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Clinical effectiveness and cost-effectiveness of imatinib dose escalation for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours that have progressed on treatment at a dose of 400 mg/day: a systematic review and economic evaluation

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Abstract

Clinical effectiveness and cost-effectiveness of imatinib dose escalation for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours that have progressed on treatment at a dose of 400 mg/day: a systematic review and economic evaluation

J Hislop,[1]* Z Quayyum,[2] A Elders,[1] C Fraser,[1] D Jenkinson,[1] G Mowatt,[1] P Sharma,[1] L Vale[1,2] and R Petty[3]

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Background: Imatinib dose escalation is advocated for gastrointestinal stromal tumour (GIST) treatment, but its effectiveness compared with sunitinib and best supportive care (BSC) after failure at the 400 mg/day dose is unknown.
Objectives: To assess the effectiveness and cost-effectiveness of imatinib at escalated doses of 600 or 800 mg/day for patients with unresectable and/or metastatic GISTs whose disease had progressed on 400 mg/day.
Data sources: Electronic databases, including MEDLINE, MEDLINE In-Process, EMBASE, BIOSIS, Science Citation Index, Health Management Information Consortium and the Cochrane Controlled Trials Register, were searched until September 2009.
Review methods: A systematic review of the literature was carried out according to standard methods. An economic model was constructed to assess the cost-effectiveness of seven alternative pathways for treating patients with unresectable and/or metastatic GISTs.
Results: Five primary studies involving 669 people were included for clinical effectiveness; four reported imatinib and one reported sunitinib. The data were essentially observational as none of the studies was designed to specifically assess treatment of patients whose disease had progressed on 400 mg/day imatinib. For 600 mg/day imatinib, between 26% and 42% of patients showed either a partial response (PR) or stable disease (SD). Median time to progression was 1.7 months (range 0.7–24.9 months). For 800 mg/day imatinib, between 29% and 33% of patients showed either a PR or SD. Median overall survival (OS) was 19 months [95% confidence interval (CI) 13 to 23 months]. Progression-free survival ranged from 81 days to 5 months (95% CI 2 to 10 months). Median duration of response was 153 days (range 37–574 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 OS was 90 weeks (95% CI 73 to 106 weeks). For the cost-effectiveness review, only one full-text study and one abstract were identified, comparing imatinib at an escalated dose, sunitinib and BSC, although neither was based on a UK context. The definition of BSC was not consistent across the studies, and the pattern of resources (including drugs for treatment) and measures of effectiveness also varied. Within the model, BSC (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 quality-adjusted life-year threshold was < £25,000. 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 > £45,000.

Limitations: The evidence base was sparse, data were non-randomised and potentially biased. The economic model results are surrounded by a considerable degree of uncertainty and open to biases of unknown magnitude and direction.

Conclusions: Around one-third of patients with unresectable and/or metastatic GIST, who fail on 400 mg/day of imatinib, may show response or SD with escalated doses. Between a threshold of £25,000 and £45,000, provision of an escalated dose of imatinib would be most likely to be cost-effective. However, these results should be interpreted with caution owing to the limited evidence available on outcomes following imatinib dose escalation or sunitinib for this group of patients.

Funding: The National Institute for Health Research Health Technology Assessment programme.

Contents

List of abbreviations

AGITG	Australasian Gastro-Intestinal Trials Group
AiC	academic in confidence
ATP	adenosine triphosphate
BNF	*British National Formulary*
BSC	best supportive care
c-KIT	cytokine-tyrosine kinase receptor
CEA	cost-effectiveness analysis
CI	confidence interval
CiC	commercial in confidence
CT	computerised tomography
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life-5 Dimensions
ESMO	European Society for Medical Oncology
FDG-PET	fluorodeoxyglucose-positron emission tomography
GI	gastrointestinal
GIST	gastrointestinal stromal tumour
HR	hazard ratio
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IM	imatinib
ISG	Italian Sarcoma Group
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KIT	tyrosine kinase
LYG	life-year gain
LYS	life-year saved
N/A	not applicable
NA	not available
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NR	not reported
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 for Interventional Procedures
RECIST	Response Evaluation Criteria in Solid Tumors
RR	relative risk
SCF	stem cell factor
SD	stable disease
SMC	Scottish Medicine Consortium
TAR	technology assessment review
VEGFR	vascular endothelial growth factor receptor

WHO	World Health Organization
WMD	weighted mean difference

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Note

This monograph is based on the Technology Assessment Report produced for NICE. The full report contained a considerable amount of data that was deemed commercial-in-confidence. The full report was used by the Appraisal Committee at NICE in their deliberations. The full report with each piece of commercial-in-confidence data removed and replaced by the statement 'commercial-in-confidence information (or data) removed' is available on the NICE website: www.nice.org.uk.

The present monograph presents as full a version of the report as is possible while retaining readability, but some sections, sentences, tables and figures have been removed. Readers should bear in mind that the discussion, conclusions and implications for practice and research are based on all the data considered in the original full NICE report.

Executive summary

Background

Fewer 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, 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 (BSC) was the main treatment available until imatinib (Glivec®, Novartis Pharmaceuticals UK) at a dose of 400 mg/day was recommended in the 2004 guidance of the National Institute for Health and Clinical Excellence (NICE), 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®, Pfizer UK), 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 and 800 mg/day following progression of disease at a dose of 400 mg/day, compared with sunitinib, or the provision of BSC 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 400 mg/day. The interventions considered were imatinib at doses of 600 and 800 mg/day, sunitinib, or BSC only. Outcomes considered included overall response, overall survival (OS), disease-free survival, progression-free survival (PFS), time to treatment failure, health-related quality of life (HRQoL) 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 *et al.*, Downs and Black, and the Generic

Appraisal Tool for Epidemiology (GATE) (Verhagen AP, de Vet HC, de Bie RA, Kessels AG, Boers M, Bouter LM, *et al.* The Delphi List: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *J Clin Epidemiol* 1998;**51**:1235–41; Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care intervention. *J Epidemiol Community Health* 1998;**52**:377–84). 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 BSC, which patients would enter if they had exhausted all other treatments in a pathway. Both deterministic and probabilistic sensitivity analyses were 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 (containing 669 patients in relevant treatment arms) met the inclusion criteria, with four ($n = 318$) reporting outcomes for patients who received escalated doses of imatinib and one ($n = 351$) reporting outcomes for patients who received sunitinib. No studies meeting our inclusion criteria were identified for BSC. 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 (PR) or stable disease (SD). Median time to progression was 1.7 months (range 0.7–24.9 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 PR or SD. The median OS was 19 months [95% confidence interval (CI) 13 to 23 months]. PFS ranged from 81 days to 5 months (95% CI 2 to 10 months). The median duration of response was 153 days (range 37–574 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 OS 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 BSC, were identified. Neither was based on a UK context. The definition of BSC was not consistent across the studies, and the pattern of resources (including drugs for treatment) and measures of effectiveness also varied.

For economic evaluation, a Markov model was developed to compare the alternative treatment strategies 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.

The assumed pathway of the model

The model was based on seven clinically plausible care pathways. The states considered in the model were those thought to reflect care pathways for people with GIST. Patients entering the pathways were those who failed on imatinib 400 mg/day. The alternative treatments considered were imatinib 600 mg/day, imatinib 800 mg/day, sunitinib (within its licensed dose regimen), and BSC. The patient pathways considered in the model were:

- start with imatinib 600 mg then imatinib 800 mg if the patient fails on 600 mg, *or*
- start with imatinib 600 mg then imatinib 800 mg if the patient fails on 600 mg, and then sunitinib if the patient progresses or fails on 800 mg, *or*
- start with imatinib 600 mg then move to treatment with sunitinib if the patient fails to respond to 600 mg.

Within the model, Path-1, BSC (which was assumed to include continuing medication to prevent tumour flare), was the least costly and least effective pathway. It would be the care pathway most likely to be cost-effective when the cost per quality-adjusted life-year (QALY) threshold was less than £25,000. Path-4, imatinib at 600 mg/day, was most likely to be cost-effective at a threshold of 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 > £45,000.

Sensitivity analysis

The results did not greatly alter under the majority of the sensitivity analyses conducted. However, all of 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, owing 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 BSC 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 few 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 patients with GIST who receive dose-escalated imatinib show either response or SD, which can be maintained over several months. However, few data were available for imatinib at 600 mg/day and median OS for imatinib at 800 mg/day and sunitinib was < 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 economic model showed that pathways involving dose escalation would be cost-effective should the cost per QALY threshold be ≥ £30,000. Treatment with sunitinib after progressing on imatinib at 400 mg/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 (QoL) outcomes, which would have informed the economic model, and 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 SD 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 OS, where reported, was < 2 years.

The results of the economic model are surrounded by a considerable degree of uncertainty due to the limited nature of the available evidence base, and the direction and magnitude of biases in the results is unclear, so these results need to be interpreted with caution. They indicate that should society's threshold for willingness to pay be less than £25,000 per QALY a pathway of BSC 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 pathway of escalated doses of imatinib followed by sunitinib, if necessary, would be most likely to be cost-effective.

In terms of policy-making, the degree of uncertainty itself, in the authors' opinion, clearly illustrates that at present there is insufficient available evidence to show that dose escalation of imatinib upon progression at the 400 mg/day dose (for patients with unresectable and/or metastatic GISTs) would be a cost-effective strategy for the NHS.

Recommendations for research

Suggested priorities for further research are made:

- Ideally, an RCT involving patients who progress on 400 mg/day imatinib in which patients are randomised to pathways describing alternative combinations of dose escalation with imatinib and the use of sunitinib should be performed. Such a study may be difficult to organise as neither patients nor practitioners may be in equipoise. Therefore, alternative quasi-experimental or observational designs should be considered but with sufficient focus on understanding and controlling for selection biases.
- The pathways most likely to be cost-effective at thresholds society might be willing to pay and hence, potentially, the most useful to assess in any further primary study are 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).

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1

Background

Description of health problem

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, 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]

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, therefore having 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 signalling cascades controlling cell proliferation, adhesion and differentiation. *KIT* mutation is necessary but not sufficient for the pathogenesis of GISTs; 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 < 2 years without further treatment.[18,19]

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 underdiagnosed 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]

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]

Gastrointestinal stromal tumours of < 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.

Current service provision

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]

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 preoperative assessment to determine stage and also the fitness of the patient for the procedure required. Preoperative assessment for staging includes (as a minimum) a computerised tomography (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 (400 mg/day for 1 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 imatinib is licensed for adjuvant treatment of patients who are at a significant risk of relapse,[34] but although Scottish guidelines recommend adjuvant imatinib (400 mg/day) in patients considered to be of moderate or high risk of relapse, according to histopathological criteria,[15] a National Institute for Health and Clinical Excellence (NICE) Technology Appraisal for this indication is still ongoing,[35] and 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 subgroups 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.[36]

Studies are ongoing to determine the role of imatinib as preoperative therapy in resectable tumours.[37] 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.

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®, Novartis Pharmaceuticals UK) 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 licence for imatinib was based on a Phase II study of 147 patients who were randomised to receive imatinib at either 400 or 600 mg orally taken once daily.[38] The treatment was well tolerated, objective response rate was the primary efficacy outcome and an overall partial response (PR) rate of 67% was demonstrated with no difference between treatment arms. Long-term results revealed median survival of 57 months for all patients.[39] A concurrent study investigated dose escalation and established 800 mg daily as the maximum tolerated dose.[40] Phase III trials performed both in Europe and Australasia [European Organisation for Research and Treatment of Cancer (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 400 mg orally per day.[41,42]

Primary resistance to imatinib is uncommon, but acquired resistance is highly likely, and manifest clinically by the observation of disease progression.[41–45] Guidelines suggest that

patients should have a CT scan every 3 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 happen only 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.[46,47] Similarly, fluorodeoxyglucose-positron emission tomography (FDG-PET) has demonstrated some efficacy in predicting early response to imatinib therapy,[48] although it should be noted that PET scanning is not widely available in the UK as very few NHS centres have access to this technology.

In addition, the assessment of progression of GISTs may be problematic if based on RECIST-based tumour size criteria, as tumour liquefaction (cystic degeneration) can occur, which may give the appearance of progressive disease (PD) although the tumour is actually responding.[47] Accordingly, it is recognised that experienced radiologists should assess CT scans before confirming progression.

It has been demonstrated that interruption of treatment results in rapid disease progression in many patients with advanced GISTs.[45] This includes patients with disease progression in whom a symptomatic worsening or 'flare' has been described.[49] Therefore, continuation of imatinib in these patients has been common practice despite progression, as part of best supportive care (BSC).

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.[39,44] However, it should be noted that current NICE guidelines for imatinib do not actually recommend dose escalation for patients with unresectable and/or metastatic GISTs who progress on an initial dose of 400 mg/day.[50]

Recently, sunitinib (Sutent®, Pfizer UK), another molecular-based treatment for GIST, became available, and has been approved by NICE for patients with unresectable and/or metastatic GIST who have progressed on treatment with imatinib.[51] 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;[52] the trial was unblinded early when interim analysis showed a significantly longer time to tumour progression (the primary end point) with sunitinib.

To date, no randomised trial has been conducted comparing imatinib and sunitinib. One had been planned but was stopped owing to poor recruitment.[53] 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.

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-aged population suffering from GIST is of concern. The median age of the GIST patients was found to be between 50 and 60 years,[22,23] and incidence of GIST was found to increase with increase in age.[54] 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 annually for patients on 400 and 600 mg/day, respectively.[55] 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 2 years it would cost the NHS approximately £31,160 to treat a patient with imatinib, and for 10 years this figure would be £56,146 (2002 price year).[54,55] Costs would differ when patients who fail to respond to imatinib are provided with higher doses or alternative treatments (e.g. sunitinib).[50]

The costs of treating patients with unresectable and/or metastatic GIST using imatinib were estimated at between £1557 and £3115 per month per patient, resulting in a cost to the NHS (England and Wales) of between approximately £5.6M and £11.2M per year (2002 price year).[55] Another study estimates that the total costs over 10 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 when managed with BSC (price year not stated).[54]

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 at 50 mg/day (4 weeks out of 6 weeks) or, alternatively, BSC only (although due to the 'symptomatic flare' already mentioned this may include continuation of imatinib at 400 mg/day). Many clinicians advocate initial dose escalation of imatinib and then consider sunitinib on subsequent progression, but there will be variation in clinical practice depending on the specific needs of individual patients.

Relevant national guidelines

UK guidelines recommend the dose escalation of imatinib, and/or sunitinib following imatinib failure,[15,56] but also suggest that clinical decisions are made on an individual case-by-case basis, reflecting uncertainty regarding optimal practice.

Description of technology under assessment

Summary of intervention

Imatinib

Imatinib (Glivec) is a rationally designed small molecule inhibitor of several oncogenic tyrosine kinases: c-Abl, PDGFRA and the KIT tyrosine kinases. Its therapeutic activity in GISTs relates to inhibition of KIT, although in cases with no *KIT* mutation the inhibition of PDGFRA is likely to be of therapeutic importance.[2] Imatinib is a derivative of 2-phenylaminopyrimidine, and a competitive antagonist of adenosine triphospate (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 UK NHS in KIT-immunoreactive positive advanced/unresectable GISTs.[50,57]

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.[58] 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.[59] However, the potent antiangiogenic activity of sunitinib as a consequence of strong VEGFR inhibition may also be important for clinical activity in GISTs.

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'.[55] It usually involves interventions to manage pain and treat fever, anaemia (due to GI haemorrhage) and GI obstruction,[50] and can include palliative measures.[60] A Cochrane review of supportive care for patients with GI cancer defined supportive care as 'the multi-professional attention to the individual's overall physical, psychosocial, spiritual and cultural needs'.[61] It was argued that this type of care should ethically be made available to all treatment groups, meaning that treatment with imatinib or sunitinib could not be provided without concomitant supportive care as well in clinical practice for patients with GIST, although it is possible that treatment with BSC could be provided without additional drug treatment with either imatinib or sunitinib. It should be noted that the amount of care required as part of BSC is likely to increase as the disease progresses and symptoms become worse.

Identification of important subgroups

The differential benefit from imatinib and sunitinib in subgroups of patients with GIST, 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 patients with GIST may acquire more than one secondary *KIT* mutation.[62]

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.[63] Similarly, objective response rates to imatinib 400 mg/day are higher in patients with exon 11 primary mutations than in those with exon 9 mutations, or those with no detectable *KIT* or *PDGFR* mutation.[14,41] 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. Recent studies have indicated that plasma monitoring in GIST patients could assist clinicians' decision-making with regard to whether or not dose escalation of imatinib is required for particular patients, including those with mutations in *KIT*.[64–66]

Secondary mutations in *KIT* exons 13, 14, 17 and 18 are associated with acquired resistance to imatinib.[43] Sunitinib activity after progression on imatinib has been demonstrated in GIST patients with imatinib resistance conferring secondary *KIT* mutations.[62] 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.[62] 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.[62] However, it is not clear how dose-escalated imatinib (800 mg/day) compares with sunitinib in patients with primary exon 9 *KIT* mutations. 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–ATP 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).[62]

Changes in FDG (fluorodeoxyglucose) 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[49] in the future as the technology becomes more widely available in NHS settings.

Current usage in the NHS

Current practice is to commence patients on imatinib 400 mg/day, and on confirmed disease progression the options are dose escalation of imatinib up to 800 mg/day or sunitinib, or BSC 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 owing to the tumour flare phenomenon, with rapid deterioration in symptoms observed in some patients.

Chapter 2

Definition of the decision problem

Decision problem

Specific information on the population, interventions, comparators and relevant outcomes considered for this review are discussed in detail in *Chapter 4* (see *Identification of studies*).

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.[50,55] 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,[40] 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]

Guidance from NICE does not currently recommend the prescription of escalated doses of imatinib upon progression on the standard 400 mg/day dose,[50] 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,[66] and if in clinical practice escalated doses are prescribed only upon progression, these trial data may not provide reliable estimates of response, progression-free survival (PFS) and overall survival (OS), 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 then 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 BSC, 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.[51] As there are now various options available for treating unresectable and/or metastatic GIST, 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.

Overall aims and objectives

The aim of this review was to assess the clinical effectiveness and cost-effectiveness of imatinib at escalated doses (i.e. 600 or 800 mg/day) within its licensed indication,[67] 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 or 800 mg/day compared with sunitinib and/or BSC
- conducting a systematic review of the cost-effectiveness of imatinib at dosages of 600 or 800 mg/day compared with sunitinib and/or BSC
- analysing available outcome data for particular subgroups of interest (e.g. patients with different *KIT* mutations) in order to establish any differences in clinical effectiveness for specific groups
- developing an economic model to compare the cost-effectiveness and cost–utility of imatinib at a dose of 600 or 800 mg/day with those of sunitinib (within its recommended dose range) or BSC only.

This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

Chapter 3

Critique of the manufacturer submission

The manufacturer of imatinib (Novartis) did not provide an economic analysis in their submission, stating that, owing to the limited amount of data available from the key clinical studies and the dearth of data comparing imatinib dose escalation with sunitinib and BSC, they were unable to submit a sufficiently robust economic analysis that 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 (CiC). Electronic copies of all the papers cited in the References section, including two labelled as CiC by the manufacturer, were provided. Apart from both of the CiC documents, these studies had already been retrieved by our searching process and are discussed in *Chapter 4*.

