beyond that threshold value Path –2, imatinib 600 mg/day to imatinib 800 mg/day to sunitinib is most likely to be cost-effective.

Figure 8 **Cost-effectiveness acceptability curve for alternative treatments over the ten year time horizon assuming uniform distributions for mortality and response rates***



* Pathways with a low probability of being cost-effective over the range of willingness to pay for a QALY values considered have not been shown

Uncertainty surrounding structure and methodological assumptions around distribution

Two different discount rates have been applied to costs and benefit to examine the sensitivity of the results to plausible changes in the discount rate (Table 17). At a 0% discount rate there is no change in the options are dominated or extendedly dominated, and the incremental cost per QALY for Path – 4, imatinib 600 mg/day compared with Path – 1, best supportive care increases to £31,183. The incremental cost per QALY for Path – 2, imatinib 600 mg/day to 800 mg/day to sunitinib compared with Path – 4, imatinib 600 mg/day increases to £54, 715.

When the discount rate was changed to 6%, the incremental cost per QALYs for the non-dominated strategies fall compared with the base case analysis. The key change is that Path – 3 imatinib 600 mg/day to sunitinib is no longer extendedly dominated by Path 4, imatinib 600 mg/day. Furthermore, the incremental cost per QALY for this comparison is less than

£30,000. Overall, the sensitivity analysis around discount rates illustrates that the results are sensitive to the choice of discount rate.

Table 18 reports the results of the sensitivity analysis around the time horizon of the model. When the time horizon is reduced to 6 years (base case = 10 years) the incremental cost per QALYs associated with the non-dominated options increases slightly. When the time horizon increases the incremental cost per QALY for Path 4, imatinib 600 mg/day compared with Path – 1, best supportive care, increases slightly. The incremental cost per QALY for Path – 2, imatinib 600 mg/day to imatinib 800 mg/day to sunitinib compared with Path 4, imatinib 600 mg/day, is virtually unchanged.

Table 17 Sensitivity around the discount rate and length of run

	Strategy	Cost (£)	QALYS	Incremental cost per QALY (£)
Base case e.g. discount rates = 3.5% on Cost and Benefit; time horizon = 10 years	Path-1 Best supportive care	92,811	2.397	
	Path- 7 Sunitinib	96,688	2.411	272,365
	Path-4 Imatinib 600 mg	147,060	4.256	27,304
	Path-3 Imatinib 600 mg to Sun	149,200	4.286	71,723
	Path 6 Imatinib 800 mg	153,901	3.635	Dominated
	Path-5 Imatinib 800 to Sunitinib	155,828	3.659	Dominated
	Path-2 Imatinib 600 mg to 800 to Sunitinib	172,152	4.803	44,359
Sensitivity analysis 1 e.g. discount rates = 0% on Cost and Benefit; time horizon = 10 years	Path-1 Best supportive care	93,137	2.706	
	Path- 7 Sunitinib	97,719	2.672	Dominated
	Path-4 Imatinib 600mg	159,462	4.833	£31,183
	Path-3 Imatinib 600 mg to Sunitinib	163,601	4.859	Ext Dom
	Path 6 Imatinib 800mg	165,641	4.087	Dominated
	Path-5 Imatinib 800 to Sunitinib	169,210	4.105	Dominated
	Path-2 Imatinib 600 mg to 800 to Sunitinib	195,193	5.486	£54,715
Sensitivity analysis 2 e.g. discount rates = 6%; time horizon = 10 years	Path-1 Best supportive care	92,614	2.209	
	Path- 7 Sunitinib	96,007	2.254	Ext Dom
	Path-4 Imatinib 600mg	139,473	3.908	£27,593
	Path-3 Imatinib 600 mg to Sunitinib	140,394	3.940	£28,801
	Path 6 Imatinib 800mg	146,627	3.360	Dominated
	Path-5 Imatinib 800 to Sunitinib	147,542	3.387	Dominated
	Path-2 Imatinib 600 mg to 800mg to Sunitinib	158,271	4.392	£39,480