Of the two CiC reports provided, one (CiC information has been removed) was a report on the randomised, Phase II, B2222 trial comparing imatinib at doses of 400 and 600 mg/day. Patient data from this trial that are relevant to this review have since been published by Blanke *et al.*[39] in the *Journal of Clinical Oncology*. The remaining CiC report (CiC information has been removed) provided a meta-analysis of data from the randomised, Phase III, intergroup S0033 trial comparing imatinib at doses of 400 and 800 mg/day, and the randomised, Phase III, EORTC-ISG (Italian Sarcoma Group)-AGITG (Australasian Gastro-Intestinal Trials Group) trial, also comparing imatinib at these doses. Crossover data from the S0033 trial have been published separately,[41,68] as have crossover data from the EORTC-ISG-AGITG trial.[44] (CiC information has been removed.)

(CiC information has been removed.) All relevant results pertaining to the population of interest for this review have been provided in *Chapter 4* (*Assessment of clinical effectiveness*). (CiC information has been removed) but as more recent results for the study population of interest have been published, only study characteristics information was used in *Chapter 4* of this review.

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

- The limited number of data available from the key clinical studies and the paucity of data comparing imatinib dose escalation with sunitinib and BSC 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[56] recommend that changing treatment to sunitinib should be considered only 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 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.[56]

- (CiC information has been removed.)
- (CiC information has been removed.)
- (CiC information has been removed.)

Chapter 4

Assessment of clinical effectiveness

Methods for reviewing effectiveness

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 BSC). 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, week 3, 2009), MEDLINE In-Process (25 September 2009), EMBASE (1980 – week 39, 2009), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (September 2009), Science Citation Index (SCI) (2000 – 26 September 2009), BIOSIS (2000 – 24 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 Health Technology Assessment (HTA) database (October 2009).

Ongoing and recently completed trials were searched in the following databases: current research registers, including Clinical Trials, Current Controlled Trials (CCT), National Institute of Health Research (NIHR) Portfolio, World Health Organization (WHO) International Clinical Trials Registry Platform, International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) Clinical Trials and the Association of the British Pharmaceutical Industry (ABPI) database. Recent conference proceedings of key oncology and GI organisations, including the American Society for Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO) and the European Cancer Organisation, were screened. 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*.

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 or 800 mg/day). Therefore, we considered all of the following types of studies for the assessment of clinical effectiveness:

1. randomised controlled trials (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, we 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 GISTs, whose disease had progressed on treatment with imatinib at a dose of 400 mg/day. If sufficient evidence was available, subgroup 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[14,41,63] (see *Chapter 1*, *Identification of important subgroups*). In addition, subgroup 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 and 800 mg/day, respectively, being prescribed with BSC. The comparators considered were sunitinib, prescribed within its recommended dose range of 27–75 mg and provided with BSC, and BSC only. As previously stated, BSC is defined as 'the multi-professional attention to the individual's overall physical, psychosocial, spiritual and cultural needs'.[61]

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 (HRQoL) [e.g. European Quality of Life-5 Dimensions (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.

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.

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. This 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,[69] Verhagen *et al.*,[70] Downs and Black,[71] 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 NICE Interventional Procedures Programme.

We planned to assess the quality of RCTs using the Cochrane Collaboration's tool for assessing risk of bias.[72] 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*.

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) would be used 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^2-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 would be derived for OS, disease-free survival and PFS. 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 *et al.*[73] 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.[74] A weighted average of survival duration across studies was to be calculated. The chi-squared 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, while 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.[75] 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.[76] WinBUGS software (MRC Biostatics Unit, Cambridge, UK) 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.

Results

Number of studies identified

We identified 3365 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 924 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 10 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*. Information on the reasons for excluding individual studies is provided in *Appendix 5*.

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 or 800 mg/day) with sunitinib or BSC that met our inclusion criteria. One ongoing trial was identified comparing imatinib and sunitinib. However, this study was stopped owing to poor recruitment.[53] We identified five full-text reports of three randomised trials of imatinib that contained relevant data for this review.[14,38,39,41,44] The studies by Zalcberg *et al.*,[44] Blanke *et al.* (S0033)[41] and Blanke *et al.* (B2222)[39] 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 *et al.*[14] met our inclusion criteria and provided additional information from the EORTC-ISG-AGITG (62005) study on response following crossover, while the study by Demetri *et al.*[52] met our inclusion criteria and provided interim data from the B2222 trial on response following crossover.

An additional three abstracts were identified, with two[68,77] reporting interim data for the S0033 trial, and one reporting interim data for the EORTC-ISG-AGITG 62005 trial.[78]

TABLE 1 Reasons for exclusion of studies

Reason for exclusion	No. of studies excluded
Patient had resectable GIST	24
Outcomes not reported separately for patients with GIST	10
< 10 patients in relevant study population	46
Imatinib dose is 400 mg/day	13
No/insufficient data reported for escalated dose patients	65
No imatinib dose reported	84
No relevant interventions	15
Treatment not evaluated	11
No outcomes of relevance	10
Other reason	61
	339
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	***908***

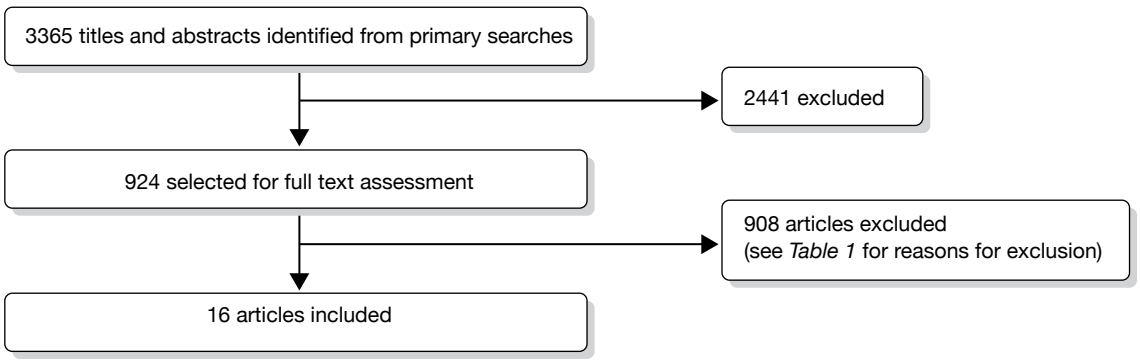

FIGURE 1 Flow diagram outlining the screening process for the review of clinical effectiveness.

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 *et al.*[79] was also included. This study met our inclusion criteria as it also provided separate outcome data for patients with metastatic or unresectable GIST, 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 ongoing, 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.[80–86] We designated the abstract by Seddon *et al.*[86] to be the primary report for this trial, as it was thought to contain its most recent results.

For the comparator treatment of BSC, 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 BSC, or provided data on relevant outcomes for the population of interest for BSC only. It should be noted that studies published on the clinical effectiveness of BSC 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 BSC 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 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 *et al.*[39,41] our requests for information were forwarded to the statistics team involved in the trials. The requested data for the S0033 trial were provided on 17 February 2010. For the study by Zalcberg *et al.*,[44] a response to our request was received, explaining that an official data request form must be completed. This was submitted, and a further response was received on 9 April 2010 explaining that the data could not be provided until September 2010 (and then only if the request were approved). It was decided not to pursue the request for data further, given the timelines for this project.

Two additional reports (CiC information has been removed) to the ones identified through our search strategy were provided for this review by the manufacturer and have been discussed in *Chapter 3*, and are also discussed below. Both of these reports were marked as CiC.

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. It should be noted that all full-text screened studies on plasma monitoring, as well as those on the use of FDG-PET technology for evaluating PD, did not meet our inclusion criteria. In addition, the types of participants were limited to an adult population, therefore studies involving children with GIST were excluded. However, it should be noted that the age range provided in the baseline data for the included study by Seddon *et al.*[86] indicates that at least one child was recruited on to 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 10 patients were also excluded. Changes to our original protocol were reported to NIHR in a progress report submitted on 9 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 (GD Demetri, Ludwig Center at Dana-Farber/Harvard Cancer Center and Sarcoma Center, Boston, MA, USA, 2010; YK Kang, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, 2010; P Rutkowski, Sklodowska-Curie Memorial Cancer Center and Institute of Oncology Department of Soft Tissue/Bone Sarcoma and Melanoma, Warsaw, Poland, 2010; P Wolter, UZ Leuven, Leuven, Belgium, 2010; personal communication). In the cases of two responses, this resulted in the exclusion of the studies (five papers in total) from the review (P Rutkowski, P Wolter, personal

communication) 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 (GD Demetri, YK Kang, personal communication). In the case of correspondence with YK Kang, it was decided that the study by Park *et al.*[79] could be included in the review without further clarification from the corresponding author.

Of the correspondences that did not result in responses, one e-mail could not be sent successfully[87] and the remaining four authors did not respond.[88–91]

Characteristics of the included studies

Study characteristics data were available for the four full-text included imatinib studies[39,41,44,79] and the primary report of the included sunitinib trial.[86] However, of these studies, only the studies by Zalcberg *et al.*[44] and Park *et al.*[79] gave specific baseline information for the crossover subgroup of interest. Therefore, *Table 2* provides details of all characteristics information provided for each crossover group, while *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 *et al.*,[44] 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 *et al.*[42] for the same trial. The paper by Verweij *et al.*[42] failed to meet the inclusion criteria for this review as it did not provide any outcome data for patients

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

	Zalcberg 2005[44]	Blanke S0033[41]	Blanke B2222[39]	Park 2009[79]	Seddon 2008[86]
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	600 mg/day, 800 mg/day	Cycle of 50 mg/day for 4 weeks, then 0 mg/day for 2 weeks
Start date	(CiC information has been removed)	December 2000	July 2000	June 2001	Unspecified
End date	April 2004	(CiC information has been removed)	May 2006	June 2006	December 2007
Study countries	Australia, Belgium, Denmark, France, Germany, Italy, the Netherlands, New Zealand, Poland, Singapore, Spain, Switzerland, UK	Canada, USA	Finland, USA	Seoul, South Korea	Unspecified but 'worldwide' and 'multicentre'
No. of institutions involved (no. of countries involved)	(CiC information has been removed)	148 (2)	4 (2)	1 (1)	96 (33)
Length of follow-up at time of analysis	Median of 25 months (maximum of 35 months)	Median of 4.5 years	Median of 63 months (maximum of 71 months)	Median of 8 months (range 1.4–22.3)	Median of 51 weeks (range 0.1–159)
Number receiving escalated dose of imatinib after failure of imatinib at 400 mg/day, out of all of those randomised to receive 400 mg/day	133/473 (28.1%)	118/345 (34.2%)	43/73 (58.9%)	24/24 (100.0%)	NA
Number receiving sunitinib after failure of imatinib at ≤ 400 mg/day, out of all of those receiving sunitinib	NA	NA	NA	NA	351/1117 (31.4%)

NA, not applicable.

TABLE 3 Characteristics of the included studies for all participants randomised

		[a]EORTC-ISG-AGITG[42]	Blanke S0033[41]	Blanke B2222[39] (CiC information has been removed)	Park 2009[79]	Seddon 2008[86]
Included in this analysis		**All those randomised to 400 mg/day**			**All those who received escalated doses of imatinib on progression at a dose of 400 mg/day[b]**	**All those receiving sunitinib**
Number included		473	345	73	24	1117
Age in years: median (range)		59 (49–67)	61.9 (18–87)	(CiC information has been removed)	52 (31–73)	59 (10–92)
Sex: M/F		283/190	187/158	(CiC information has been removed)	18/6	665/451
ECOG/WHO Performance Status Score:	0	217		(CiC information has been removed)	4	420
	1	191		(CiC information has been removed)	18	515
	2	48		(CiC information has been removed)	2	134
	≤2	(456)	332	(CiC information has been removed)		(1069)
	>2	17	13	(CiC information has been removed)		38
Missing						10
Race/ethnicity (*n*)		NR			NR	NR
White			273	CiC information has been removed)		
Black			37	(CiC information has been removed)		
Asian			25	(CiC information has been removed)		
Other/unknown			10	(CiC information has been removed)		
Number having previous chemotherapy		156 (32.9%)	NR	(CiC information has been removed)	3 (12.5%)	225 (26.8%)
Number having previous radiotherapy		26 (5.5%)	NR	(CiC information has been removed)	NR	78 (7.9%)
Number having prior surgery		410 (86.7%)		(CiC information has been removed)	20 (83.3%)	NR

ECOG, Eastern Cooperative Oncology Group; NR, not reported.

a Baseline data for only the crossover patients from this treatment arm were available and are reported in *Appendix 8*.

b Participants in this study were part of a retrospective cohort. Treatment was not randomised. The population of interest received escalated imatinib doses.

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 *et al.*[44]), it was felt that the baseline data from this excluded study could still be used.

Four of the included trials reported data for imatinib,[39,41,44,79] while the remaining trial reported data for sunitinib.[86] Two of the imatinib trials randomised patients to imatinib doses of either 400 or 800 mg/day,[41,44] one randomised patients to imatinib doses of either 400 or 600 mg/day,[39] and

the other was a retrospective study looking only at patients with GIST who had received escalated doses of imatinib at either 600 or 800 mg/day on progression at a dose of 400 mg/day.[79] The sunitinib trial is an ongoing, non-randomised, open-label study and participants are provided with a 6-week cycle of sunitinib, at a dose of 50 mg/day for 4 weeks followed by 2 weeks without the drug.[86]

The study start date was reported for three out of the four included imatinib trials[39,41,79] and was made available for the study by Zalcberg *et al.*[44] by the manufacturer (CiC information has been removed). From this it can be seen that the earliest study start date is that of the study (CiC information has been removed)[39] (CiC information has been removed). The included sunitinib abstract did not report a start date.

Three out of the four included imatinib studies reported an end date,[39,44,79] and in the case of the sunitinib study by Seddon *et al.*[86] a date was reported for the most recent analysis. The manufacturer also made this information available for the study by Blanke *et al.*[41] (CiC information has been removed). The ongoing sunitinib trial has the most recent update, while the study by Zalcberg *et al.* was completed first, in April 2004.[44]

With the exception of the study by Park *et al.*,[79] which involved one centre in one country, all trials were international and multicentre,[39,41,44,86] with the sunitinib trial involving the most countries[85] and the S0033 trial involving the most institutions.[41] The B2222 trial involved the fewest countries and fewest institutions.[39]

The longest length of follow-up occurred in the B2222 trial reported by Blanke *et al.*,[39] in which patients were followed up for a median of 63 months, while the shortest length of follow-up was found in the study by Park *et al.*,[79] 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.[39,41,44] In the imatinib study by Park *et al.*,[79] 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 *et al.*,[86] 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,[86] while the study by Park *et al.*[79] had the smallest study population.

The Park study[79] had the youngest population, whereas the S0033 trial[41] had the oldest study population. In (CiC information has been removed) 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 (see *Chapter 1, Epidemiology and incidence*).

(CiC information has been removed) studies reported data on the performance status score of participants, although the study by Blanke *et al.* for the S0033 trial[41] had combined the Eastern Cooperative Oncology Group (ECOG) performance status categories 0–2. Doing the same for the remaining studies shows that the vast majority of participants, 456/473 (96.4%), 332/345 (96.2%), (CiC information has been removed), 24/24 (100%) and 1069/1107 (96.6%) in the EORTC-ISG-AGITG trial,[42] S0033 trial,[41] B2222 trial,[39] (CiC information has been removed) Park study[79] and the sunitinib trial,[86] respectively, had a performance status score of ≤ 2.

(CiC information has been removed.)

In terms of prior treatment, (CiC information has been removed) two reported the number having previous radiotherapy,[42,86] (CiC information has been removed). For the imatinib studies, 3/24 (12.5%), 156/473 (32.9%) and (CiC information has been removed) of participants had undergone previous chemotherapy in the study by Park *et al.*,[79] the EORTC-ISG-AGITG trial[42] and the B2222 trial[39] (CiC information has been removed), respectively, while 26.8% (225/1117) of patients had received prior chemotherapy in the study by Seddon *et al.*[86] With regard to radiotherapy, 26/473 (5.5%) of patients in the EORTC-ISG-AGITG trial[42] and 78/1117 (7.9%) of patients in the sunitinib trial[86] had received prior radiotherapy. (CiC information has been removed) of participants involved in the B2222 trial reportedly had received prior surgery, (CiC information has been removed) while this figure was 86.7% (410/473) for participants in the EORTC-ISG-AGITG trial,[42] and 83.3% (20/24) in the study by Park *et al.*[79]

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[39] or 800 mg/day.[41,44] The fourth study[79] 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 subgroup in three studies,[39,41,44] and a subgroup of consecutively treated patients in the remaining study,[79] quality was assessed using the checklist for non-randomised studies (detailed in *Methods*, above). Questions within this checklist that 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 (see *Appendix 4*).

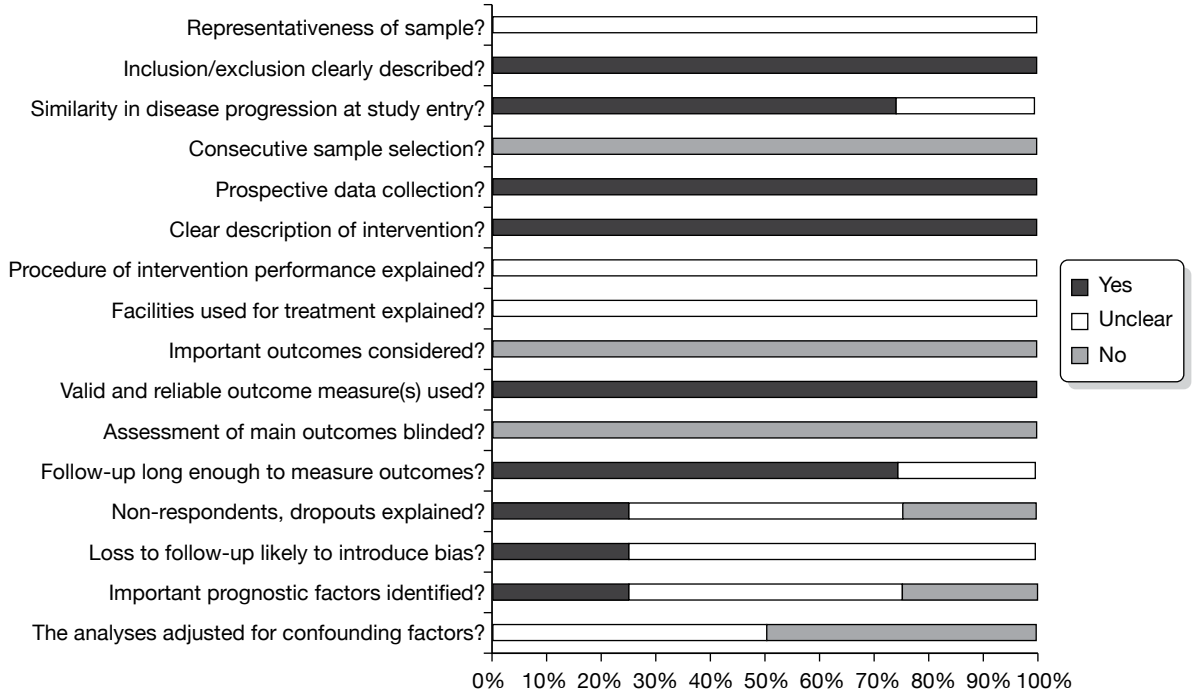

FIGURE 2 Quality assessment results summary.