Ext Dom = extended dominance

Table 18 Sensitivity around the time horizon of the model

	Strategy	Cost (£)	QALYS	Incremental cost per QALY (£)
Base case e.g. discount rates = 3.5% on Cost and Benefit; time horizon = 10 years	Path-1 Best supportive care	92,811	2.397	
	Path- 7 Sunitinib	96,688	2.411	272,365
	Path-4 Imatinib 600 mg	147,060	4.256	27,304
	Path-3 Imatinib 600 to Sunitinib	149,200	4.286	71,723
	Path 6 Imatinib 800 mg	153,901	3.635	Dominated
	Path-5 Imatinib 800 mg to Sunitinib	155,828	3.659	Dominated
	Path-2 Imatinib 600 to 800 mg to Sunitinib	172,152	4.803	44,359
Sensitivity analysis 3 e.g. discount rates = 3.5%; time horizon = 6 years	Path-1 Best supportive care	73,246	1.960	
	Path- 7 Sunitinib	79,720	2.032	Ext Dom
	Path-4 Imatinib 600 mg	114,433	3.402	28,560
	Path-3 Imatinib 600 mg to Sunitinib	117,729	3.455	Ext Dom
	Path 6 Imatinib 800 mg	126,750	3.017	Dominated
	Path-5 Imatinib 800 mg to Sunitinib	129,873	3.066	Dominated
	Path-2 Imatinib 600 to 800 mg to Sunitinib	131,848	3.758	48,969
Sensitivity analysis 4 e.g. discount rates = 3.5%; time horizon = 12 years	Path-1 Best supportive care	98,464	2.510	
	Path- 7 Sunitinib	101,589	2.509	Dominated
	Path-4 Imatinib 600mg	156,943	4.489	29,553
	Path-3 Imatinib 600 mg to Sunitinib	158,421	4.507	Ext Dom
	Path 6 Imatinib 800 mg	161,295	3.790	Dominated
	Path-5 Imatinib 800 mg to Sunitinib	162,637	3.803	Dominated
	Path-2 Imatinib 600 to 800 mg to Sunitinib	183,961	5.093	44,736

Ext Dom = extended dominance

Uncertainty surrounding transition probabilities of survival and response to treatment with imatinib 600 mg/day.

The data available for imatinib given at a dose of 600 mg/day was sparse and what little data there was suggested a superior effectiveness compared with imatinib 800 mg/day. These data

are (i) potentially unreliable because they are based upon non-randomised and non comparative data, and (ii) potentially counter intuitive (in a direct comparison would we expect imatinib 800 mg/day to perform worse than imatinib 600 mg/day?). Therefore, in this sensitivity analysis it was assumed that the mortality and response to treatment with imatinib 600 mg/day was the same as imatinib 800 mg/day.

As Table 19, shows the incremental cost per QALY for Path 4, imatinib 600 mg/day compared with Path – 1, best supportive care falls. This is because the reduction in cost of medications as the probabilities that patients die or make the transition to best supportive care increase, more than compensate for the fall in QALYs. The QALYs associated with Path – 3, imatinib 600 mg/day to imatinib 800 mg/day to sunitinib fall but the incremental cost per QALY compared with Path 4, imatinib 600 mg/day, is virtually unchanged.

Table 19 Changes to mortality and response rates

	Strategy	Cost (£)	QALYS	Incremental cost per QALY (£)
Base case	Path-1 Best supportive care	92,811	2.397	
	Path- 7 Sunitinib	96,688	2.411	272,365
	Path-4 Imatinib 600 mg	147,060	4.256	27,304
	Path-3 Imatinib 600 mg to Sunitinib	149,200	4.286	71,723
	Path 6 Imatinib 800 mg	153,901	3.635	Dominated
	Path-5 Imatinib 800 to Sunitinib	155,828	3.659	Dominated
	Path-2 Imatinib 600 mg to 800 to Sunitinib	172,152	4.803	44,359
Sensitivity analysis 5 Survival rate and response rate to Imatinib 600 mg treatment same as Imatinib 800.	Path-1 Best Supportive Care	92,811	2.397	
	Path- 7 Sunitinib	96,688	2.411	272,365
	Path-4 Imatinib 600 mg	126,074	3.635	24,019
	Path-3 Imatinib 600 mg to Sunitinib	128,001	3.659	80,476
	Path-2 Imatinib 600 mg to 800 to Sunitinib	149,703	4.145	44,603
	Path 6 Imatinib 800 mg	153,901	3.635	Dominated
	Path-5 Imatinib 800 to Sunitinib	155,828	3.659	Dominated

Uncertainty surrounding utility values

The sensitivity of a lower and higher value of utility with the health status of disease progression was examined. In this analysis the lower value was 0.52 and a higher utility value for those patients who progressed with GIST of 0.712 was assumed instead of 0.577 as was used in the base case (Table 20). Reducing the utility value increased the QALYs for treatments that had higher probabilities of response. The incremental cost per QALY for Path - 4, imatinib 600 mg/day compared with Path – 1, best supportive care slightly falls and the incremental cost per QALY for Path –2, imatinib 600 mg/day to imatinib 800 mg/day to sunitinib compared with Path 4, imatinib 600 mg/day falls to approximately £40,000.

Conversely, increasing the utility associated with progressive disease reduced the opportunity for pathways which are clinically more effectiveness to generate additional QALYs. As a consequence in this sensitivity analysis the incremental cost per QALYs for the non-dominated pathways increases.

Table 20 Sensitivity analysis around the utility assumed for disease progression

	Strategy	Cost (£)	QALYS	Incremental cost per QALY (£)
Base case e.g. Utility of Progressive state =0.577	Path-1 Best supportive care	92,811	2.397	
	Path- 7 Sunitinib	96,688	2.411	272,365
	Path-4 Imatinib 600 mg	147,060	4.256	27,304
	Path-3 Imatinib 600 to Sunitinib	149,200	4.286	71,723
	Path 6 Imatinib 800 mg	153,901	3.635	Dominated
	Path-5 Imatinib 800 mg to Sunitinib	155,828	3.659	Dominated
	Path-2 Imatinib 600 to 800 mg to Sunitinib	172,152	4.803	44,359
Sensitivity analysis 6 Utility of Progressive state =0.52	Path-1 Best supportive care	92,811	2.160	
	Path- 7 Sunitinib	96,688	2.242	Ext Dom
	Path-4 Imatinib 600 mg	147,060	4.158	27,156
	Path-3 Imatinib 600 to Sunitinib	149,200	4.219	34,911
	Path 6 Imatinib 800 mg	153,901	3.543	Dominated
	Path-5 Imatinib 800 mg to Sunitinib	155,828	3.596	Dominated
	Path-2 Imatinib 600 to 800 mg to Sunitinib	172,152	4.782	40,759
Sensitivity analysis 7 Utility of Progressive state =0.712	Path-1 Best supportive care	92,811	2.958	
	Path- 7 Sunitinib	96,688	2.812	Dominated
	Path-4 Imatinib 600 mg	147,060	4.488	35,440
	Path-3 Imatinib 600 to Sunitinib	149,200	4.444	Dominated
	Path 6 Imatinib 800 mg	153,901	3.853	Dominated
	Path-5 Imatinib 800 mg to Sunitinib	155,828	3.808	Dominated
	Path-2 Imatinib 600 to 800 mg to Sunitinib	172,152	4.853	68,837

Ext Dom = extended dominance

Uncertainty surrounding the cost of Imatinib and Sunitinib

In this set of sensitivity analyses reductions in the cost of imatinib 600 mg/day, imatinib 800 mg/day and sunatinib are explored (Table 21). Over most of these sensitivity analyses the pathways that are dominated or are extendedly dominated does not change. As would be expected reducing the costs of each medication individually reduces the cost of pathways involving that medication. Over all these sensitivity analyses there are only relatively modest changes in the ICERs reported. One of the more substantive changes is that when the cost of sunitinib is reduced Path – 7, sunitinib becomes the least costly option. This is primarily because this pathway uses the potentially unreliable data on mortality for sunitinib which means that patients on this pathway do not survive long enough to incur higher costs.

Table 21 Sensitivity around the costs of imatinib and sunitinib

	Strategy	Cost (£)	Eff (QALYS)	Incr cost per QALY (£)
Base case:	Path-1 Best supportive care	92,811	2.397	
Imatinib 600 mg	Path- 7 Sunitinib	96,688	2.411	272,365
£2406,	Path-4 Imatinib 600 mg	147,060	4.256	27,304
Imatinib 800mg	Path-3 Imatinib 600 to			
$3208.16,	Sunitinib	149,200	4.286	71,723
Sunitinib £3138.8	Path 6 Imatinib 800 mg	153,901	3.635	Dominated
	Path-5 Imatinib 800 mg to			
	Sunitinib	155,828	3.659	Dominated
	Path-2 Imatinib 600 to 800 mg			
	to Sunitinib	172,152	4.803	44,359
Sensitivity analysis 8	Path-1 BSC	92,811	2.397	
(Change in Imatinib	Path- 7 Sunitinib	96,688	2.411	Ext Dom
600mg Price)	Path-4 Imatinib 600 mg	130,272	4.256	20,150
Imatinib 600 mg	Path-3 Imatinib 600 to			
£2005,	Sunitinib	132,412	4.286	Ext Dom
Imatinib 800mg	Path 6 Imatinib 800 mg	153,901	3.635	Dominated
$3208,	Path-2 Imatinib 600 to 800 mg			
Sunitinib £3138.8	to Sunitinib	155,364	4.803	45,850
	Path-5 Imatinib 800 mg to			
	Sunitinib	155,828	3.659	Dominated
Sensitivity analysis 9	Path-1 Best supportive care	92,811	2.397	
(Change in Imatinib	Path- 7 Sunitinib	96,688	2.411	Ext Dom
800mg Price)	Path 6 Imatinib 800 mg	139,988	3.635	Ext Dom
Imatinib 600 mg	Path-5 Imatinib 800 mg to			
£2406,	Sunitinib	141,915	3.659	Ext Dom

	Strategy	Cost (£)	Eff (QALYS)	Incr cost per QALY (£)
Imatinib 800mg $2807, Sunitinib £31398	Path-4 Imatinib 600 mg	147,060	4.256	29,181
	Path-3 Imatinib 600 to Sunitinib	149,200	4.286	Ext Dom
	Path-2 Imatinib 600 to 800 mg to Sunitinib	166,000	4.803	34,609
Sensitivity analysis 10 (Change in Sunitinib Price) Imatinib 600 mg £2406, Imatinib 800mg $3208, Sunitinib £2092	Path- 7 Sunitinib	87,533	2.411	
	Path-1 Best supportive care	92,811	2.397	Dominated
	Path-3 Imatinib 600 to Sunitinib	144,524	4.286	30,400
	Path-4 Imatinib 600 mg	147,060	4.256	Dominated
	Path-5 Imatinib 800 mg to Sunitinib	151,560	3.659	Dominated
	Path 6 Imatinib 800 mg	153,901	3.635	Dominated
	Path-2 Imatinib 600 to 800 mg to Sunitinib	170,364	4.803	49,940