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.

Sample definition and selection

In three studies[39,41,44] 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 the sample.[79] With regard to the randomisation process at trial level, the studies by Blanke *et al.*[41] and Zalcberg *et al.*[44] used methods that adequately generated the allocation sequence to avoid influence of confounding factors while Blanke *et al.*[39] did not report sufficient data on the randomisation process. In the study by Zalcberg *et al.*,[44] allocation to treatment was not concealed. Both the B2222[39] and S0033[41] studies by Blanke *et al.* reported inadequate information on allocation concealment. All four studies adequately described inclusion and exclusion criteria (Q2). To consider whether participants entered the study at a similar point in their disease progression, we looked at data on their performance status. Three of the studies[39,41,79] involved participants whose performance status at the time of study entry was similar, while the study by Zalcberg *et al.*[44] included participants with different performance status at study entry (Q3), although most of the participants in all populations had a performance status of < 2, 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 of the outcomes of interest, but all reported the objective response of escalated imatinib dosing in patients with GIST, while one[41] reported OS and two[41,44] measured PFS. The study by Park *et al.*[79] reported time to progression, and the study by Zalcberg *et al.*[44] was the only study that also reported adverse events for those on an escalated dose of imatinib. No study reported outcomes related to QoL.

All four studies used valid and reliable outcome measures (Q11), such as 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[79] (Q13). Information on those lost to follow-up was either not provided[39] (and thereby likely to introduce bias) or not provided at a sufficient level of detail[41,44,79] 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 *et al.*,[39,41] important prognostic factors such as sex, performance status, neutrophils counts, etc., were investigated and multivariate analyses were performed at trial level but this was not carried out for the subset of patients who crossed over. Similarly, Park *et al.*[79]

identified possible prognostic factors (but did not adjust for confounding factors during analysis). The study by Zalcberg *et al.*[44] also did not identify any prognostic factors or 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.

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 *et al.*[39] and the study by Park *et al.*[79] In the study by Blanke *et al.*,[39] the median follow-up at this time was 63 months (maximum 71 months), and, at that time, 43 patients had crossed over from 400 to 600 mg/day. Of these 43 patients, 11 (25.6%) showed either PR or stable disease (SD). However, it should be noted that one patient showed response only after further escalation from 600 to 800 mg/day. 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 PD.[39] Interim data for this study population are provided in the study by Demetri *et al.*,[38] where, after a median follow-up of 288 days (maximum 9 months), nine patients had crossed over, with one showing PR at that point, and two with SD.[38]

In the study by Park *et al.*,[79] median follow-up was eight months (range 1.4–22.3 months) and, of the 12 patients who received an escalated dose of 600 mg/day of imatinib, five (41.7%) showed either PR or SD.

With regard to response data provided by the manufacturer, (CiC information has been removed). 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 are available from the S0033 study by Blanke *et al.*,[41] the EORTC-ITG-AGITG trial by Zalcberg *et al.*[44] and the study by Park *et al.*[79] Of the crossover populations in the S0033[41] and EORTC trials[44] (117 and 133 patients, respectively), three patients in each trial (i.e. six in total) had a PR, while 33 patients in the S0033 trial[41] and 36 patients in the EORTC-ISG-AGITG trial[44] had SD 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 *et al.*[79] did not provide separate data for those with SD and those achieving PR. 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 PR or SD.[79]

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 400-mg arm had a best/only response of PD (or 'early death'),[41] and in the study by Zalcberg *et al.*[44] this figure was 61/473 (12.9%).[42]

Interim data for the EORTC-ISG-AGITG trial were provided for a data cut-off point of 7 December 2003, at which point there were 2/97 (2.1%) patients showing a PR, 30/97 (30.9%) patients with SD, and 65/97 (67.0%) patients with PD.[78] Interim data for the S0033 trial, also from December 2003, showed that there were 5/68 (7.4%) patients with PR, and 20/68 (29.4%) patients with SD, during crossover treatment with 800 mg/day of imatinib, following failure of treatment at 400 mg/day.[68]

In addition, secondary analysis for the EORTC-ISG-AGITG trial in the study by Debiec-Rychter *et al.*[14] indicated, without stating the number of patients involved, that response following crossover was significantly more likely to occur in patients with wild-type GIST than with *KIT* exon 11 mutation ($p = 0.0012$), and response following crossover was also significantly more likely to occur in patients with *KIT* exon 9 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 4 weeks-on-treatment/2 weeks-off-treatment 6-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, OS data were not reported by Blanke *et al.*[39] (CiC information has been removed) 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 *et al.*[44] did not report OS outcomes. However, the S0033 trial by Blanke *et al.*[41] 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.[41] Median OS was 19 months (95% CI 13 to 23 months) starting from the commencement of crossover. Interim data for the S0033 trial were also provided in the study by Rankin *et al.*,[68] which stated that median OS at December 2003 was 19 months.[68]

(CiC information has been removed.)

(CiC information has been removed.)

TABLE 4 (CiC information has been removed.)

(CiC information has been removed.)

(CiC information has been removed.)

TABLE 5 (CiC information has been removed.)

For sunitinib, OS 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.[82,86] The data from the study by Reichardt *et al.*[82] were analysed after a median of four cycles. Median survival at this point was 93 weeks (95% CI 72 to 100 weeks) and 231/339 (68.1%) of patients were still alive.[82] The data from the report by Seddon *et al.*[86] were analysed after a median of 51 weeks (range 0.1–159 weeks). Median survival at that time was 90 weeks (95% CI 73 to 106 weeks) and 193/351 (55%) were still alive.[86] It should also be noted that further interim OS data were provided in another study by Seddon *et al.*,[85] but although the date of analysis is the same month as that reported by the studies by Reichardt *et al.*[82] and Rutkowski *et al.*,[83] the median OS reported differed, at 80.4 weeks (95% CI 60.3 to NA weeks), while the population who had failed on doses of imatinib of ≤ 400 mg/day was also less (307 patients).[85]

It was possible to compare OS with an escalated dose of 800 mg/day, from the S0033 trial reported by Blanke *et al.*,[41] with that with sunitinib at a dose of 50 mg/day (provided in

4 weeks-on/2 weeks-off cycles of 6 weeks), for patients who had progressed on imatinib at a dose of 400 mg/day. Quarterly OS estimates for the sunitinib participants reported in a Kaplan–Meier chart by Seddon *et al.*[86] were obtained using the method proposed by Parmar *et al.*[73] and compared with OS estimates for the S0033 trial provided by the authors. The results are provided in *Figure 3*.

The study by Zalcberg *et al.* did not report information on OS and was therefore not included in the comparison in *Figure 3*. However, data are available from the (CiC information has been removed), and data from the study by Seddon *et al.*[86] on treatment with sunitinib are provided in *Table 6*.

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.

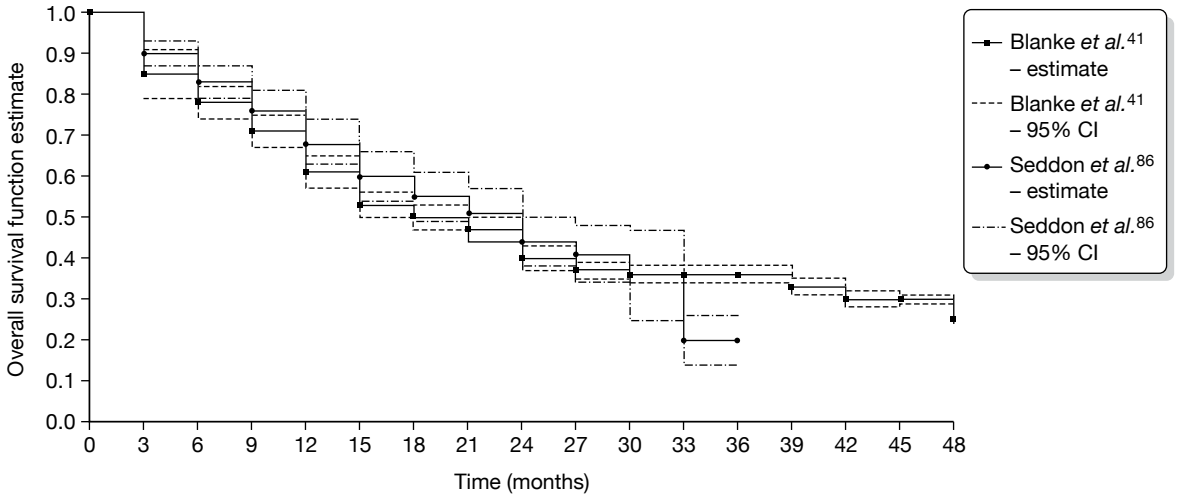

FIGURE 3 Comparison of OS estimates for imatinib at 800 mg/day and sunitinib at 50 mg/day.

TABLE 6 Comparison of OS estimates for imatinib at 800 mg/day and sunitinib at 50 mg/day

	Seddon 2008[86] (*n* = 351)		(CiC information has been removed)		
No. years elapsed	Survival estimate	95% CI	(CiC information has been removed)	(CiC information has been removed)	
1	0.684	0.626 to 0.741	(CiC information has been removed)	(CiC information has been removed)	(CiC information has been removed)
2	0.441	0.379 to 0.503	(CiC information has been removed)	(CiC information has been removed)	(CiC information has been removed)
3	0.200	0.140 to 0.261	(CiC information has been removed)	(CiC information has been removed)	(CiC information has been removed)
4	NR		(CiC information has been removed)	(CiC information has been removed)	(CiC information has been removed)

NR, not reported

Progression-free survival

For imatinib at an escalated dose of 600 mg/day following progression at a dose of 400 mg/day, PFS data were not reported by Blanke *et al.*[39] (CiC information has been removed) 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 *et al.*,[41] and for the EORTC-ISG-AGITG trial by Zalcberg *et al.*[44]

For the S0033 trial, at the time of the analysis, median follow-up of 4.5 years (54 months), 99/118 (83.9%) of the crossover cohort for whom data were available had progressed.[41] Median PFS was estimated to be 5 months (95% CI 2 to 10 months). Of the 99 patients who had PD 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 PFS to be 4 months following crossover, for 68 patients.[68]

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 crossover cohort with data available had progressed. Median PFS was 81 days. Sixty-seven patients (50.4%) had progressed or died within 3 months (Kaplan–Meier survival estimate 0.467). At 1 year, the Kaplan–Meier survival estimate was 0.181.[44]

(CiC information has been removed.)

The estimates of PFS provided at 3-month intervals by the authors of the S0033 study,[41] and available as a Kaplan–Meier chart in the published paper of this study by Blanke *et al.*,[41] were compared with PFS estimates at 3-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 *et al.*[44] The number of events in each time period was then calculated using the method proposed by Parmar *et al.*,[73] corrected to ensure that the total number of patients censored was consistent with the number reported in the published paper.[44] 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% CIs for each.

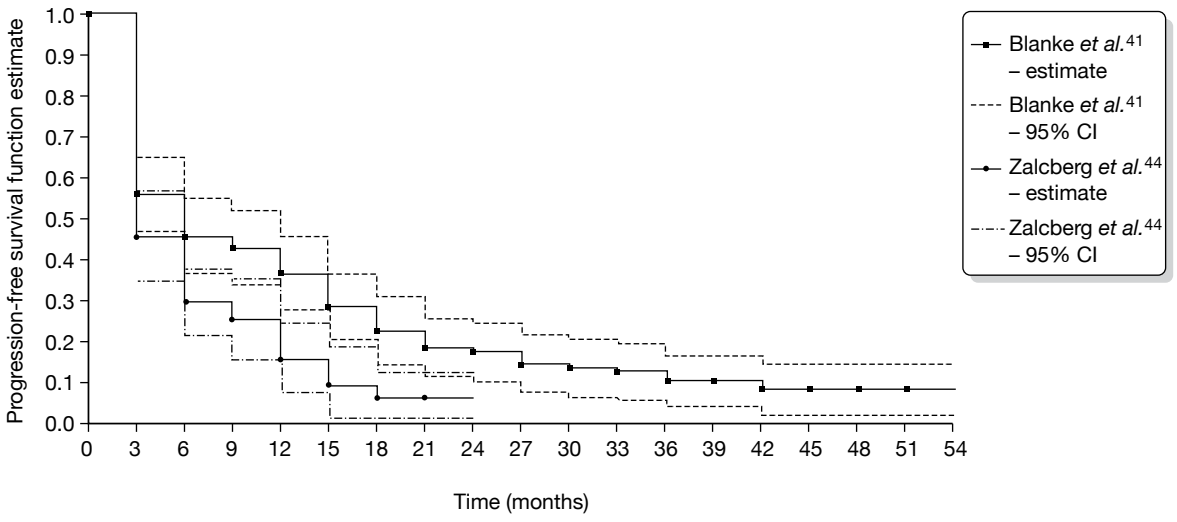

FIGURE 4 Kaplan–Meier plot for PFS with 800 mg/day imatinib.

A meta-analysis of these two survival curves was attempted, using the methods described in Arends *et al.*[92] However, no valid results could be achieved owing to the lack of data.

For sunitinib at a dose of 50 mg/day for a 6-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 *et al.*,[79] which showed that, of the 12 patients who had their imatinib 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, while the remaining 11 patients eventually progressed on imatinib treatment at the escalated dose after a median of 1.7 months (range 0.7–24.9 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 PR or SD after crossover, the median duration of 'stabilisation' (i.e. PR or SD after crossover) was 153 days (range 37–574 days).[44] Interim data from this trial (7 December 2003 data cut-off) gave a median time to progression of 78 days.[78]

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).[80]

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-AGITG trial reported by Zalcberg *et al.*,[44] and there was some information on dose reductions in the S0033 trial report by Dileo *et al.*[77]

The number of discontinuations due to adverse events was not explicitly stated for the EORTC-ISG-AGITG trial[44] reported in the study by Zalcberg *et al.*, but they did report that the vast majority of discontinuations (88.4%, i.e. approximately 86/97 withdrawals) were due to disease progression, suggesting that the maximum possible adverse event withdrawals possible would be 11.6% of all 97 withdrawals, i.e. 11 patients. Interim data for this trial at a December 2003 data cut-off point showed that there were two toxicity withdrawals at that time.[78]

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

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

TABLE 7 Adverse event data from the study by Zalcberg *et al.*[44]

Adverse event	No. with adverse event	Less severe after crossover (*n*, %)	More severe after crossover (*n*, %)	No. achieving new grade 3- to grade 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 ($p=0.015$)

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.[44]

Interim data reported by Zalcberg *et al.*[78] for this trial showed that 31% of patients (exact number not calculable) required a dose reduction (note: stated as 'cumulative incidence'). No information was provided on the dose given following dose reduction.

Interim data for the S0033 trial reported by Dileo *et al.*[77] showed that, of the 77 patients who had crossed over from an imatinib dose of 400 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.

(CiC information has been removed.)

(CiC information has been removed.)

TABLE 8 (CiC information has been removed.)

TABLE 9 (CiC information has been removed.)

For sunitinib at a dose of 50 mg/day for a 6-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): months	*n* (%) with PR or SD	Duration of response/ time to treatment failure	Median OS (95% CI)	*n* (%) still alive	Median progression-free survival (95% CI)	*n* (%) progression free	Reference source
Sunitinib at 50 mg/day	4.5 (0–22.1)		Median treatment duration did not differ based on prior imatinib dose					Kang 2007[80]
	< 6 ?			20.1 months (15.1 to N/A months)	?/307			Seddon 2007[85]
	6			23.3 months (18–25 months)	231/339 (68.1)			Reichardt 2008[82]
Imatinib at 600 mg/day	8	5/12 (41.6)	1.7 months (range 0.7–24.9 months)					Park 2009[79]
Imatinib at 800 mg/day	8	4/12 (33.3)						Park 2009[79]
Imatinib at 600 mg/day	9.5 (?–9)	3/9 (33.3)						Demetri 2002[38]
Sunitinib at 50 mg/day	12 (0–39.8)			22.5 months (18.3–26.5 months)	193/351 (55)			Seddon 2008[86]
Imatinib at 800 mg/day	< 25 (< ? to < 35)	32/65 (49.2)	2.8 months					Zalcberg 2004[78]
	25 (?–35)	39/133 (29.3)	5.5 months (range 1.3–20.5 months)			2.9 months	25/133 (18.8)	Zalcberg 2005[44]
	< 54	25/68 (36.8)		19 months (not stated)				Rankin 2004[68]
	54	36/117 (30.8)		19 months (13–23 months)	42/118 (35.6)	5 months (2–10 months)	19/118 (16.1)	Blanke S0033[41]
Imatinib at 600 mg/day	63 (?–71)	11/43 (25.6)						Blanke B2222[39]
Imatinib at 800 mg/day		Significantly more likely to occur in patients with wild-type and exon 9 mutations than exon 11 mutations						Debiec-Rychter 2006[14]

All units of measurement for time have been converted into months by dividing by four for weeks, by 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.

Chapter 5

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 GISTs, whose disease has progressed on treatment with imatinib at a dose of 400 mg/day.

The specific objectives are:

1. To determine, by undertaking a systematic review of the literature, the cost-effectiveness of using imatinib at an escalated dose of 600 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 BSC.
2. To develop an economic model to compare the cost-effectiveness and cost–utility of imatinib at a dose of 600 or 800 mg/day; the use of sunitinib (within its recommended dose range); or BSC 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 owing to intolerance.

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).

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, SCI, Health Management Information Consortium, NHS Economic Evaluation Database (NHS EED), the HTA database, Cost-effectiveness Analysis (CEA) Registry and the Research Papers in Economics (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 the International Society for Pharmacoeconomics and Outcomes Research (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 are described below, although, as noted in *Chapter 3*, no industry submission was reviewed for this technology assessment

review (TAR). 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.[69] Modelling studies were assessed against the Philips checklist.[93]

Inclusion and exclusion criteria

To be included, studies had to include a cost analysis or a cost-effectiveness analysis (CEA) 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 was based on a modelling exercise, additional data extraction criteria developed by Philips *et al.* were applied.[93,94]

Handling industry submissions

Information from the manufacturer was to be considered if it was submitted in accordance with the 3 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 *Economic modelling* (below), highlighting any differences in results. Any 'CiC' data taken from a company submission were to be reported in accordance with NICE guidelines.[94]

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 while predicting results.

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.

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

Characteristics of included studies

Out of the nine studies, seven[55,95–100] reported a full economic evaluation that assessed both the costs and cost-effectiveness of the alternatives compared. Of the remaining two studies, the study by Reddy[54] 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,[101] which is also a review of the management of GIST with sunitinib, reports on, amongst other things, the cost of treatment with sunitinib.