7.3 Summary

The systematic review of economic evaluations reported in this chapter was not especially informative. This was anticipated at the outset and hence an economic modelling exercise was planned. The modelling exercise compared alternative treatment pathways for patients with unresectable GIST who failed to respond to imatinib 400 mg/day. Over almost all the sensitivity analyses Path - 1, best supportive care, is the least costly and least effective intervention. Similarly, Path – 4, imatinib 600 mg/day, typically has an incremental cost per QALY that is less than £30,000 compared with Path-1: best supportive care. Path-2 (Imatinib 600 mg/day to imatinib 800 mg/day to Sunitinib) is the only other pathway which is not dominated or extendedly dominated over most of the analyses conducted. However, in this case the incremental cost per QALY (compared to the next most costly option (Path – 4: imatinib 600 mg/day) tends to be in excess of £40,000.

When society's willingness to pay for a QALY is less than approximately £25,000 Path – 1, best supportive care is the most cost-effective. When society's willingness to pay for a QALY is between approximately £25,000 and £45,000 Path – 4, imatinib 600 mg/day is most likely to be considered cost-effective. Beyond a threshold of approximately £45,000 Path – 2, imatinib 600 mg/day to imatinib 800 mg/day to sunitinib is most likely to be cost-effective.

The results of the economic analysis are based upon spare data that is potentially biased and are surrounded by considerable imprecision. In particular data for sunitinib and for imatinib 600 mg/day are the most suspect. The analysis has also not considered three main areas of uncertainty due to lack of data:

- Alternative assumptions about how probabilities of death and response change over time; and
- Reductions in utility associated with side effects of treatment.

The impact of making alternative assumptions about how probabilities for death and response change is unknown but it is anticipated that the assumption of constant probabilities over time will exaggerate estimated life expectancy (and hence QALYs and cost) for all pathways. The net impact on relative cost-effectiveness is unclear as it depends upon the magnitude of any changes in both costs and QALYs that might occur.

The net impact of adjusting scores for side effects is also uncertain but it might be expected that it will reduce the QALYs associated with each medication and, although there is limited data available from the systematic review of effectiveness, this reduction may be greater for pathways involving sunitinib because its side-effect profile is believed to be worse than imatinib.

A further factor not considered by the economic model was the cost-effectiveness of treatment with specific gene mutations. Again this was not addressed due to lack of data.

Finally, the economic evaluation has assumed that patients who move on to best supportive care remain on treatment to prevent tumour flare. This has the impact of increasing the cost of best supportive care. It is further assumed that there is no impact on effectiveness (the implicit assumption is that discontinuing the medication would reduce life expectancy). Within the analysis it has been assumed that all patients on best supportive care or moving on to best supportive care after failing to respond on a medication would receive imatinib 400 mg/day. This assumption appears reasonable for Path – 1, best supportive care but may not be appropriate for the other pathways where patients would move on to best supportive care after failing to respond on an escalated dose of imatinib or on sunitinib. Should these patients continue with the last active medication that they received then costs, and incremental costs per QALY would increase.

8 ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES

GISTs are a rare cancer accounting for less than 1% of all cancers of the gastrointestinal tract. NICE guidance on imatinib for the treatment of unresectable and/or metastatic GIST does not recommend an increase in the dose of imatinib for people receiving imatinib who develop progressive disease after initially responding at the 400 mg/day dose.[48] Some guidelines however do advocate dose escalation for such patients, particularly those with KIT exon 9 mutations.[15,109,110]

Since the availability of sunitinib, guidance on the treatment of patients with unresectable and/or metastatic GIST has been adapted to take account of this drug as a possible second line treatment[15] in circumstances where patients either are intolerant to imatinib, or have progressed on treatment with imatinib at a 400 mg/day dose. NICE guidance recommends sunitinib as a treatment option for people with unresectable and/or metastatic malignant GISTs if imatinib treatment has failed because of resistance or intolerance, and the drug cost of sunitinib for the first treatment cycle is met by the manufacturer.

In clinical practice the treatment of patients with unresectable and/or metastatic GIST is generally decided on a case by case basis by multidisciplinary teams. Many clinicians advocate initial dose escalation of imatinib and then consider sunitinib on subsequent progression, although practice will vary depending on the specific needs of individual patients.

9 DISCUSSION

9.1 Statement of principal findings

9.1.1 Clinical effectiveness

This review is a part update of a previous review on imatinib for the treatment of patients with unresectable and/or metastatic gastrointestinal stromal tumours (GISTs).[53] This review focused on patients with KIT (CD117) positive unresectable and/or metastatic GISTs whose disease had progressed on treatment with imatinib at a dose of 400 mg/day. Five studies involving 2032 patients on relevant treatment arms, met the inclusion criteria. Of these studies, four involving 318 patients reported imatinib outcomes and one involving 351 patients, who had received a prior imatinib dose of ≤ 400 mg/day reported sunitinib. No studies reporting best supportive care were identified that met our inclusion criteria.

Although the study designs for most of the included trials were RCTs (plus one retrospective cohort study) none of these trials had, as their primary objective, the assessment of the effects of dose escalation following progression on 400 mg/day imatinib. Only a proportion of the overall patient populations received an escalated dose, and these patients were not randomised at the point of dose escalation to receive either an escalated dose of imatinib or remain on 400 mg/day. Therefore the nature of the evidence base for patients who progress on 400 mg/day imatinib and receive escalated doses of 600 or 800 mg/day is observational and therefore open to extensive bias.

The sample sizes involved ranged from 24[73] to 1117[82] participants, and each study had more male than female participants. The vast majority of participants in each study had an ECOG performance status of ≤2, meaning that they were ambulatory and confined to bed for less than 50% of their waking hours.[111] Of the studies that reported the proportion of the study population receiving prior surgery,[37,42,73] most patients had undergone prior surgery for treatment of their disease.

At an escalated imatinib dose of 600 mg/day, between 25.6% (11/43)[37] and 41.7% (5/12)[73] of patients with unresectable and/or metastatic GIST who had previously progressed on a dose of 400 mg/day of imatinib, either developed a partial response or maintained stable disease at the higher dose. At an escalated imatinib of 800 mg/day, the proportions achieving partial response or stable disease ranged between 29.3%[42] to 33.3%.[73] These data were used to inform transition probabilities of non-response to imatinib at escalated doses of 600 mg/day and 800 mg/day respectively. However, response data were not available for patients receiving sunitinib following treatment with imatinib at a dose of ≤400 mg/day. The

economic model was therefore required to use sources excluded from the review of clinical effectiveness on account of failure to report response data separately for those progressing on a 400 mg/day dose, and make the assumption that response was unaffected by prior treatment received. From the data on imatinib, it can be seen that approximately one third of patients progressing on 400mg/day imatinib will respond to escalated doses.

Median overall survival data were not reported for those receiving an escalated imatinib dose of 600 mg/day upon progression at a 400 mg/day dose. Therefore, the economic model calculated the probability of death from the available trial data on median overall survival according to best response, and the proportion of patients receiving escalated doses who will have had a response to imatinib at the initial 400 mg/day dose prior to eventual progression and dose escalation.

For those receiving an escalated imatinib dose of 800 mg/day upon progression, median overall survival was reported to be 19 months (95% CI 13 to 23 months) in the S0033 trial.[39] Median overall survival was not reported for the EORTC-ISG-AGITG study for the population of interest, [redacted] For those receiving sunitinib after a prior imatinib dose of ≤400 mg/day, median overall survival was reported as 22.5 months (95% CI 18.3 to 26.5 months).[82]

Figure 3 provided a visual comparison of the median overall survival times for imatinib at an escalated dose of 800 mg/day and sunitinib, showing overlapping confidence intervals until 33 months from commencement of treatment, at which point the estimated proportion of sunitinib patients surviving appeared to be less than the proportion surviving on the 800 mg/day imatinib dose. [redacted]. It is difficult to draw any conclusions with regard to possible differences in overall survival between imatinib at an escalated dose of 800 mg/day and sunitinib at 50 mg/day (with a four week on/two week off cycle), owing to the lack of data, but as the 95% confidence intervals for median overall

survival overlap, there does not appear to be any significant difference in median overall survival with dose escalation, compared with sunitinib.

Park and colleagues reported that the median time to progression for those receiving an escalated dose of imatinib to 600 mg/day was 1.7 months (range 0.7 to 24.9 months).[73] For studies looking at dose escalation of imatinib to 800 mg/day, progression-free survival ranged from 2.9 months (reported without confidence intervals as "81 days")[42] to 5 months (95% CI 2 to 10 months).[39] A meta-analysis of progression-free survival for patients receiving imatinib at an escalated dose of 800 mg/day was attempted but it was not possible to obtain valid results due to the lack of data available. A visual representation of these data in Figure 4 gives 95% confidence intervals that do not overlap, for all time points between 12 and 21 months, indicating that progression-free survival was signficantly shorter in the EORTC-ISG-AGITG study reported by Zalcberg and colleagues[42] than in the S0033 trial reported by Blanke and colleagues.[39]

Both trials providing information on progression-free survival for patients receiving an escalated dose of imatinib at 800 mg/day reported that between 16.1% (19/118) and 18.8% (25/133) of patients were progression free at the time of the analysis. This represented a proportion of between 52.8% (19/36) and 64.1% (25/39) of all those achieving partial response and stable disease on the escalated dose of 800mg/day. This suggests that a small proportion (i.e. <20%) of those receiving an escalated dose of 800 mg/day imatinib on progression, may maintain their response/stable disease for a median of at least 25 months (i.e. the shorter of the median follow up times reported by these trials), and those who achieve a response or maintain stable disease on the escalated dose may have a greater than 50% likelihood of maintaining this in the longer term.