TABLE 11 Search results

Database	No. retrieved
MEDLINE (2000 – October, week 4, 2009), EMBASE (2000 – week 44, 2009)	227
MEDLINE In-Process (3 November 2009) (after de-duplication in Ovid)	0
SCI[a] (2000 to 3 November 2009)	16
Health Management Information Consortium[a] (September 2009)	0
NHS EED[a] (October 2009)	0
HTA database (October 2009)	0
ISPOR conference abstracts 2006–9	7
Total	250

a Numbers retrieved after de-duplication against MEDLINE and EMBASE search.

Five studies[55,95,96,99,100] conducted a modelling exercise rather than incorporating data from actual patient follow-up. Two studies[96,98] used non-randomised or non-trial patient data (from retrospective cohorts) to inform their economic evaluations.

One study[55] reported an economic evaluation in a UK context, which was based on an industry submission to NICE for a previous TAR. Two studies[95,98] reported a Canadian context, and one study was from a US context.[97] The remaining three studies were conducted in the context of Mexico,[96] Spain[99] and Brazil,[100] respectively. *Table 12* summarises the main features of the included studies.

Comparative studies

Imatinib and best supportive care

Three studies[55,97,98] compared imatinib with BSC. The study by Wilson *et al.*[55] used the manufacturer submissions (Novartis model) and compared imatinib and BSC, but in the imatinib group allowed for escalation of doses from 400 to 600 mg/day for those who failed to respond or were intolerant to imatinib at the 400 mg/day dose. The study by Mabasa *et al.*[98] 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 and 800 mg/day. Six out of 56 patients in the imatinib groups of patients considered in this economic evaluation were then allowed to switch to sunitinib therapy. The economic evaluation by Huse *et al.*[97] considered imatinib at 400 mg/day (see *Table 12*).

Imatinib, sunitinib and best supportive care

Two studies[96,100] compared sunitinib, escalated doses of imatinib, and BSC or palliative care as comparators for their economic evaluations. The Contreras-Hernandez *et al.*[96] study compared treatment with imatinib, sunitinib and palliative care. Both treatments (sunitinib and imatinib) were compared with BSC 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 *et al.*[100] compared sunitinib, imatinib at 800 mg/day and BSC (see *Table 12*).

Sunitinib and best supportive care

The studies by Chabot *et al.*[95] and Paz-Ares *et al.*[99] compared treatment with sunitinib and BSC for patients with GIST who were imatinib resistant or intolerant. Chabot *et al.*[95] did not specify the dose of sunitinib used, or mention whether patients who were imatinib resistant or

TABLE 12 Characteristics of included CEA 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	BSC	Sunitinib		OS	Median OS	Survival rate	PFS	Progression-free life-years	Time to progression	PFM	Life-years gained	QALY	Cost-effectiveness ratio	ICER	
Chabot 2008[95]	Canada, Canadian $, 2005	Provincial health authority				✓	✓	Yes	✓			✓				✓	✓		✓	Markov model
Contreras-Hernandez 2008[96]	Mexico, US$, 2006[a]	Health insurance system			✓	✓	✓	Yes							✓	✓			✓	Markov model
Mabasa 2008[98]	Canada, Canadian $, 2006	BCCA	✓			✓		No	✓	✓		✓				✓			✓	CEA using cost-effectiveness ratios and ICERs
Paz-Ares 2008[99]	Spain, €, 2007	Health-care system				✓	✓	Yes					✓		✓	✓	✓		✓	Markov model
Huse 2007[97]	USA, US$, 2005	Societal perspective (payers for health care)	✓			✓		NA									✓	✓		CEA
Teich 2009[100]	Brazil, Brazilian $ (R$), 2005[b]	Health-care system			✓	✓	✓	Yes					✓			✓			✓	Markov model
Wilson 2005[55]	UK, GB£, (2004?)	Health-care system	✓	✓		✓		Yes			✓						✓		✓	Markov model

BCCA, British Columbia Cancer Agency; ICER, incremental cost-effectiveness ratio; PFM, progression-free month; PPP, purchasing power parity; QALY, quality-adjusted life-year.
a 1 US$ = 11 Mexican pesos.
b US$ at PPP, 1 US$ = 1.4 R$.

intolerant were initially treated with 400 mg/day and then with escalated imatinib doses (e.g. 600 or 800 mg/day). Paz-Ares *et al.*[99] specified a dose of 50 mg/day for the patients in the sunitinib group. The patients in the sunitinib group were provided with BSC. Therefore, this study compared sunitinib plus BSC with BSC alone. BSC in this study included diagnostic tests and routine palliative treatment.[99]

The definition of BSC in the economic evaluation studies was not the same across the studies. Chabot *et al.*[95] did not clearly define what BSC included, while Contreras-Hernandez *et al.*[96] defined clearly that BSC included treatment with imatinib. Paz-Ares *et al.*[99] defined BSC as essentially consisting of diagnostic tests and routine palliative care. In the other three studies,[55,97,98] the control group of patients, who are considered as effectively being treated with BSC, were not provided with treatment with imatinib. As a full-text paper of the study by Teich *et al.*[100] was not available, information on how this study defined BSC was not available.

All treatments

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 or imatinib 800 mg/day, sunitinib and BSC) for patients who failed on imatinib at a dose of 400 mg/day.

Study design

Among the seven studies that conducted a full economic evaluation, five used Markov modelling.[55,95,96,99,100] Huse *et al.*[97] used a very simple modelling framework and Mabasa *et al.*[98] also used patient-level data and had 46 and 47 patients in their imatinib and BSC (historical group) groups, respectively. Contreras-Hernandez *et al.*[96] also used patient-level data (for 21 patients) collected at the Hospital de Oncología to estimate the costs of care associated with imatinib, BSC and other procedures, and used these costs in their model.

Perspective

Three studies[55,99,100] adopted the perspective of a national health-care system. The study by Contreras-Hernandez *et al.*[96] was from Mexico's health insurance system's perspective. The study by Huse *et al.*[97] 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 *et al.*[95] and Mabasa *et al.*[98] considered a provincial health authority and a specialised agency (British Columbia Cancer Agency) perspective, respectively, for their economic evaluations. None of the seven studies[55,95–100] 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 PFS,[95,96,98–100] OS,[95,98] life-years gained[95,96,98–100] and quality-adjusted life-years (QALYs).[55,95,97,99] Four studies[55,95,97,99] reported the incremental cost per QALY gained. The remaining three studies[96,98,100] used incremental cost per life-year gained, and incremental cost per progression-free life-year gained.

Data sources

Most of the studies,[95,96,99] which were based on modelling exercises, used effectiveness or health outcome data from major trials[38,52,102–104] and adapted them for their specific contexts. The sources of cost data were mainly from relevant patients' records, and health-care cost databases. Wilson *et al.*[55] 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 *et al.*[100] 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 2008[95]	Published literature and Canadian government benefit schedule and medical oncologist	Published literature and Canadian government benefit schedule and medical oncologist	Phase III trial NCT00075218[52]
Contreras-Hernandez 2008[96]	Hospital records (Hospital de Oncología) 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[52,104]
Mabasa 2008[98]	BCCA	BCCA registry	Patients' data in two arms (imatinib groups and 46 non-imatinib group) were compared with Demetri 2002[38] and Verweij 2003[102]
Paz-Ares 2008[99]	Health costs database eSalud (for administration, radiotherapy, nephrectomy and monitoring costs). General Council of Pharmacists Official Colleges for drug costs. Ojeda *et al.* (2003)[105] for 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 2006,[52] adverse events[105]
Huse 2007[97]	Drug acquisition costs: published average wholesale price (*Red Book*: *Pharmacy's Fundamental Reference*. Montvale, NJ: Thomson Health Care; 2005, and *Physicians' Desk Reference 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 use by GIST patients	Demetri 2002,[38] Phase II and Blanke 2006[103]
Wilson 2005[55]	Industry submission: Novartis model – Novartis submission to NICE 2003	Novartis model – Novartis submission to NICE 2003	QoL based on ECOG data from B2222 trial,[39] and Goss study (data AiC)

AiC, academic in confidence; BCCA, British Columbia Cancer Agency; IMSS, Instituto Mexicano del Seguro Social.

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[95,99] that had sunitinib and BSC as comparator treatments used a time horizon of 6 years and a treatment cycle length of 6 weeks in the modelling exercise. Of the other studies, the study by Contreras-Hernandez *et al.*,[96] which had sunitinib as a comparator along with imatinib and BSC, used a lifetime time horizon and also a 6-week cycle of treatment (to be consistent with the sunitinib treatment cycle of 6 weeks). Huse *et al.*[97] used a 10-year time horizon for the analysis, while Teich *et al.*[100] used a 6-year time horizon, and a 6-week treatment cycle.

Discount rate

A 5% discount rate for costs and health outcomes was used in two studies.[95,96] Wilson *et al.*[55] 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 *et al.*[99] and Huse *et al.*[97] used 3% and 3.5%, respectively. Mabasa *et al.*[98] used 3% for discounting costs and outcomes. The abstract by Teich *et al.*[100] 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 cost in relation to the health outcomes, the incremental cost-effectiveness ratios (ICERs) from the studies are noted in the table with respect to the main

TABLE 14 Summary of cost of treatment from studies reviewed

Study	Comparator	Mean cost of treatment per patient	ICER1	ICER2
Chabot 2008[95]	Sunitinib	C$46,125	SUN vs BSC	SUN vs BSC
Costs in Canadian $ at 2005 prices			C$49,826 per life-year saved	C$79,884 per QALY
	BSC	C$11,632		
Contreras-Hernandez 2008[96]	Sunitinib	US$17,806		SUN vs BSC
Costs in US$ at 2006 prices		Standard deviation US$695		$15,734 per patient treated with sunitinib and $56,612 per year of PFS, and $46,108 per life-year gained
		95% CI US$15,377 to 19,816		
	Imatinib	US$35,057		
		SD US$1253		
		95% CI US$31,381 to 38,705		
	BSC	US$2071		
		Standard deviation US$473		
		95% CI US$1543 to 2869		
Mabasa 2008[98]	Imatinib	C$79,839	Imatinib vs BSC (control)	
Costs in Canadian $ at 2006 prices			C$15,882 per life-year saved	
	BSC	C$1743		
Paz-Ares 2008[99]	Sunitinib	€23,259	SUN vs BSC	SUN vs BSC
Costs in € at 2007 prices			€30,242 per life-year saved	€4090 per PFM
				€49,090 per QALY gained
	BSC	€1622		
Huse 2007[97]	Imatinib	US$416,255		
Cost in US$ at 2005 price	BSC	US$341,886		
Wilson 2005[55]	Imatinib	£18,896 (400 mg/day)		Cost per QALY: £70,206 (year 2), £51,514 (year 3), £36,479 (year 5) and £25,859 (year 10)
Cost in £ at 2004 prices		£24,368 (600 mg/day)		
		Other cost of treatment £1136		
	BSC	£562		

PFM, progression-free month; SUN, sunitinib.

outcomes, i.e. life-year saved (LYS), PFS and QALYs. Although the Contreras-Hernandez *et al.* study[96] considered three alternative treatments (sunitinib, imatinib and BSC), it did not report an ICER for imatinib versus BSC.

Higher doses of imatinib versus BSC

The Contreras-Hernandez *et al.*[96] study suggested that a higher dose of imatinib (800 mg/day) might be cost-effective compared with BSC (where BSC included treatment with imatinib at a lower dose). Wilson *et al.*,[55] using the modified Novartis model in a UK context and from an NHS perspective, estimated the incremental cost per QALY gained at £51,515–98,889 at 2 years, and £27,331–44,236 at 5 years compared with BSC.

Sunitinib versus higher dose of imatinib and/or BSC

Sunitinib treatment was associated with an estimated gain of 0.7 years and 0.4 QALYs compared with BSC.[95] Sunitinib treatment also resulted in a higher number of progression-free months (PFMs) than both the imatinib and BSC therapies. The mean number of PFMs was found to be 5.64 for sunitinib, while it was 5.28 and 2.58, respectively, for imatinib and BSC. The incremental effectiveness of sunitinib therapy compared with BSC was 3.1 PFMs and compared with a high

dose of imatinib was 0.3 PFMs. Over the 5-year treatment horizon, Contreras-Hernandez *et al.*[96] found that patients with sunitinib had a mean life-year gain (LYG) of 1.4 compared with 1.31 and 1.08 for imatinib and BSC, respectively. The study also suggested that patients taking imatinib at a dose of 800 mg/day had the highest mean costs of treatment. Teich *et al.*[100] reported that sunitinib was cost-effective compared with imatinib at a dose of 800 mg/day for a 6-year time horizon. Their study suggested that sunitinib increased life-years and progression-free life-years by 0.3 and 0.26, respectively, with an incremental cost of R$86,756 (Brazilian dollars) [US$61,968 purchasing power parity (PPP) 2005] in comparison with BSC. 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 6 years.

Assessment of uncertainty

All six full-text studies[55,95–99] used some form of sensitivity analysis. Chabot *et al.*[95] varied the most influential model parameters, i.e. utility of progression and no progression, OS (HR), PFS, 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 the results of the economic evaluation were most sensitive to the health-state utility value and rate of OS and PFS. The sensitivity analysis also suggested that the results were robust. Contreras-Hernandez *et al.*[96] 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 *et al.*[98] varied the median OS rate, the rate of PFS 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 C$0–550 (Canadian dollars), and for each median progression-free year it ranged from C$0 to C$75,505. Paz-Ares *et al.*[99] 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 BSC group, by assuming all patients in the palliative care group would be given imatinib 400 mg/day. The most sensitive variables affecting the results were efficacy of treatment, and the unit cost of sunitinib. The study by Huse *et al.*[97] 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 PD, 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 *et al.*[55] 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.

Summary of the review

We found that most of the economic evaluation studies reviewed used a modelling exercise. However, only two studies[96,100] compared both imatinib and sunitinib with BSC for patients who had failed or become resistant to imatinib 400 mg/day. The full paper for only one of these[96] was available. Among the five studies[55,95,96,99,100] that used modelling exercises, Contreras-Hernandez *et al.*[96] and Teich *et al.*[100] did not use QALYs as health outcome measures. Although Contreras-Hernandez *et al.*[96] used patient-level data as the basis of their cost estimates, they used survival and PFS as effectiveness measures in their model, which was based on the studies by Motzer *et al.*[104] and Demetri *et al.*[52]

The two studies[95,99] that used modelling exercises to compare the cost-effectiveness of sunitinib only with BSC used the same trial data (A6181004).[52] 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[55] 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/day to cross over to a higher dose of imatinib 600 mg/day rather than 800 mg/day.

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

For a comprehensive economic evaluation of the alternative treatments for GIST patients who fail on or become 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 were used 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 end points. In cases where the patients in placebo groups or in BSC 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/BSC 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. However, NICE's guidance[94] suggests that costs and resources falling to the NHS and Personal Social Services (PSS) should be used. This approach by NICE is not universally accepted and costs and benefits falling on other groups may be relevant, for example in helping to illustrate additional choices and trade-offs that a decision-maker may wish to consider.

Economic modelling

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 was developed to compare the alternative treatment strategies 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 owing to intolerance. According to the scope for the review the treatment strategies to be compared in the models were:

1. treatment with an escalated dose of 600 mg/day, regulating symptoms with BSC
2. treatment with an escalated dose of 800 mg/day, regulating symptoms with BSC
3. treatment with sunitinib (within its recommended dose range), regulating symptoms with BSC
4. regulating symptoms with BSC 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 were dose T1 = imatinib 600 mg/day, T2 = imatinib 800 mg/day, T3 = sunitinib (with recommended dose 50 mg/day) and BSC.

A Markov model was developed to model these care pathways using TreeAge Pro 2009 (TreeAge Software Inc., Williamstown, MA, USA). 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 owing to intolerance enter one of the seven care pathways. *Figure 6* is an illustrative example of the model structure for Path-4, where patients are treated with imatinib 600 mg/day, and if the disease progresses on this treatment the patients are treated with BSC. *Appendix 12* illustrates the model for all seven pathways of alternative treatments.

Path-1 shows the patients with BSC treatment. It is assumed that the patients with BSC are still treated with imatinib and palliative care. Path-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 PR (CR/Stable IM 600). From this point, a proportion of patients will survive and continue to respond to treatment. Those who stop responding to imatinib 600 mg/day move to a state where they receive imatinib 800 mg/day (PD at IM 600). A proportion of patients will remain with the escalated dose 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 PR (CR/Stable with sunitinib). From this point, a proportion of patients may continue to respond to the treatment and remain stable, or they may stop responding to sunitinib and receive BSC for the remainder of their life.

Path-3 represents treatment options through which 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 IM 600). 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 PR (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

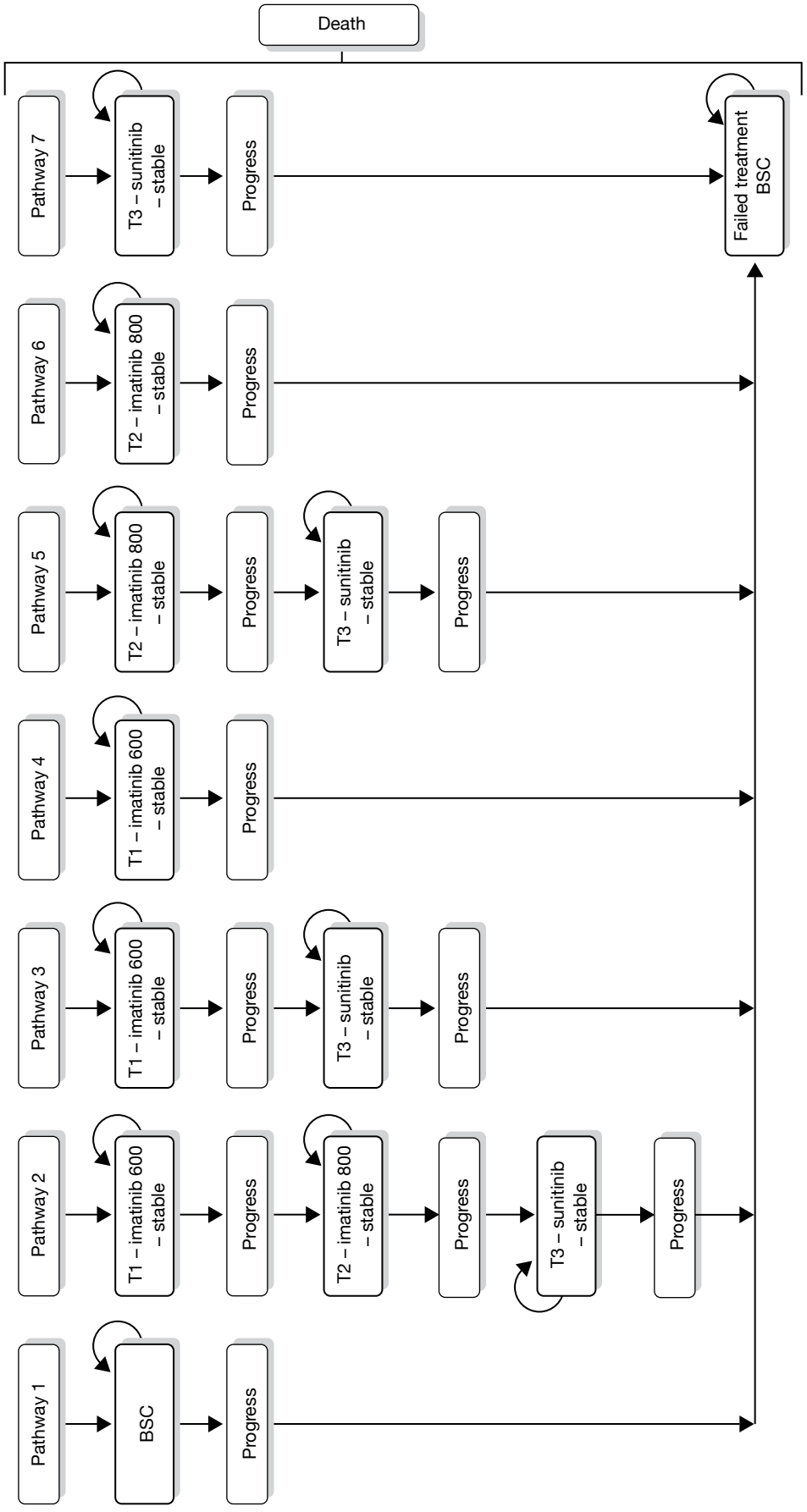

FIGURE 5 Markov model for GIST patients who have failed with imatinib 400 mg/day.

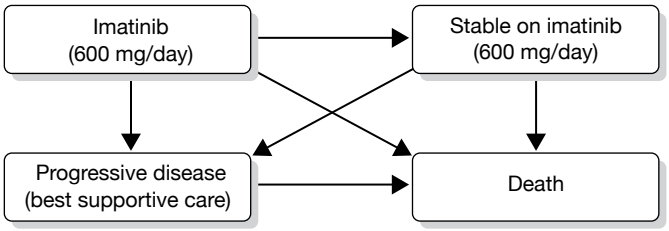

FIGURE 6 Example of model structure for care pathway Path-4 (imatinib 600 mg/day – BSC).

response or PR (CR/Stable with sunitinib). Should they fail to respond to sunitinib or if at some point they cease to respond they continue with BSC for the remainder of their life.

In Path-4, all patients start the treatment with imatinib 600 mg/day and no switching to other treatments 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 BSC for the remainder of their life. This option has been considered as a treatment option in the model, although actual clinical practice may favour further escalation to 800 mg/day. Nevertheless, for this model, care pathways were developed with clinical advice on *plausible* pathways of care, some of which may be more typical of current practice than others.

The remaining care pathways are variants of earlier pathways. Path-5 is similar to Path-3 with respect to the combination of escalated dose of imatinib and sunitinib, the main difference in this case is that the escalated dose is imatinib 800 mg/day. Apart from this difference the pathways are identical. Path-6 is similar to Path-4. However, in this pathway the escalated dose is imatinib 800 mg/day instead of imatinib 600 mg/day. Path-7 is similar to Path-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*).

The care pathways chosen for our model are not exhaustive and do not include every single possible clinical intervention available to oncologists treating GIST after failure at 400 mg/day of imatinib, but the care pathways chosen reflect the scope of this research as agreed with NICE. Other possible treatments (e.g. surgery for those whose tumours become resectable following treatment with escalated doses of imatinib) were not considered.

Key assumptions of the modelling exercise

The key assumptions of the model are:

1. The time horizon of the model is 10 years, over which time all patients are expected to die, and the cycle length is 1 month.
2. The model assumes that patients entering a pathway will remain in a health state and on the treatment for one cycle only. If they respond and remain stable they continue on the treatment in the next cycle. If they do not respond but survive in the treatment arm they are considered to move to an escalated dose, move to another alternative (if allowed by a treatment pathway) or continue with BSC for the remaining time horizon of the model.
3. The model assumes that the probabilities of progressing and dying do not change over time. This assumption was made because of the limited data available.
4. The utilities of the health outcome from treatment with imatinib 600 mg/day, imatinib 800 mg/day and sunitinib are assumed to be the same. This assumption was made because of the limited data available.

5. All patients failing or not responding to the treatment in any of the treatment arms of the model continue with BSC for the remainder of the model time horizon or until they die, and are assumed to derive the same utility as from the health state of progression. Owing to lack of data, time-dependent changes in transition rates of response were not built into the model.

Data requirements and model inputs

For our model, data on the clinical effectiveness of interventions were 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 patients with GIST.

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, few of which were 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 consideration should be treated cautiously.

Probability of death for BSC

The data for BSC were taken from two studies[106,107] and a pooled weighted estimate suggested that 87.9% (51/58) 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 BSC after previously being treated with imatinib at an escalated dose or with sunitinib. The data from the review of clinical effectiveness were not appropriate to populate the BSC states in the model, as no BSC studies met the inclusion criteria. The second best source of data would have been information on follow-up of non-crossover patients following failure at 400 mg/day, but these patients were not followed up in any of the included studies looking at dose escalation of imatinib. The only other data available on BSC come from the pre-imatinib era (where it would not have been possible for people to have failed on 400 mg/day of imatinib). The two sources chosen from the studies identified (see *Appendix 13*) were chosen because they had larger sample sizes and longer median follow-up times. However, one of the sources relates to a study conducted before there was awareness of GIST as being a distinct tumour. Alternative data for this parameter are outlined in *Appendix 13*; however, it is likely that these data would provide similar, imprecise and potentially biased estimates for this probability.

Probability of death for imatinib at 600 and 800 mg/day

The data on mortality for the imatinib 600 mg/day treatment groups were taken from the available trial data[39] and 55% (6/11) of those who crossed over to imatinib 600 mg/day died over the trial period of 60 months. Although the sample size is very small, in the absence of any better alternative it has been used in the model. The data on mortality for imatinib 800 mg/day were taken from Blanke *et al.*[41] [where the data suggest that 64.41% (76/118) died in the imatinib 800 mg/day group]. Again the monthly mortality rate was derived as an exponential rate. It should be noted that the study was not designed to assess dose escalation, and the use of data from the crossover groups from the studies used are not ideal estimates for probability of death for these patients. In the absence of other suitable data we have used these data for our model.

Probability of death for sunitinib

The mortality data for those treated with sunitinib came from Reichardt *et al.*[81] In this study 231/331 patients receiving sunitinib survived. The monthly mortality rate was derived assuming an exponential rate. In the analysis it was also assumed that the mortality rate for those receiving sunitinib was the same regardless of any possible differences in prior treatment. It should also be noted that the survival estimate from this trial was based on those who failed on imatinib at doses of ≤ 400 mg/day, but it is not clear whether the patients failed on the 400 mg/day dose or at lower doses.

Response rates for the treatments

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

The response rate for imatinib 600 mg/day was based upon data from the B2222 trial.[39] This study reported that 25.5% (11/43) of patients had responded and remained stable during a median follow-up of 63 months. The sample size of this study was small, but these were the only data available for the specific population of interest. It should be noted that the B2222 trial[39] was not designed to assess dose escalation and there was no randomisation of patients at the point of disease progression.

The S0033[41] and EORTC[44] trials data were used to provide evidence of the response rate for imatinib 800 mg/day. These studies reported that 30% (75/250) of patients responded to treatment with imatinib 800 mg/day and showed PR or stable condition after a median follow-up of 54 months.

For sunitinib none of the studies meeting the inclusion criteria for the review of effectiveness reported data on response rate. Therefore, this parameter was estimated from the weighted average response rate from two studies reporting this outcome.[38,108] In these two studies in total 266/382 patients responded, and a simple weighted mean was used to derive the pooled response rate. This response rate was assumed to be unaffected by prior treatment received. It should be noted that the patient groups in these two studies may not be the same. The Prior *et al.* study[108] does not report the previous imatinib dose for participants, whereas in Demetri *et al.*[38] most of the population failed on 800 mg/day imatinib. As there was no statistically significant difference in the response rates, we took these two studies as a second-best source. 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 *British National Formulary* (BNF), etc.] and the review of economic evaluations. Costs have been considered from a NHS perspective only. An identification of the potential direct and indirect resource costs for the NHS and PSS that would be expected from the introduction of the technology is presented.

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 medication for 4 weeks and then no medication for the following 2 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 the BNF no. 58.[109] It has been assumed that patients on BSC still receive medications and it has been assumed that the cost of these is equivalent to the cost of imatinib at 400 mg/day.

Resource use by the treatments was based on the study by Wilson *et al.*,[55] 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), at 2004 prices. These cost estimates were used for our model after adjusting for inflation with the Hospital and Community Health Services (HCHS) Index for pay and prices inflation for the year 2008–9.[110] Based on these estimates, the total monthly cost of management with imatinib treatment is £128.16. These other treatment costs represent approximately 5% of the total cost of the drug itself. In the absence of better data these costs have been used for imatinib at both 600 and 800 mg/day.

For the sunitinib group we have used the resources based on the Pfizer single technology assessment submission[60] for patient monitoring, outpatient and GP visits (£799.73 per year), CT imaging (£336 for 7.3 months) 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 BSC, data from the Pfizer submission were again used:[60] the suggested costs in 2008 prices for patient monitoring, outpatient and GP visits were £249 per year, and £105 per year for CT imaging. These costs were inflated to 2009 prices using the same methods described above.

The different estimates for the costs of CT scanning between the two drugs can be accounted for by the fact that different sources were used to derive the costs of CT scanning. When inflated to 2008–9 prices, this gave the monthly cost of CT scans as £15.01 for BSC groups, £64.92 for the imatinib groups and £48.04 for the sunitinib groups.[51,55]

The monthly cost of adverse events in the model is £13.25 for the imatinib groups (600 and 800 mg/day) and £21.78 for sunitinib, which is about 10% of all other costs for imatinib and 12% of all other costs for sunitinib. There were insufficient data on disutility to incorporate this as a parameter within the model, despite evidence to suggest differences in the adverse event profiles of imatinib and sunitinib that could influence disutility.[111]

Utility data

There were few data relating to health-state utilities. Our model has used data in which the health-state valuations are derived from the EQ-5D, and the values used were taken from Wilson *et al.*[55] and Chabot *et al.*[95] The utility associated with PFS for those responding to imatinib (regardless of dose) was 0.935.[55] The utility for those receiving BSC was taken from Chabot *et al.*[95] and was taken to be 0.577. 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 valuations 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) has been assumed to be similar to the value based on the BNF price,[109] 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 a 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	For sensitivity analysis		Distribution	Values	Data source and assumptions
			Low	High			
Cost parameters (£)							
clmat600	Cost of drugs: imatinib 600	2406	2005	2406			BNF 58:[109] low value is average of imatinib 400 and 600 mg
clmat800	Cost of drugs: imatinib 800	3208	2807	3208			BNF 58:[109] low value is average of imatinib 600 and 800 mg
CNott	Cost of BSC	1604	1283	1604			Includes cost of imatinib 400 mg (BNF 58[109])
CSunb	Cost of drugs: sunitinib	3138.8	2092.5	3138.8			BNF 58:[109] low value is average of reduced dose of sunitinib
OthCostBSC	Other costs and management of treatment in BSC arm	50.61					Resource use in the treatment was based on the study by Wilson 2005[55]
OthCostIm	Other costs and management of treatment in imatinib treatment arm	128.16					Resource use in the treatment was based on the study by Wilson 2005.[55] Assumed to be same for imatinib 600 and imatinib 800
OthCostSun	Other costs and management of treatment in sunitinib treatment arm	185.11					Resource use in the treatment was based on the study by Wilson 2005[55] and single technology appraisal of Pfizer[60]
Mortality and response to treatment							
deathBSC	Probability of death in the BSC treatment arm	0.014627			Beta	$\alpha = 0.8448898$ $\beta = 57.775$	Pooled weighted rate[106,107]
dth600	Probability of death in imatinib 600 treatment arm	0.007472			Beta	$\alpha = 0.08162$ $\beta = 10.91838$	B2222 study[39]
dth800	Probability of death in imatinib 800 treatment arm	0.011857			Beta	$\alpha = 1.39948$ $\beta = 116.600$	S0033 study[41]
Dthsun	Death due to GIST: sunitinib	0.026706			Beta	$\alpha = 9.3284$ $\beta = 341.62$	Reichardt 2008[81]
nonresplm600	Transition probability of non-response to imatinib 600	0.011743			Beta	$\alpha = 0.504949$ $\beta = 42.495051$	B2222 study[39]
nonresplm800	Transition probability of non-response to imatinib 800	0.012879			Beta	$\alpha = 3.21875$ $\beta = 246.780$	S0033 study[41] and Zalcberg 2005[44]
nonrespSun	Transition probability of non-response to sunitinib	0.080959			Beta	$\alpha = 12.30$ $\beta = 139.6945$	Weighted average response rate[52,108]
ulmat600	Utility with imatinib 600	0.935	0.712	0.939			Wilson 2005[55]
ulmat800	Utility with imatinib 800	0.935	0.712	0.939			Wilson 2005[55]
uProg	Utility for PD	0.577	0.52	0.712			Chabot 2008[95] and Wilson 2005[55] for lower level values for sensitivity analysis
uSun	Utility with sunitinib treatment	0.935	0.712	0.939			Chabot 2008[95]

TABLE 15 Model parameters, values and data sources *(continued)*

Parameters	Description	Value	For sensitivity analysis		Distribution	Values	Data source and assumptions
			Low	High			
Structural and methodological parameters							
Cycle length	Time period that utilities, costs and probabilities relate to	1 month					Assumption
Length of run	No. of cycles model is run for	120 (10 years)	72 (6 years)	144 (12 years)			Assumption
DR	Discount rate	0.002917	0	0.005			NICE guideline[94]

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 1 month to reflect the natural history of the condition.

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 guidelines. As described below, both deterministic and probabilistic sensitivity analyses were conducted with a net benefit framework being used to compare the different treatment strategies.

Sensitivity analysis

Probabilistic sensitivity analyses

Probabilistic sensitivity analyses of the base-case scenario were 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 *Data requirements and model inputs*, above.

The beta distribution as defined above might arguably be considered to be too precise and to not truly reflect the degree of uncertainty that exists. To examine the uncertainties around the distribution assumed for the base-case 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 to be 90% less than and 90% more than the mean value used in our model, respectively. 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 bias are uncertain.

Deterministic sensitivity analyses

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

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*.

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 than 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 for treatment with imatinib 800 mg/day also applied to imatinib 600 mg/day.

Results

Base-case analysis

Table 16 shows the mean estimates of cost and effectiveness of the seven alternative treatment strategies modelled. As this table shows, effectiveness has been reported in two ways: life-years and QALYs. Path-4, imatinib 600 mg/day has an incremental cost per QALY that is < £30,000 compared with Path-1, BSC. The only other non-dominated or non-extendedly dominated strategy is Path-2, imatinib 600 to imatinib 800 mg/day to sunitinib. However, in this case the incremental cost per QALY (compared with 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/day (Path-7) was estimated to have a lower life expectancy than BSC 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 BSC when effectiveness was measured in life-years but not dominated when effectiveness was measured in QALYs illustrates the importance of

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 BSC	92,811		4.154		2.397		
Path-7 Sunitinib	96,688	3877	3.716	(Dominated)	2.411	0.014	272,365
Path-4 Imatinib 600 mg	147,060	50,372	5.211	1.057	4.256	1.845	27,304
Path-3 Imatinib 600 mg to sunitinib	149,200	2139	5.032	Dominated	4.286	0.030	71,723
Path 6 Imatinib 800 mg	153,901	4702	4.506	Dominated	3.635	–0.651	Dominated
Path-5 Imatinib 800 mg 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 BSC	92,811		4.154		2.397		
Path-4 Imatinib 600 mg	147,060	54,249	5.211	1.057	4.256	1.859	29,181
Path-2 Imatinib 600 mg to 800 mg to sunitinib	172,152	25,092	5.278	0.067	4.803	0.547	45,850

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 BSC (at the very least the incremental cost per QALY would have increased from the £272,365 reported in *Table 16*).

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, BSC. When society's willingness to pay for a QALY is between approximately £25,000 and £45,000 then 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.

Sensitivity analysis

Uncertainty around the distributions used for mortality and response rates

The beta distributions used to generate *Figure 7* 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 previous section (see *Probabilistic sensitivity analyses*), this is because the data are used essentially 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, BSC, is still the most likely to be considered cost-effective. However, Path-7, sunitinib, is more

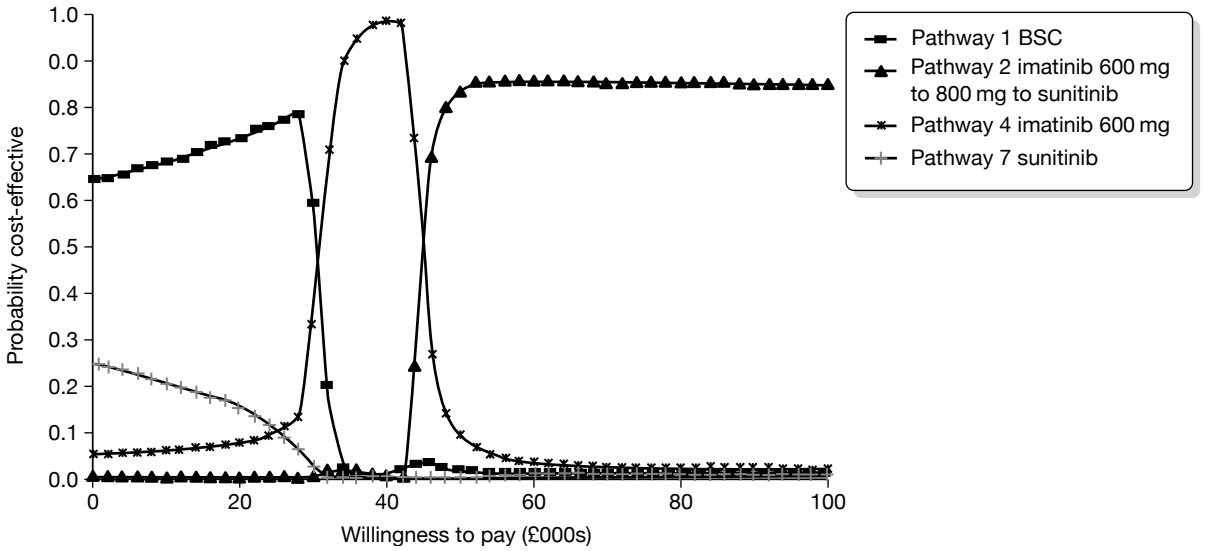

FIGURE 7 Cost-effectiveness acceptability curve for alternative treatments over the 10-year time horizon. Pathways with a low probability of being cost-effective over the range of willingness to pay for a QALY values considered have not been shown.