For those receiving an escalated dose of 800 mg/day, the study by Zalcberg reported a median duration of "stabilisation" among those showing response or stable disease with treatment, of 153 days (range 37 to 574 days).[42] Data were not reported for the treatment duration of patients given sunitnib following failure on imatinib at a dose of ≤400 mg/day. Kang and colleagues reported that treatment duration "did not significantly differ based on the dose of prior imatinib therapy".[76] It was not reported whether this statement was still accurate at the time further analysis was undertaken by Seddon and colleagues. At the time the Seddon and colleagues analysis was undertaken, it was reported that the treatment duration for all patients receiving sunitinib (i.e. regardless of the dose of prior imatinib therapy) was 126 days (range 1 to 618 days).[82] If these data are considered along with the data on median progression-free survival or time to progression, it can be seen that for patients with unresectable and/or

metastatic GIST, the duration of response following either dose escalation of imatinib, or sunitinib treatment, after progression on imatinib at a 400mg/day dose, is likely to be short (i.e. best measured in terms of months rather than years). However it should be noted that the consistency of defintions across studies is unclear, as these were not stated within the study reports, and the use of "duration of treatment" may not be an appropriate substitute in the absence of data on "duration of response", as patients who stop responding may still remain on the study drug to prevent an acceleration of disease and symptoms following withdrawal.

Data on adverse events were not available from any studies where the population of interest received imatinib at 600mg/day, or sunitinib following progression at 400mg/day. For the trials reporting outcomes following dose escalation from 400mg/day to 800mg/day after progression at the lower dose, it was reported that the vast majority (88.4%) of study discontinuations were due to disease progression and not study drug toxicity.[42]

[redacted]

Nevertheless, it was also reported that between 15.6%[74] and 31%[75] of patients receiving an escalated imatinib dose of 800mg/day required a dose reduction. It was also reported that 23.3% (18/77) patients required at least one dose delay.[74] However, it was not possible to take possible dose reductions into account with regard to any of the outcomes. This was because information on the dose provided following reduction, the median duration of any dose delay or dose reduction, and any other factors besides toxicity contributing to any of the dose delays or reductions, were not reported.

These data on discontinuations and dose modifications indicate that whilst disease progression is far more likely than adverse events to contribute to the decision to stop escalated imatinib treatment at the 800 mg/day dose, approximately one third of patients will require dose modifications (i.e. dose reduction or interruption) during treatment at this escalated dose.

With regard to specific adverse events, data were reported by Zalcberg and colleagues showing that a higher proportion of patients with skin rash, nausea, leucopenia, neutropenia and throbocytopenia reported a reduction in the severity of these events compared with the proportion of patients reporting an increase in these events. This reduction was significant in

the case of neutropenia (p=0.002). However, the proportion of patients with oedema, fatigue, dyspnoea and anaemia who reported an increase in severity of these events following dose escalation, was greater than the proportion of patients who reported a reduction in these events. This increase in severity was significant in the case of fatigue (p<0.001) and anaemia (p=0.015).[42]

[redacted] It is difficult to draw any conclusions about specific adverse events from these data, aside from noting that fatigue and anaemia may significantly increase upon dose escalation from 400 mg/day imatinib to 800 mg/day.

The only data available for any of the pre-specified sub-groups of interest, was reported by Debiec-Rychter and colleagues for the EORTC-ISG-AGITG trial which looked at imatinib dose escalation from 400mg/day to 800mg/day following progression at the lower dose. They noted that patients with wild-type, and those with exon 9 mutation, were significantly more likely to have a response to dose escalation than those with exon 11 mutations, but no numerical data were reported for the population of interest.[14]

[redacted] Furthermore, it has been argued that subgroups with certain exon mutations might have improved response and/or survival outcomes if they initially receive an escalated imatinib dose, rather than receiving dose escalation only if there was progression at the 400 mg/day dose.[109]

It was outwith the remit of this review to consider outcomes for patients receiving escalated dosing other than following progression on the initial 400 mg/day dose. The lack of data

available meant it was not possible to assess for specific mutational population subgroups the effects of escalation to an imatinib dose of 800 mg/day following progression at the initial 400 mg/day dose.

9.1.2 Review of cost-effectiveness

The economic component of this study included both a review of the existing economic evaluations and an economic modelling exercise. The evidence from the review of economic evaluations was sparse and there was no published economic evaluation conducted for a UK context which compared the all the interventions for the patient group of interest.

The modelling exercise compared alternative treatment pathways for patients with unresectable GIST who failed to respond to imatinib 400 mg/day. Over almost all the sensitivity analyses Path – 1, best supportive care, is the least costly and least effective intervention. Similarly, Path – 4, imatinib 600 mg/day, typically has an incremental cost per QALY that is less than £30,000 compared with Path–1: best supportive care. Path – 2 (Imatinib 600 mg/day to imatinib 800 mg/day to sunitinib) is the only other pathway which is not dominated or extendedly dominated over most of the analyses conducted. However, in this case the incremental cost per QALY (compared to the next most costly option (Path – 4: imatinib 600 mg/day) tends to be in excess of £40,000.

When society's willingness to pay for a QALY is less than approximately £25,000 Path – 1, best supportive care, is the most cost-effective. When society's willingness to pay for a QALY is between approximately £25,000 and £45,000 Path – 4, imatinib 600 mg/day is most likely to be considered cost-effective. Beyond a threshold of approximately £45,000 Path – 2, imatinib 600 mg/day to imatinib 800 mg/day to sunitinib is most likely to be cost-effective.

9.2 Strengths and limitations of the assessment

In terms of strengths, the review of the evidence base was detailed and thorough. It was unclear from the information provided in a substantial number of abstracts whether the studies met the inclusion criteria and full text papers for all of these reports were obtained and assessed. Non-English language studies were not excluded. Authors were contacted in an attempt to obtain additional information concerning their studies. For the review of economic evaluation, a rigorous systematic approach was adopted. The economic model considered a larger number of plausible alternative treatments and also incorporated both a probabilistic and deterministic estimates of cost effectiveness. The former was limited to clinical effectiveness parameters but this limitation was chosen specifically to draw attention to the uncertainties surrounding these data.

In terms of limitations, there was a dearth of evidence available on the specific population of interest, despite the overall large evidence base on the treatment of GISTs with imatinib or sunitinib. The quality of reporting of dose information in reports of imatinib or sunitinib for GISTs was poor and the data on the population of interest for the studies that were included was non-randomised, non-comparative and therefore observational. Therefore lack of quality data as well as lack of data itself, severely limited both assessments of clinical and cost-effectiveness.

There was also a lack of evidence on quality of life outcomes, which may be of fundamental importance to patients given the potentially palliative nature of treatment following progression, and there was also a lack of evidence on best supportive care. This is important as following the introduction of imatinib and sunitinib, it no longer represents the only treatment option for those with unresectable/metastatic disease. There was little evidence on the response to escalated doses of imatinib based on mutational status, specifically for those who had already failed on an initial imatinib dose of 400 mg/day. It was also not possible to account for the effects of required dose interruptions and reductions, or the effects of sunitinib on those intolerant to imatinib, owing to the lack of available data. This lack of data also prevented an comparative analysis of adverse events between the intervention and comparator treatments.

For sunitinib, it was also necessary to assume that the vast majority of those receiving sunitinib after imatinib treatment at ≤400 mg/day had actually received imatinib at 400 mg/day, and this may not be a valid assumption. However, it was not possible to confirm the validity of the assumption despite contacting the study authors (Personal correspondence, P Reichardt). In addition, much of the evidence base for sunitinib generally relates to its use following the failure of escalated doses of imatinib rather than failure on 400 mg/day, suggesting that the role of sunitinib is seen more as a third line treatment rather than a potential comparator to 600 or 800 mg/day imatinib treatment. This was highlighted by the manufacturer of imatinib in their submission for this Technology Appraisal, and is noted in Chapter 5 of this report.

For the economic model, sufficient sound comparative data for the different plausible treatments was not available, despite conducting an extensive review of relevant studies. Therefore sufficient and appropriate data needed to populate the model were difficult to identify. This led to a number of simplifying assumptions being made with respect to the model and also on the use of data that were potentially unreliable. The model assumes that

patients entering a pathway will remain in that treatment for one cycle only if they do not respond and survive in the treatment arm. In these cases they are either considered to move to the escalated doses or to another alternative (if allowed by a treatment pathway) or continue with best supportive care for the remainder of the model time horizon or until they die. A further simplifying assumption was not to model the complications and side effects of therapy. This latter assumption was made due the very limited evidence available. This is coupled with the assumptions made that the utility associated with stable response or progression did not vary between treatments. One impact of this assumption is that no utility decrement has been assumed for the arguably worse side effect profile of sunitinib. This means that pathways involving sunitinib may overestimate QALYs.

Perhaps a more important limitation is caused by the limited evidence base available. With respect to the clinical effectiveness data used to derive transition probabilities these data, as already noted, were based upon non-randomised, non comparative data. Such data are potentially biased as well as being imprecise. In particular, it is worth noting that point estimates of death and response used within the model may be misleading, for example, the point estimates used suggest that sunitinib has a higher mortality rate than best supportive care.

9.3 Uncertainties

For the assessment of clinical effectiveness:

- The diagnosis of GIST as stated in the final scope document was based on a positive KIT (CD117) test. However this is not a perfect test and in a small (<5%) number of cases a patient can have a GIST despite having a negative KIT (CD117) test.[4,7,25] More recent tests (e.g. PDGRFA and DOG1) may clarify diagnosis. 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.
- It was not possible to conduct any sub-group analysis for patients with particular mutations, or consider the methods used to identify response (e.g. FDG-PET or CT scanning), or possible factors related to the provision of dose escalated imatinib in an adjuvant or neoadjuvant setting.
- Following progression, the proportion of patients subsequently progressing on escalated doses, who are kept on the study drug on the basis that progression of disease might be slower than if the patient were to be taken off the drug, is not known. It is also not clear whether there is a standard dose used for this purpose. Within the economic model it has been assumed that this would be the case (400 mg/day)

- This review only considered drug treatments that were licensed for patients with GISTs and did not consider other drugs that may be being used in the treatment of GISTs, or licensed drugs that are being used 'off licence' to treat GIST (e.g. imatinib at doses exceeding 800 mg/day, or sunitinib provided in a continuous daily dosing regime).