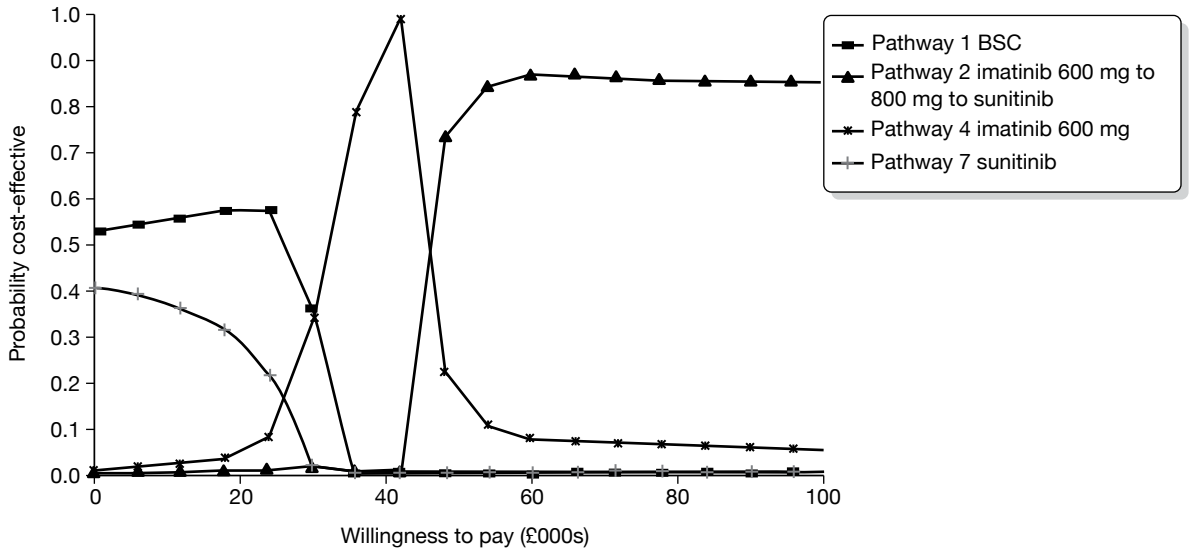

FIGURE 8 Cost-effectiveness acceptability curve for alternative treatments over the 10-year time horizon assuming uniform distributions for mortality and response rates. Pathways with a low probability of being cost-effective over the range of willingness to pay for a QALY values considered have not been shown.

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 towards a slightly higher mortality rate than BSC. 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 cost-effective as Path-1, BSC, 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.

Uncertainty surrounding structure and methodological assumptions around distribution

Two different discount rates have been applied to costs and benefits 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 that are dominated or extendedly dominated, and the incremental cost per QALY for Path-4, imatinib 600 mg/day, compared with Path-1, BSC, 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 is changed to 6%, the incremental cost per QALYs for the non-dominated strategies falls 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 < £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, BSC, increases slightly. The incremental cost per QALY for Path-2, imatinib

TABLE 17 Sensitivity around the discount rate and length of run

	Strategy	Cost (£)	QALYs	Incremental cost per QALY (£)
Base case, i.e. discount rates = 3.5% on cost and benefit; time horizon = 10 years	Path-1 BSC	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 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 1, i.e. discount rates = 0% on cost and benefit; time horizon = 10 years	Path-1 BSC	93,137	2.706	
	Path-7 Sunitinib	97,719	2.672	Dominated
	Path-4 Imatinib 600 mg	159,462	4.833	31,183
	Path-3 Imatinib 600 mg to sunitinib	163,601	4.859	Extendedly dominated
	Path 6 Imatinib 800 mg	165,641	4.087	Dominated
	Path-5 Imatinib 800 mg to sunitinib	169,210	4.105	Dominated
	Path-2 Imatinib 600 to 800 mg to sunitinib	195,193	5.486	54,715
Sensitivity analysis 2, i.e. discount rates = 6%; time horizon = 10 years	Path-1 BSC	92,614	2.209	
	Path- 7 Sunitinib	96,007	2.254	Extendedly dominated
	Path-4 Imatinib 600 mg	139,473	3.908	27,593
	Path-3 Imatinib 600 mg to sunitinib	140,394	3.940	28,801
	Path 6 Imatinib 800 mg	146,627	3.360	Dominated
	Path-5 Imatinib 800 mg to sunitinib	147,542	3.387	Dominated
	Path-2 Imatinib 600 to 800 mg to sunitinib	158,271	4.392	39,480

TABLE 18 Sensitivity around the time horizon of the model

	Strategy	Cost (£)	QALYs	Incremental cost per QALY (£)
Base case, i.e. discount rates = 3.5% on cost and benefit; time horizon = 10 years	Path-1 BSC	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 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, i.e. discount rates = 3.5%; time horizon = 6 years	Path-1 BSC	73,246	1.960	
	Path-7 Sunitinib	79,720	2.032	Extendedly dominated
	Path-4 Imatinib 600 mg	114,433	3.402	28,560
	Path-3 Imatinib 600 mg to sunitinib	117,729	3.455	Extendedly dominated
	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, i.e. discount rates = 3.5%; time horizon = 12 years	Path-1 BSC	98,464	2.510	
	Path-7 Sunitinib	101,589	2.509	Dominated
	Path-4 Imatinib 600 mg	156,943	4.489	29,553
	Path-3 Imatinib 600 mg to sunitinib	158,421	4.507	Extendedly dominated
	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

600 mg/day to imatinib 800 mg/day to sunitinib, compared with Path-4, imatinib 600 mg/day, is virtually unchanged.

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 were sparse and what few data there were suggested a superior effectiveness compared with imatinib 800 mg/day. These data are (1) potentially unreliable because they are based upon non-randomised and non-comparative data and (2) potentially counterintuitive (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 that with imatinib 800 mg/day.

As *Table 19* shows the incremental cost per QALY for Path-4, imatinib 600 mg/day, compared with Path-1, BSC, falls. This is because there is a reduction in the cost of medications as the probabilities that patients die or make the transition to BSC increases, which more than compensates 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.

As noted in *Data requirements and model inputs* (above), the two sources[106,107] of mortality data that we have used for BSC were chosen because these studies had larger sample sizes and longer median follow-up times (*Appendix 13*). We conducted sensitivity analysis using different sources of mortality data for BSC, i.e. using a pooled mortality estimate of 19.8% that is based on survival estimates from Pierie *et al.*,[107] Dougherty *et al.*[112] and Artyan *et al.*[113] The monthly mortality rate would be higher (0.02349) than what we have used in the base case (0.014627). As mortality for BSC increases, the cost and QALYs for the pathways fall because BSC is part of each pathway. As a consequence the incremental cost per QALYs do not change greatly although all slightly increase compared with less costly but less effective pathways because the increase in mortality for BSC has proportionately a greater effect on costs than on QALYs.

Uncertainty surrounding utility values

The sensitivity of a lower and higher value of utility for 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, BSC, 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 PD reduced the opportunity for pathways that are clinically more effective to generate additional QALYs. As a consequence, in this sensitivity analysis the incremental cost per QALYs for the non-dominated pathways increase.

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 sunitinib are explored (*Table 21*). Over most of these sensitivity analyses the pathways that are dominated or are extendedly dominated do 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

TABLE 19 Changes to mortality and response rates

	Strategy	Cost (£)	QALYs	Incremental cost per QALY (£)
Base case	Path-1 BSC	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 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 5: survival rate and response rate to imatinib 600 mg treatment same as that with imatinib 800 mg	Path-1 BSC	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 to 800 mg 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
Sensitivity analysis 6: survival rate for BSC = 0.02349	Path-1 BSC	65,412	1.729	
	Path-7 Sunitinib	77,669	1.954	Dominated
	Path-4 Imatinib 600 mg	137,060	4.022	31,239
	Path-3 Imatinib 600 mg to sunitinib	142,643	4.134	Extendedly dominated
	Path-2 Imatinib 600 to 800 mg to sunitinib	144,349	3.411	Dominated
	Path-6 Imatinib 800 mg	149,517	3.512	Dominated
	Path-5 Imatinib 800 to sunitinib	170,340	4.762	44,603

TABLE 20 Sensitivity analysis around the utility assumed for disease progression

	Strategy	Cost (£)	QALYs	Incremental cost per QALY (£)
Base case: utility of progressive state = 0.577	Path-1 BSC	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 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 BSC	92,811	2.160	
	Path-7 Sunitinib	96,688	2.242	Extendedly dominated
	Path-4 Imatinib 600 mg	147,060	4.158	27,156
	Path-3 Imatinib 600 mg 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 BSC	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 mg 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

TABLE 21 Sensitivity around the costs of imatinib and sunitinib

	Strategy	Cost (£)	QALYs	Incremental cost per QALY (£)
Base case:	Path-1 BSC	92,811	2.397	
Imatinib 600 mg £2406	Path-7 Sunitinib	96,688	2.411	272,365
Imatinib 800 mg $3208	Path-4 Imatinib 600 mg	147,060	4.256	27,304
Sunitinib £3138.8	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 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 (change in imatinib 600 mg price):	Path-1 BSC	92,811	2.397	
Imatinib 600 mg £2005	Path-7 Sunitinib	96,688	2.411	Extendedly dominated
Imatinib 800 mg $3208.16	Path-4 Imatinib 600 mg	130,272	4.256	20,150
Sunitinib £3138.8	Path-3 Imatinib 600 mg to sunitinib	132,412	4.286	Extendedly dominated
	Path-6 Imatinib 800 mg	153,901	3.635	Dominated
	Path-2 Imatinib 600 to 800 mg to sunitinib	155,364	4.803	45,850
	Path-5 Imatinib 800 mg to sunitinib	155,828	3.659	Dominated
Sensitivity analysis 9 (change in imatinib 800 mg price):	Path-1 BSC	92,811	2.397	
Imatinib 600 mg £2406	Path-7 Sunitinib	96,688	2.411	Extendedly dominated
Imatinib 800mg $2807	Path-6 Imatinib 800 mg	139,988	3.635	Extendedly dominated
Sunitinib £3138.8	Path-5 Imatinib 800 mg to sunitinib	141,915	3.659	Extendedly dominated
	Path-4 Imatinib 600 mg	147,060	4.256	29,181
	Path-3 Imatinib 600 mg to sunitinib	149,200	4.286	Extendedly dominated
	Path-2 Imatinib 600 to 800 mg to sunitinib	166,000	4.803	34,609
Sensitivity analysis 10 (change in sunitinib price):	Path-7 Sunitinib	87,533	2.411	
Imatinib 600 mg £2406	Path-1 BSC	92,811	2.397	Dominated
Imatinib 800mg $3208.16	Path-3 Imatinib 600 mg to sunitinib	144,524	4.286	30,400
Sunitinib £2092	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

reduced, Path-7, sunitinib, becomes the least costly option. This is primarily because this pathway uses potentially unreliable data on mortality for sunitinib which means that patients on this pathway do not survive long enough to incur higher costs.

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, BSC, 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, BSC. 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 with 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, BSC, is the most cost-effective. When society's willingness to pay for a QALY is between approximately £25,000 and £45,000 then 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 sparse data that are 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 two main areas of uncertainty due to lack of data:

- The considerable uncertainty around the extrapolation from the sparse data on death and response rate and the impact of alternative assumptions about how probabilities of death and response change over time.
- Reductions in utility associated with adverse effects of treatment.

By assuming constant probabilities over time, death may be overestimated at earlier time points and underestimated at later stages of the time horizon of the model. The probability of death may increase over time as the disease progresses. Similarly the probability of non-response may increase over time and patients may have an increasing need for an escalated dose of imatinib, or sunitinib. The assumption of constant probability over time generally delays the transition to patients' deaths. This means that our analysis has a bigger impact on the most effective treatments. These treatments will also incur high treatment costs over a longer period. The net impact of these two changes on cost-effectiveness is unclear.

The net impact of adjusting scores for adverse effects is also uncertain but it might be expected that it will reduce the QALYs associated with each medication and, although there are limited data available from the systematic review of clinical effectiveness, this reduction may be greater for pathways involving sunitinib because its adverse effect profile is believed to be worse than that of imatinib.[111]

Owing to sparse data for this analysis, few data were available on the utility values for defined disease states in the model. Furthermore, the disease states selected in the model may not be complete and exhaustive as data on alternative plausible disease states were not available. Sensitivity analysis explored uncertainty in key parameter estimates but clearly this does not investigate the influence of structural assumptions such as the limited number of disease states chosen for the modelling. A more sophisticated model would have allowed further sensitivity analysis but without at least some data to guide assumptions we would have needed to identify threshold values for many individual parameters and combinations of parameters. This would have resulted in a substantially expanded economics chapter reporting extensive speculative results that would have been very difficult to interpret.

A further factor not considered by the economic model was the cost-effectiveness of treatment for those with specific gene mutations. Again this was not addressed owing to lack of data, and as there were also no data available to assess the impact of plasma monitoring on the study population of interest, this was also not considered by the economic model.

Finally, the economic evaluation has assumed that patients who move on to BSC remain on treatment to prevent tumour flare. This has the impact of increasing the cost of BSC. 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 BSC or moving on to BSC after failing to respond on a medication would receive imatinib 400 mg/day. This assumption appears reasonable for Path-1, BSC, but may not be appropriate for the other pathways where patients would move on to BSC 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.

Chapter 6

Assessment of factors relevant to the NHS and other parties

Gastrointestinal stromal tumours are a rare cancer, accounting for < 1% of all cancers of the GI tract. The incidence and subsequent overall burden on the NHS is not large, and only a small proportion of patients with GIST will have unresectable and/or metastatic disease that progresses on imatinib at a dose of 400 mg/day. 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 PD after initially responding at the 400 mg/day dose.[50] Some guidelines, however, do advocate dose escalation for such patients, particularly those with *KIT* exon 9 mutations, indicating that escalated doses may help this group of GIST patients and offer them the opportunity to continue with a normal life for a longer period of time.[15,114,115]

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 GIST 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.

Chapter 7

Discussion

Statement of principal findings

Review of clinical effectiveness

This review is a part update of a previous review on imatinib for the treatment of patients with unresectable and/or metastatic GISTs.[55] We 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 669 patients from within the 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 outcomes. No studies reporting BSC 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 open to bias.

The sample sizes of the studies from which the 669 patients were drawn from ranged from 24[79] to 1117[86] participants. 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.[116] Of the studies that reported the proportion of the study population receiving prior surgery,[39,44,79] most patients had undergone prior surgery for treatment of their disease. Information on the characteristics of all the 669 patients relevant to this review was not provided separately.

From the data on imatinib it can be seen that approximately one-third of patients progressing on 400 mg/day of imatinib will respond to escalated doses. With 600 mg/day, between 25.6% (11/43)[39] and 41.7% (5/12)[79] of patients with unresectable and/or metastatic GIST, who had previously progressed on a dose of 400 mg/day of imatinib, either developed a PR or maintained SD. With 800 mg/day, the proportions achieving PR or SD ranged between 29.3%[44] and 33.3%.[79] These data were used to inform transition probabilities of non-response to imatinib at escalated doses of 600 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. As an alternative to excluding sunitinib entirely, which could arguably have been appropriate given the lack of data, the economic model used data that did not meet the inclusion criteria for the review of clinical effectiveness because it failed to report response data separately for those progressing on a 400 mg/day dose. A further assumption made in the economic model was that response was unaffected by prior treatment received. This assumption was made because of a lack of data on how response might change over time and be affected by prior treatments other than imatinib at 400 mg/day.

Median OS 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 OS 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 OS was reported to be 19 months (95% CI 13 to 23 months) in the S0033 trial.[41] Median OS was not reported for the EORTC-ISG-AGITG study[44] for the population of interest, (CiC information has been removed). For those receiving sunitinib after a prior imatinib dose of ≤ 400 mg/day, median OS was reported as 22.5 months (95% CI 18.3 to 26.5 months).[86]

Figure 3 provided a visual comparison of the median OS times for imatinib at an escalated dose of 800 mg/day and sunitinib, showing overlapping CIs 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. (CiC information has been removed.) It is difficult to draw any conclusions with regard to possible differences in OS between imatinib at an escalated dose of 800 mg/day and sunitinib at 50 mg/day (with a 4-weeks-on/2-weeks-off cycle), owing to the lack of data, but as the 95% CIs for median OS overlap, there does not appear to be any significant difference in median OS with dose escalation, compared with sunitinib.

The median time to progression and PFS was reported for imatinib 600 mg/day as 1.7 months (range 0.7–24.9 months),[79] and for imatinib 800 mg/day it ranged between 2.9 months (reported without CIs as '81 days')[44] and 5 months (95% CI 2 to 10 months).[41] A visual representation of these data for imatinib 800 mg/day in *Figure 4* gives 95% CIs that do not overlap, for all time points between 12 and 21 months, indicating that PFS was significantly shorter in the EORTC-ISG-AGITG study reported by Zalcberg *et al.*[44] than in the S0033 trial reported by Blanke *et al.*[41]

In addition, those studies looking at an 800 mg/day dose of imatinib 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 of those achieving PR and SD on the 800 mg/day dose. This suggests that a small proportion (i.e. < 20%) of those receiving an escalated dose of 800 mg/day of imatinib on progression may maintain their response/SD for a median time period 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 SD 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 *et al.*[44] reported a median duration of 'stabilisation' among those showing response or SD with treatment of 153 days (range 37–574 days). For sunitinib, the treatment duration for all patients receiving sunitinib (i.e. regardless of the dose of prior imatinib therapy) was 126 days (range 1–618 days).[86]

Data on adverse events were not available from any of the studies where the population of interest received imatinib at 600 mg/day or sunitinib following progression at 400 mg/day. For the trials reporting outcomes following dose escalation from 400 to 800 mg/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.[44] (CiC information has been removed.)

Nevertheless, it was also reported that between 15.6%[77] and 31%[78] of patients receiving an escalated imatinib dose of 800 mg/day required a dose reduction. It was also reported that 23.3% (18/77) of patients required at least one dose delay.[77] 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, although 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 *et al.*[44] showing that a higher proportion of patients with skin rash, nausea, leucopenia, neutropenia and thrombocytopenia reported a reduction in the severity of these events following dose escalation 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 ($p = 0.015$).[44] (CiC information has been removed.) 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 prespecified subgroups of interest were reported by Debiec-Rychter *et al.*[14] for the EORTC-ISG-AGITG trial, which looked at imatinib dose escalation from 400 to 800 mg/day following progression at the lower dose. They noted that patients with wild type, and those with exon 9 mutations, 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. (CiC information has been removed.) 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 is progression at the 400 mg/day dose.[114]

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.

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 that compared all of 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, BSC, 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, BSC. Path-2 (imatinib 600 mg/day to 800 mg/day to sunitinib) is the only other pathway that is not dominated or extendedly dominated over most of the analyses conducted. However, in this case the incremental cost per QALY (compared with the next most costly option: Path-4, imatinib 600 mg/day) tends to be > £40,000.

When society's willingness to pay for a QALY is < ~£25,000, Path-1, BSC, is the most cost-effective intervention. 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.

As discussed below, these data should be treated cautiously, as the data used are observational and non-comparative. Furthermore, the data on sunitinib and imatinib 600 mg/day are particularly sparse and potentially unreliable. For example, data on treatment with sunitinib show a lower life expectancy than those on treatment with BSC (although sunitinib has greater QALYs). This means that when the cost of sunitinib is reduced it becomes more cost-effective than BSC, as the potentially unreliable source data for life expectancy on sunitinib mean that patients on sunitinib will not survive long enough to incur higher costs of treatment. Although sufficient evidence on the effectiveness of sunitinib compared with BSC following treatment on imatinib at a 400 mg/day dose was not available, evidence on the effectiveness of sunitinib compared with BSC regardless of prior imatinib dose suggests that life expectancy with sunitinib is superior.