The economic model has also not considered three main areas of uncertainty due to lack of data:

- Alternative assumption about how probabilities of death and response change over time;
- Reductions in utility associated with side effects of treatment; and
- Impact on cost-effectiveness for people with different gene mutations.

The impact of making alternative assumptions about how probabilities for death and response change is unknown but it is anticipated that the assumption of constant probabilities over time will exaggerate estimated life expectancy (and hence QALYs and cost) for all pathways. The net impact on relative cost-effectiveness is unclear as it depends upon the magnitude of any changes in both costs and QALYs that might occur.

The net impact of adjusting utility scores for side effects is also uncertain but it might be expected that it will reduce the QALYs associated with each medication and, although there is limited data available from the systematic review of effectiveness, this reduction may be greater for pathways involving sunitinib because its side-effect profile is believed to be worse than imatinib.

A further factor not considered by the economic model was the cost-effectiveness of treatment with specific gene mutations. Again this was not addressed due to lack of data.

Finally, the economic evaluation has assumed that patients who move on to best supportive care still receive medication to prevent tumour flare. This has the impact of increasing the cost of increasing the cost of best supportive care. It is further assumed that there is no impact on effectiveness (the implicit assumption is that discontinuing the medication would reduce life expectancy). Within the analysis it has been assumed that all patients on best supportive care or moving on to best supportive care after failing to respond on a medication would receive imatinib 400 mg/day. This assumption appears reasonable for Path – 1, best supportive care only, but may not be appropriate for the other pathways where patients would move on to best supportive care after failing to respond on an escalated dose of imatinib or on

sunitinib. Should these patients continue with the last active medication that they received then costs, and incremental costs per QALY would increase.

10 CONCLUSIONS

10.1 Implications for service provision

- There was very limited evidence available from very few studies on the effects of escalated doses of imatinib 600 mg/day and 800 mg/day or treatment with sunitinib for people with unresectable and/or metastatic GIST whose disease had progressed on the 400 mg/day dose. The evidence that was available was essentially observational in nature and subject to the biases associated with such data, consisting mostly of reporting of subgroups of patients in RCTs that were not designed to assess the effects of dose escalation.
- The limited evidence base suggests that around one third of patients with unresectable and/or metastatic GIST who have failed on a dose of 400 mg/day, may show response or stable disease with escalated doses of imatinib, and those who do respond may have a reasonable chance of maintaining this response over a longer period of time than would otherwise have been the case.
- For all patients receiving either dose escalated imatinib, or sunitinib, median overall survival, where reported, was less than two years.
- Although the results should be interpreted with caution due to the limitations of the evidence base, should society's threshold for willingness to pay be less than £25,000 per QALY a pathway of best supportive care only has the highest probability of being cost-effective. Between a threshold of £25,000 and £45,000 provision of an escalated dose of imatinib would be most likely to be cost-effective. Above a threshold of £45,000 a threshold a pathway of escalated doses of imatinib followed by sunitinib, if necessary, would be most likely to be cost-effective.

10.2 Recommendations for research

Further evidence is needed in order to provide a comprehensive assessment of effectiveness and cost-effectiveness of the alternative treatments for GIST patients who fail on or become resistant to imatinib 400 mg/day. Ideally such data should come from RCTs involving patients who progress on 400 mg/day imatinib, where patients are randomised to 600 mg/day, 800 mg/day, sunitinib, or to remain on 400 mg/day. Dose escalation appears to be used within the NHS already and hence health care professionals may not find it acceptable that their patients could be randomised to 'best supportive care'. Therefore, the following suggested priorities for further research are made:

- An RCT involving patients who progress on 400 mg/day imatinib where patients are randomised to pathways describing alternative combinations of dose escalation with imatinib and the use of sunitinib. The pathways most likely to be cost-effective at thresholds society might be willing to pay and hence potentially the most useful to assess were: dose escalation with imatinib and dose escalation with imatinib followed by sunitinib if necessary. Such studies should as a matter of course include an economic evaluation and measurement of health state utilities.
- Such studies would need to measure outcomes over a sufficiently long time period to capture the main impact on costs and outcomes and in order to avoid the limitation of existing economic evaluations, which relied on extrapolated short-time clinical trial data.
- Where possible further studies should also report outcomes for subgroups of patients with specific KIT mutations.
- There is a dearth of evidence for the utility estimates for the relevant health states of GIST patients. Further UK-relevant information on health state utilities would be useful, collected either as part of a clinical trial, as noted above, or in a stand-alone study.
- With respect to costs, should a further prospective comparative study be conducted the use of health services might usefully be collected. A wider perspective on the consideration of costs might also be informative (e.g. costs that fall on personal social services, which would be relevant for NICE to consider, and costs for patients and their families, which goes beyond NICE's reference case).

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