In addition, the data available for imatinib at a dose of 600 mg/day suggested superior effectiveness compared with the 800 mg/day dose. This is because the evidence on imatinib at the 600 mg/day dose was based on a smaller sample size (43 patients), making the model results for this pathway potentially counterintuitive if we expect higher drug doses to have greater effectiveness than lower doses.

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 evaluations, a rigorous systematic approach was adopted. The economic model considered a large number of plausible alternative treatments and also incorporated both 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 were 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 effectiveness and cost-effectiveness.

There was also a lack of evidence on QoL 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 BSC. This is important as since the development of imatinib and sunitinib, it no longer represents the only treatment option for those with unresectable/metastatic disease. There was little evidence on 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 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, which may not be a valid assumption. However, it was not possible to confirm the validity of the assumption despite contacting the study authors (P Reichardt, HELIOS Klnikum Bad Saarow, Germany, 2010, personal correspondence). 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 mg/day 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 3* of this report.

For the economic model, sufficient sound comparative data for the different plausible treatments were not available, despite conducting an extensive review of relevant studies. This necessitated a number of simplifying assumptions being made with respect to the model and also 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 considered to move to the escalated doses, move to another alternative (if allowed by a treatment pathway) or continue with BSC for the remainder of the model time horizon or until they die. The care pathways considered in the economic model are not an exhaustive list of all possible treatment options available but represent plausible treatment scenarios. Some are likely to be more representative of clinical practice than others. Whilst additional clinical advice during the development of the care pathways might have increased the extent to which the chosen scenarios reflect true clinical practice, it may also have increased the level of complexity required within the model. Given the lack of robust data it was felt that a more sophisticated model would be difficult to populate.

Within the model, several simplifying assumptions had to be made for individual parameters. For example, it was necessary to consider the costs and utilities associated with BSC as consistent across all care pathways despite the fact that in clinical practice the costs of BSC may increase as an individual's health deteriorates. Unfortunately, there were no data available to model how costs of BSC might increase and QoL might fall over time.

A further simplifying assumption was not to model the complications and side effects of therapy. This latter assumption was made owing to the very limited evidence available. This is coupled with the assumption 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 BSC.

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 GI 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 subgroup 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.
- It was not possible within the time frame of this review for sufficient information to be provided that would have enabled meta-analysis of outcomes for the 800 mg/day dose of imatinib. This evidence may have enabled more robust estimates of survival following dose escalation to 800 mg/day. However, the data would still be prone to bias (being taken from data from a non-randomised patient population) and uncertainty surrounding other parameters (e.g. BSC, sunitinib and imatinib at 600 mg/day) would still be likely to make the model difficult to interpret.
- 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).
- Surgical interventions were also not considered even though surgery is an important treatment option for GIST patients, and even though those with unresectable disease may be eligible for surgery if their tumours become resectable following treatment with an escalated dose of imatinib. The role of emergency surgery as part of BSC was also not considered.

The economic model 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
- reductions in utility associated with side effects of treatment
- 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.

A further uncertainty is the probability of death for BSC. No studies for this comparator met the inclusion criteria for the review. The only sources available for this parameter were from studies published in the pre-imatinib era where the population could not have been exposed to a prior 400 mg/day dose of imatinib, and the proportion of the study populations with KIT-positive

GIST was not known. With regard to the impact of this uncertainty on the economic model, it is reasonable to assume that if, for example, there was an increase in mortality for BSC, the costs and QALYs associated with each of the pathways would fall because BSC is included within each pathway.

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 are 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 that of imatinib.

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

No studies looking at plasma monitoring met our inclusion criteria, but its potential, along with that of mutation testing, as an early predictor of the need for escalated imatinib dosing may have implications for both the costs and effects of escalated doses, because it may allow the identification of those people who are expected to respond better to escalated doses quickly and hence they may be given escalated doses immediately rather than waiting for progression to occur at the 400 mg/day dose. If either of these practices become widely adopted within the NHS then the evidence on the effect of imatinib dose escalation following progression at the standard 400 mg/day dose will become less relevant to clinical practice. Should mutation testing and plasma monitoring allow the tailoring of dose escalation then we might expect the benefits to those who receive therapy to be increased, particularly at earlier stages of treatment (although this also means that there may be fewer remaining treatment options following failure at the escalated dose). Costs would also increase owing to both the cost of mutation testing or plasma monitoring, and also the costs of escalated doses that are incurred earlier. The net impact of this on cost-effectiveness is unclear.

Finally, the economic evaluation has assumed that patients who move on to BSC still receive medication to prevent tumour flare. This has the impact of increasing the cost of BSC. 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 BSC or moving on to BSC after failing to respond to a medication would receive imatinib 400 mg/day. This assumption appears reasonable for Path-1, BSC only, but may not be appropriate for the other pathways where patients would move on to BSC after failing to respond to 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.

Chapter 8

Conclusions

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 SD 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, the median OS, where reported, was < 2 years.
- There is a need to interpret all results from the economic model with caution owing to the limitations of the evidence base. The results themselves indicate that should society's threshold for willingness to pay be less than £25,000 per QALY a pathway of BSC 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 pathway of escalated doses of imatinib followed by sunitinib, if necessary, would be most likely to be cost-effective.
- In terms of policy-making, the results of this review and economic model show that the current evidence available on the effectiveness of imatinib dose escalation for GIST patients following progression on the standard 400 mg/day dose is characterised by such a high degree of uncertainty that, in the authors' opinion, it would be inappropriate to conclude that dose escalation of imatinib would be a cost-effective strategy for the NHS.

Recommendations for research

Further evidence is needed in order to provide a comprehensive assessment of the effectiveness and cost-effectiveness of the alternative treatments for patients with GIST who fail on or become resistant to imatinib 400 mg/day. Ideally, such data would come from RCTs involving patients who progress on 400 mg/day of imatinib, where patients are randomised to 600 mg/day imatinib, 800 mg/day imatinib or sunitinib, or to remain on 400 mg/day imatinib. However, such a study may be difficult to organise, as neither patients nor practitioners may be in equipoise. 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 'BSC'. Therefore, alternative quasi-experimental or observational designs should be considered but with sufficient focus on understanding and controlling for selection biases.

The pathways most likely to be cost-effective at thresholds society might be willing to pay and hence potentially the most useful to assess would be 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 (where there is currently a dearth of evidence for each of the relevant health states for GIST patients), and would need to measure outcomes over a sufficiently long time period to capture the main impact on costs and outcomes. Where possible further studies should also report outcomes for subgroups of patients with specific *KIT* mutations.

With respect to costs, should further comparative studies be conducted, estimates of the usage of health services might usefully be collected. A wider perspective on the consideration of costs might also be informative, for example costs that fall on PSS (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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Contributions of authors

Jenni Hislop (Research Fellow) and Pawana Sharma (Research Fellow) screened the search results for clinical effectiveness, assessed full-text studies for inclusion, and undertook data extraction and quality assessment. Jenni Hislop drafted the chapters of the report other than the background and cost-effectiveness chapters, and coordinated the review. Pawana Sharma contributed to the chapter on clinical effectiveness and the appendices. Graham Mowatt (Senior Research Fellow) and Luke Vale (Professor of Health Technology Assessment) commented on drafts. Zahidul Quayyum (Research Fellow) screened the search results on cost-effectiveness, undertook data extraction and quality assessment, drafted the chapter on cost-effectiveness and developed the economic model, supervised by Luke Vale. Russell Petty (Clinical Senior Lecturer in Medical Oncology) drafted the background chapter, and provided expert advice on clinical aspects of the review. David Jenkinson and Andrew Elders (Statisticians) contributed to the data analysis section of the assessment of clinical effectiveness and conducted the statistical analysis. Cynthia Fraser (Information Specialist) developed and ran the search strategies, obtained papers and formatted the references. All authors assisted in preparing the manuscript and commenting on drafts. Graham Mowatt is guarantor.

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Appendix 1

Search strategies

MEDLINE (2000 – September, week 3, 2009), EMBASE (2000–9, week 39), MEDLINE In-Process (25 September 2009)

Ovid Multifile Search URL: https://shibboleth.ovid.com/

1. Gastrointestinal Stromal Tumors/use mesz
2. Gastrointestinal Stromal Tumor/use emez
3. gastrointestinal neoplasms/use mesz
4. exp digestive system tumor/use emez
5. gist.tw
6. ((gastro$or gastric) adj3 stromal).tw.
7. (3 or 4) and (kit or cd117 or cd 117).tw.
8. (3 or 4) and (stromal or connective or mesenchymal).tw.
9. or/1-2,5-8
10. imatinib.tw,rn.
11. gleevec.tw,rn.
12. glivec.tw,rn.
13. (sti571 or sti 571).tw,rn.
14. or/10-13
15. sunitinib.tw,rn.
16. sutent.tw,rn.
17. (su11248 or su 11248).tw,rn
18. or/15-17
19. dt.fs
20. 9 and 19
21. 20 not (14 or 18)
22. Palliative Care/
23. ((palliative or support$) adj3 (care or treatment)).tw.
24. (symptom$adj3 control$).tw.
25. or/21-24
26. 9 and 14
27. 9 and 18
28. 9 and 25
29. or/26-28
30. exp clinical trial/
31. randomized controlled trial.pt.
32. controlled clinical trial.pt.
33. randomization/use emez
34. randomi?ed.ab.
35. placebo.ab.
36. drug therapy.fs.
37. randomly.ab.
38. trial.ab
39. groups.ab.
40. or/30-39

41. comparative study/use mesz
42. follow-up studies/use mesz
43. time factors/use mesz
44. Treatment outcome/use emez
45. major clinical study/use emez
46. controlled study/use emez
47. clinical trial/use emez
48. (preoperat$or pre operat$).mp. use mesz
49. (chang$or evaluat$or reviewed or baseline).tw
50. (prospective$or retrospective$).tw. use mesz
51. (cohort$or case series).tw. use mesz
52. (compare$or compara$).tw. use emez
53. or/41-52
54. 29 and (40 or 53)
55. animals/not (humans/and animals/)
56. nonhuman/not (human/and nonhuman)
57. 54 not (55 or 56)
58. remove duplicates from 57
59. limit 58 to yr="2000 -Current"

SCI (2000 – 26 September 2009), BIOSIS (2000 – 24 September 2009), ISI Proceedings (2000 – 26 September 2009)

Web of Knowledge URL: http://wok.mimas.ac.uk/

#1 ts=gist
#2 ts=((gastric or gastro*) SAME stromal)
#3 ts=((gastric or gastro*) AND (KIT or cd117 or cd 117))
#4 ts=((gastic or gastro*) and mesenchymal)
#5 #1 OR #2 OR #3 OR #4
#6 ts=(imatinib or gleevec or glivec or sti571 or sti 571)
#7 #5 AND #6
#8 ts=(sunitinib or sutent or su11248 or su 11248)
#9 #5 AND #8
#10 ts=(palliative same (care or treatment))
#11 #5 AND #10
#12 ts=(support* SAME (care or treatment))
#13 #5 AND #12
#14 ts=(symptom* SAME control*)
#15 #5 AND #14
#16 #15 OR #13 OR #11 OR #9 OR #7
#17 #16 CPCI-S Timespan=2000–2009

CINAHL (September 2009)

EBSCOhost URL: http://web.ebscohost.com/

S1 (MH "Gastrointestinal Neoplasms+")
S2 TX gastric or gastro*
S3 S1 OR S2
S4 TX (stromal or connective or mesenchymal)
S5 S3 and S4

S6 TX kit or cd117 or cd 117
S7 S3 and S6
S8 S5 or S7
S9 TX gist
S10 (S8 or S9)
S11 TX (imatinib or gleevec or glivec or sti571 or sti 571)
S12 S10 and S11
S13 TX (sunitinib or sutent or su11248 or su 11248)
S14 S10 and S13
S15 (MH "Palliative Care")
S16 (MH "Hospice and Palliative Nursing
S17 TX (palliative N3 care) OR (palliative N3 treatment)
S18 TX (support* N3 care) OR (support* N3 treatment)
S19 TX (symptom* N3 control*)
S20 (S15 or S16 or S17 or S18 or S19)
S21 S10 and S20
S22 S12 OR S14 OR S21

Cochrane Library Issue 3, 2009 [Cochrane Central Register of Controlled Trials (CENTRAL) and CDSR]

URL: www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME

#1 MeSH descriptor Gastrointestinal Stromal Tumors, this term only
#2 (gist)
#3 (gastric or gastro*) NEAR/3 stromal
#4 MeSH descriptor Gastrointestinal Neoplasms explode all trees
#5 (kit or cd117 or cd 117) or (stromal or connective or mesenchymal)
#6 (#4 AND #5)
#7 (#1 OR #2 OR #3 OR #6)
#8 (imatinib or gleevec or glivec or sti571 or sti 571) or (sunitinib or sutent or su11248 or su 11248)
#9 (#7 AND #8)
#10 Any MeSH descriptor with qualifier: DT
#11 (#7 AND #10)
#12 MeSH descriptor Palliative Care, this term only
#13 (symptom* NEAR/3 control*) or (palliative NEAR/3 (care or treatment)) or (support* NEAR/3 (care or treatment))
#14 (#7 AND (#12 OR #13))
#15 (#9 OR #11 OR #14)

DARE and HTA Databases (October 2009)

NHS Centre for Reviews and Dissemination URL: http://nhscrd.york.ac.uk/welcome.htm

1 MeSH Gastrointestinal Stromal Tumors EXPLODE 1 2 3
2 gist
3 (gastric OR gastro*) AND (kit OR cd117 OR cd AND 117)
4 (gastric OR gastro*) AND (stromal OR connective OR mesenchymal)
5 #1 or #2 or #3 or #4
6 (imatinib OR gleevec OR glivec OR sti571 OR sti AND 571)

7 #5 and #6
8 (sunitinib OR sutent OR su11248 OR su AND 11248)
9 #5 and #8
10 MeSH Palliative Care EXPLODE 1 2
11 palliative
12 #5 and (#10 or #11)
13 #7 or #9 or #12

Health Management Information Consortium (September 2009)

Ovid Multifile Search URL: http://gateway.ovid.com/athens

1. gist.tw.
2. ((gastro$or gastric$) adj3 stromal).tw.
3. gastrointestinal cancer/94
4. 3 and (kit or CD117 or cd 117).tw.
5. 3 and (stromal or connective or mesenchymal).tw.
6. or/1–2,4–5

Clinical Trials (September 2009)

URL: http://clinicaltrials.gov/ct/gui/c/r

"GIST":Topic

CCT (September 2009)

URL: www.controlled-trials.com/

Gastro% stromal OR GIST

WHO International Clinical Trials Registry Platform (ICTRP) (September 2009)

URL: www.who.int/ictrp/en/

Gastro% stromal OR GIST

Clinical Study Results Database (September 2009)

URL: www.clinicalstudyresults.org/

Sutent and GIST
Gleevec and GIST
Glivec and GIST

Association of the British Pharmaceutical Industry (ABPI) (September 2009)

URL: www.cmrinteract.com/clintrial

Sutent or gleevec or glivec

International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) (September 2009)

URL: http://clinicaltrials.ifpma.org

Sutent or gleevec or glivec

Conference proceedings

American Society of Clinical Oncology

Annual Meeting, Chicago, 1–5 June 2007.
Annual Meeting, Chicago, 30 May to 3 June 2008.
Annual Meeting, Orlando, 29 May to 2 June 2009.

European Society for Medical Oncology

9th World Congress on Gastrointestinal Cancer, Barcelona, 28 June to 1 July 2007.
10th World Congress on Gastrointestinal Cancer, Barcelona, 25–28 June 2008.
33rd Congress, Stockholm, 12–16 September 2008.

European Cancer Organisation

ECCO 14: European Cancer Conference, Barcelona, 22–27 September 2007.
ECCO 15: European Cancer Conference, Berlin, 24–29 September 2009.

Appendix 2

Full-paper screening tool

Escalated dose of imatinib for patients with gastro intestinal stromal tumours

Assessor initials: Date:

Study identifier (Surname of first author + year of publication)	
Type of study Is the study an RCT in which all participants are randomised to imatinib, sunitinib or best supportive care (either provided in addition to imatinib or sunitinib or as only care)? OR Is the study a non-randomised comparative study on patients using either imatinib or sunitinib or best supportive care? OR Is the study case series or case study of more than one patient on same type of diagnosis?	☐ Yes ☐ Unclear ☐ No ⇩ ⇩ ⇩ Go to next question **Exclude**
Participants in the study Does the study contain participants with KIT (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST)? ☐ Unresectable ☐ Metastatic Does the study state that disease has progressed on treatment with imatinib at a dose of 400 mg/day? ☐ Yes ☐ No	☐ Yes ☐ Unclear ☐ No ⇩ ⇩ ⇩ Go to next question **Exclude**
Doses and other comparisons Does the study contain at least one group using escalated doses of imatinib (600mg or 800mg per day)? OR Does the study contain at least one group using sunitinib within its recommended dose range (i.e. 25-75 mg/day)? OR Does the study contain at least one group receiving best supportive care	☐ Yes ☐ Unclear ☐ No ⇩ ⇩ ⇩ Go to next question **Exclude**
Outcomes reported Does the study report any one of the following outcomes? ☐ Overall response ☐ Overall survival ☐ Disease-free survival ☐ Progression-free survival ☐ Time to treatment failure ☐ Health-related quality of life ☐ Adverse effects of treatment	☐ Yes ☐ Unclear ☐ No ⇩ ⇩ ⇩ Go to next question **Exclude**

Decision	☐ **Include** ☐ **Unclear** ☐ **Exclude** Clarification required

Appendix 3

Data extraction form

Reviewer ID: **Date:**

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

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

Inclusion Criteria

Exclusion Criteria

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

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

Method of GIST diagnosis (if specified):

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

Additional Information on Participants

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

Adverse Events Reported	Intervention 1	Comparator 1	Comparator 2	All
Additional Study Information				

Appendix 4

Quality assessment tool

TABLE 22 Quality assessment tool for non-randomised studies (comparative studies and case series)[a]

Criteria	Yes	No	Unclear	Comments
Participants: sample definition and selection				
1. Were participants a representative sample selected from a relevant patient population?				
2. Were the inclusion/exclusion criteria of participants clearly described?				
3. Were participants entering the study at a similar point in their disease progression?				
4. Was selection of patients consecutive?				
5. Was data collection undertaken prospectively?				
6. Were the groups comparable on demographic characteristics and clinical features?				
Intervention				
7. Was the intervention (and comparison) clearly defined?				
8. Was the intervention undertaken by someone experienced at performing the procedure?				
9. Were the staff, place and facilities where the patients were treated appropriate for performing the procedure? (e.g. access to back-up facilities)				
Outcome measures				
10. Were all the important outcomes considered?				
11. Were objective (valid and reliable) outcome measure/s used?				
12. Was the assessment of main outcomes blind?				
Follow-up				
13. Was follow-up long enough to detect important effects on outcomes of interest?				
14. Was information provided on non-respondents, dropouts?				
15. Were participants lost to follow-up likely to introduce bias? (e.g. high drop-out rate; differential dropout; no description of those lost)				
16. Was length of follow-up similar between comparison groups?				
Analysis				
17. Were important prognostic factors identified?				
18. Were the analyses adjusted for confounding factors?				

a Items specific to comparative studies are in italic text.

TABLE 23 Checklist for quality assessment at trial entry if study itself is randomised

Quality criteria	Yes	No	Unclear	Comments
1. Was the allocation sequence adequately generated? (RevMan5, selection bias) ■ Yes = adequate, e.g. random number table, use of computer random number generator, shuffling cards or envelopes ■ No = inadequate, e.g. use of alternation, case record numbers, birth dates, date of admission ■ Unclear = insufficient information to permit judgement of yes or no 2. Was allocation adequately concealed? (quality of random allocation concealment) ■ Yes (adequate, A) = good attempt at concealment; method should not allow disclosure of assignment (telephone randomisation, third party involvement in allocation procedure, etc.) ■ Unclear (B) = states concealment but no description given ■ No (inadequate, C) = definitely not concealed (open random numbers tables or quasi-randomised, e.g. day of week, date of birth, alternation) or an attempt at concealment but real chance of disclosure of assignment prior to formal entry (envelopes without third party involvement, random numbers table but procedures not described)				

Appendix 5

Information on the reasons for exclusion

Resectable GIST (*n* = 24)

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Appendix 6

List of included studies

Blanke B2222 study

Primary reference

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Primary reference

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Park 2009

Primary reference

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Primary reference

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Appendix 7

Protocol (4 September 2009, HTA 09/21/01)

Title of the project

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

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Plain English summary

Gastrointestinal stromal tumours (GISTs) are a rare type of cancerous tumours that most commonly arise in the stomach or small intestine. People will be diagnosed with this type of cancer only if a biopsy of their tumours tests positive for a particular protein (called 'KIT' or 'CD117'). In around half of all cases it is possible to remove the tumour surgically; however, overall at least 50% of those operated on will develop recurrent disease within 5 years. In these patients with recurrence, and other patients with inoperable disease at diagnosis, survival beyond a period of 2 years is uncommon without further treatment. The usual treatment for patients with inoperable GISTs is the drug imatinib, prescribed at a dose of 400 mg per day. Over 75% of patients will show either response or stable disease (SD) with the standard dose of imatinib, which typically provides control of the GISTs for a period of 2–3 years. Approximately 50% of

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

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

Decision problem

Gastrointestinal stromal tumours are tumours of the connective tissue of the gastrointestinal (GI) tract arising in the interstitial cells of Cajal. They are rare cancers and estimated to account for 1% of all tumours arising in the GI tract.[1] It is estimated that the vast majority (between 60% and 70%) will arise in the stomach, though they can also occur in the small bowel (25–35%), colon and rectum (5%), and, to a lesser extent, the oesophagus.[2] Estimates of the number of people affected by GIST vary, but it is thought that the annual incidence is unlikely to exceed 240.[3] However, previous estimates have suggested that it could be as high as 2000 cases per year.[3] The median age at time of first presentation is approximately 60 years.[4] Prognosis for patients with GISTs is highly dependent on the resectability of the tumour and approximately half of patients with GISTs will have resectable disease at first presentation. GISTs are resistant to the 'conventional' oncology treatments of cytotoxic chemotherapy and radiotherapy. For resectable/non-metastatic tumours, prognosis gives a 10-year survival rate of 30–50% of patients, and at least 50% will relapse within 5 years,[5] but for unresectable tumours prognosis is poor, with survival generally < 2 years without further treatment.[6]

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

Imatinib is manufactured by Novartis under the names Glivec® (in Europe) and Gleevec® (in the USA). Having originally been licensed as a treatment for chronic myeloid leukaemia, it was first

licensed for treatment of GIST in 2002 and is now the standard first-line treatment for 'locally advanced, inoperable patients and metastatic patients' with GIST.[11] The 2004 National Institute for Health and Clinical Excellence (NICE) Technology Appraisal no. 86 on the use of imatinib for the treatment of unresectable and/or metastatic GISTs recommends 400 mg per day as first-line management. At present the NICE guidance does not recommend dose escalation of imatinib for those whose disease progresses after initially responding at the 400 mg per day dose, although dose escalation has been noted to be the standard approach to disease progression where patient non-adherence or intolerance to imatinib are not factors in disease progression.[11]

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

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

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

Report methods for synthesis of evidence of clinical effectiveness

A systematic review of the evidence of the clinical effectiveness of imatinib at escalated doses of 600 or 800 mg per day will be undertaken following the general principles of the guidance of the Centre for Reviews and Dissemination (CRD) for undertaking reviews in health care[16] and reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[17]

Inclusion and exclusion criteria

Types of studies

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

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

Population

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

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

Intervention

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

Comparators

The comparators considered will be sunitinib, prescribed within its recommended dose range of 27–75 mg, and provided with BSC, and BSC only. BSC has been defined above (see *Decision problem*).

Outcomes

The following outcomes will be considered:

- overall response
- overall survival (OS)
- disease-free survival
- progression-free survival (PFS)
- time to treatment failure
- health-related quality of life (HRQoL)
- adverse effects of treatment.

Exclusion criteria

We will exclude the following types of studies:

- animal models
- preclinical and biological studies
- reviews, editorials, opinions
- case reports
- reports investigating technical aspects of the intervention.

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

Search strategy

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

A preliminary MEDLINE search strategy is provided in the appendix* and will be adapted for use in the other databases. Current research registers, including Clinical Trials, Current Controlled Trials, UK Clinical Research Network Study Portfolio, WHO International Clinical Trials Registry Platform, International Federation of Pharmaceutical Manufacturers & Associations Clinical Trials and the Association of the British Pharmaceutical Industry (ABPI) database will be searched to identify ongoing and recently completed trials. Recent conference proceedings of key oncology and GI organisations will also be screened and will include the American Society for Clinical Oncology, the International Society of Gastrointestinal Oncology, and the National Cancer Research Institute.

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

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

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

Data extraction strategy

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

A data extraction form will be developed and piloted. One reviewer will extract details of study design, participants, intervention, comparator and outcomes. A second reviewer will check the data extraction. Any disagreements will be resolved by consensus or arbitration by a third party.

Quality assessment strategy

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

Randomised controlled trials will be assessed using the Cochrane Collaboration's tool for assessing risk of bias.[18] The tool addresses six specific domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and 'other issues'.

* Protocol appendices were not provided but are available from the authors on request.

Non-randomised comparative studies will be assessed using an 18-question checklist, with the same checklist minus four questions used to assess the quality of case series. The checklist for non-randomised studies and case series was adapted from several sources, including the CRD's guidance for those carrying out or commissioning reviews,[16] Verhagen *et al.*,[19] Downs and Black[20] and the Generic Appraisal Tool for Epidemiology (GATE), which 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 NICE Interventional Procedures Programme (IPP).

Methods of analysis/synthesis

For relevant outcomes from randomised studies, where appropriate, meta-analysis will be used to estimate a summary measure of effect. Dichotomous outcome data for the overall response outcome will be combined using the Mantel–Haenszel relative risk (RR) method and continuous outcomes will be combined using the inverse-variance weighted mean difference (WMD) method. For the estimates of RR and WMD 95% CIs and *p*-values will be calculated. Chi-squared tests and I^2-statistics will be used to explore statistical heterogeneity across studies. Possible reasons for heterogeneity will be explored using sensitivity analysis. Where there is no obvious reason for heterogeneity, the implications will be explored using random effects methods.

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

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

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

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

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

Report methods for synthesising evidence of cost-effectiveness

Economic evaluation

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

Objectives

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

The specific objectives are:

1. To determine, by undertaking a systematic review of the literature, the clinical effectiveness and cost-effectiveness of using imatinib at an escalated dose of 600 or 800 mg per day to treat patients with GISTs (whose disease has progressed with imatinib at a dose of 400 mg per day), compared with treating them with sunitinib and BSC.
2. To develop an economic model to compare the cost-effectiveness and cost–utility of use of imatinib at a dose of 600 or 800 mg per day, or use of sunitinib, or BSC only, for treating people with KIT (CD117)-positive unresectable and/or metastatic gastrointestinal tumours (GISTs) whose disease has progressed on treatment with imatinib at a dose of 400 mg per day.

The economic assessment will be a comparison of alternative treatments for people with GISTs whose disease has progressed despite treatment with imatinib at a dose of 400 mg per day, or those whose treatment with imatinib has failed owing to resistance or intolerance. The alternative treatments that will be considered are (1) treating with escalated doses of 600 or 800 mg per day; (2) treating with sunitinib (within its recommended dosage); and (3) providing BSC to manage symptoms. It should be noted here that BSC is often not provided exclusively. For treatment with imatinib, and treatment with sunitinib, it will be assumed that BSC would be provided alongside these treatments.

The economic assessment will be based on two components: (1) a systematic review of existing economic evaluations of the above alternative treatments and (2) an economic evaluation modelling exercise. More specifically, the economic assessment will consider alternative treatment strategies used for treatment of GISTs (particularly for patients whose disease has progressed with imatinib at a dose of 400 mg per day).

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

Data sought

With respect to costs, data will be sought to gather information on costs to the health services (NHS) in treating patients with GISTs and on costs to patients, in order to estimate overall mean costs. Specific information will also be collected on (1) the cost of treating the different clinical outcomes (e.g. cost of achieving total survival for patients with GISTs whose disease has progressed on treatment with imatinib at a dose of 400 mg per day – the base case); (2) the costs of maintaining patients with GISTs at a disease progression-free state for a specific period of time under alternative treatment strategies; and (3) the cost per life-year gained under alternative treatment strategies. Data will be sought on the costs associated with each alternative. For costs to the health services this will include, for example, the mean number of visits to the oncologist, number of laboratory tests and examinations, radiology examinations, the number of inpatient-days and the costs of drugs. Costs associated with the treatment of adverse effects will be included within the costs of treatment under different strategies (most of the adverse effects noted in the literature include fatigue and fever, hypertension, GI illnesses, dermatological, haemorrhagic events, etc.), and data will be sought accordingly. Data on costs to patients in seeking care and for BSC under different strategies will also be collected.

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

More specifically, we will seek to identify any data on the QALY loss caused by GI cancer or GISTs, tumour progression, and adverse effects of the different treatment strategies.

Types of studies

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

Search strategy for identification of published reports

A comprehensive search will be undertaken to identify studies that assess the cost or cost-effectiveness of the alternative treatments used for GISTs. Databases to be searched will include MEDLINE, MEDLINE In-Process, EMBASE, SCI, Health Management Information Consortium, NHS EED, the HTA database, the Cost-effectiveness Analysis (CEA) Registry and the Research Papers in Economics (RePEc). There will be no language restriction and all databases will be searched from 2000 onwards.

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

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

The description of how the industry submissions will be handled is described below [see *Handling the company submission(s)*].

Quality assessment

All included studies will be assessed using the guidelines of the CRD.[16] Modelling studies will also be quality assessed against the Philips checklist.[26]

Report methods for synthesising evidence of cost-effectiveness

The titles and abstracts of all published reports, literature and industry submissions identified by the search strategy will be examined to select relevant studies. The full texts of potentially relevant reports, publications and industry submissions will be obtained and assessed in terms of their relevance to the economic evaluation or cost analysis. Data will be extracted by an economist according to the guidelines produced by the CRD for the critical appraisal of economic evaluations. Where the economic evaluation has been based on a modelling exercise, additional data extraction criteria developed by Philips *et al.* will apply.[26,27]

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

Economic modelling

Model structure

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

1. Treatment of GIST patients (whose disease has progressed on treatment with imatinib at a dose of 400 mg per day) with an escalated dose of 600 mg per day, regulating symptoms with BSC.
2. Treatment of GIST patients (whose disease has progressed on treatment with imatinib at a dose of 400 mg per day) with an escalated dose of 800 mg per day, regulating symptoms with BSC.
3. Treatment with sunitinib (within its recommended dose range), regulating symptoms with BSC.
4. Regulating symptoms with BSC only.

The model will consider the above treatment strategies as different types of intervention, and will consider the costs and consequences of patients following these different pathways of care. When building the model we will also consider whether the use of FDG-PET to predict non-response

should be built into the model. The inclusion of this imaging technology may alter estimates of cost-effectiveness because (1) it is costly and (2) it may provide an early indication of non-responders who may benefit from the early introduction of an alternative therapy.

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

The model used will be a Markov model, where the following health states will be considered (all are associated with clinical effectiveness): OS, treatment failure, time to tumour progression, and PFS. In an earlier HTA of imatinib at a dose of 400 mg per day,[2] and other studies,[28] the health states within the economic model were (1) 'imatinib treatment' with different doses or 'sunitinib treatment' that stops disease progression, or at least leads to a partial response (PR); (2) PD; and (3) death. It is likely that the health states used in our model will be similar to these analyses, although the final choice will depend upon advice and also the literature as described in the section *Economic evaluation*. Where evidence is available, subgroup analysis will be undertaken on patients with different gene mutation types that may affect their response to escalated doses of imatinib.

Data requirements

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

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

Time horizon for the model

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

Analysis methods

The results of the model will be presented in terms of a cost–consequence analysis and cost–utility analysis. The cost–consequence analysis will examine the costs and effects on natural

and clinical measures. The likely consequences that are expected to be included in the analysis would include OS and PFS. In the cost–utility analysis, results will be presented in terms of an incremental cost per QALY, incremental cost per OS (life-years gained) and incremental cost per months/year of PFS.

Where appropriate, costs and outcomes will be discounted at 3.5% for both the cost–consequence and cost–utility analyses.[27] The economic evaluation will consider the different subgroups noted earlier.

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

Handling the company submission(s)

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

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

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

Competing interests of authors

None.

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Appendix 8

Characteristics of included studies

Study ID	Participants	Intervention(s) and comparators	Outcomes summary
B2222 Blanke 2008[38,39] Time period: July 2000 to May 2006 Countries involved: 2 (Finland, USA) No. of institutions involved: 4	***n* receiving intervention(s):** 43 ***n* receiving comparator(s):** 0 **Baseline characteristics:** not stated	**Escalated dose intervention(s):** imatinib at 600 mg/day **Comparator(s):** NA	***n* (%) showing response or SD:** 11/43 (25.6%)
S0033 Blanke 2008[41,68,77] Time period: December 2000 to (CiC information has been removed) Countries involved: 2 (Canada, USA) No. of institutions involved: 148	**n receiving intervention(s):** 118 **n receiving comparator(s):** 0 **Baseline characteristics:** not stated	**Escalated dose intervention(s):** imatinib at 800 mg/day **Comparator(s):** NA	***n* (%) showing response or SD:** 36/117 (30.8%) **Median OS:** 19 months (95% CI 13 to 23 months) ***n* (%) still alive at data cut-off point:** 42/118 (35.6%) **Median PFS:** 5 months (2–10 months) ***n* (%) still progression free at data cut-off point:** 19/118 (16.1%)
Park 2009[79] Time period: June 2001 to June 2006 Countries involved: 1 (Republic of Korea) No. of institutions involved: 1	***n* receiving intervention:** 24 ***n* receiving comparator(s):** 0 **Baseline characteristics:** *Age*: Median, years (range): 52 (31–73) *Sex*: *n* (%) male: 18 (75.0%) *n* (%) female: 6 (25.0%) *ECOG performance status*: 0: 4 (16.7%) 1: 18 (75.0%) 2: 2 (8.3%) *Primary tumour site*: Stomach: 5 (20.8%) Small bowel: 15 (62.5%) Colon or rectum: 3 (12.5%) Omentum: 1 (4.2%) n *receiving previous treatment of*: Surgery: 20 (83.3%) Conventional chemotherapy: 3 (12.5%) Radiofrequency ablation: 1 (4.2%) Transarterial chemoembolization: 1 (4.2%) *Site(s) of metastases at time of dose escalation*: Liver: 20 (83.3%) Peritoneum: 15 (62.5%) Retroperitoneum: 5 (20.8%)	**Escalated dose intervention(s):** imatinib at 600 mg/day; imatinib at 800 mg/day **Comparator(s):** NA	***n* (%) showing response or SD:** at 600 mg/day – 5/12 (41.6%); at 800 mg/day – 4/12 (33.3%) **Median time to progression:** at 600 mg/day – 1.7 months (range 0.7–24.9 months).

Study ID	Participants	Intervention(s) and comparators	Outcomes summary
	n *(%) with prior response to standard-dose imatinib of*: PR: 9 (37.5%) SD: 8 (33.3%) PD: 7 (29.2%) n *(%) whose time to progression (TTP) with standard-dose imatinib was*: ≤ 6 months: 8 (33.3%) > 6 months: 16 (66.7%) n *(%) given initial escalated dose of imatinib at*: 600 mg/day: 12 (50.0%) 800 mg/day: 12 (50.0%)		
Seddon 2008[80–86] Time period: not stated to December 2007 Countries involved: 33 (not stated) No. of institutions involved: 96	***n* receiving intervention:** 0 ***n* receiving comparator(s):** 351 **Baseline characteristics:** not stated	**Escalated dose intervention(s):** NA **Comparator(s):** sunitinib at 50 mg/day in a 6-week cycle of 4 weeks on treatment/2 weeks off treatment	**Median OS:** 90 weeks (95% CI 73 to 106 weeks) ***n* (%) still alive at data cut-off point:** 193/351 (55.0%)
Zalcberg 2005[44] Time period: (CiC information has been removed) to April 2004 Countries involved: 13: (Australia, Belgium, Denmark, France, Germany, Italy, the Netherlands, New Zealand, Poland, Singapore, Spain, Switzerland, UK) No. of institutions involved: 56	***n* receiving intervention:** 133 ***n* receiving comparator(s):** 0 **Baseline characteristics:** *Age*: Median, years (range): 59 (20–85) *Sex*: *n* (%) male: 87 (65%) *n* (%) female: 46 (36%) *ECOG performance status*: 0: 63 (47%) 1: 49 (37%) 2: 12 (9%) 3: 9 (7%) n *(%) whose primary tumour site was*: GI: 109 (82%) Gastric: 34 (26%) Small bowel: 35 (26%) Duodenum: 20 (15%) Other GI: 20 (15%) Other abdominal 20 (15%) Retroperitoneal: 4 (3%) n *(%) with time since primary diagnosis of*: < 12 months: 70 (53%) 12–24 months: 29 (22%) > 24 months: 34 (26%)	**Escalated dose intervention(s):** imatinib at 800 mg/day **Comparator(s):** NA	***n* (%) showing response or SD:** 39/133 (29.3%) 'Response to cross-over … occurred significantly more often in wild-type cases (83%) compared with *KIT* exon 11 mutants (7%) ($p = 0.0012$, Fisher's exact test), and in *KIT* exon 9 mutants (57%) compared to *KIT* exon 11 mutants ($p = 0.0017$, Fisher's exact test)' **Median PFS:** 81 days ***n* (%) still progression free at data cut-off point:** 24/133 (18.8%) **Median duration of response:** 153 days (range 37–574 days) ***n* (%) of patients requiring at least one dose reduction:** 12/77 (15.6%) ***n* (%) of patients requiring at least one dose delay:** 18/77 (23.4%) ***n* (%) with adverse events:** Oedema: 99/124 (79.8%) Skin rash: 45/124 (36.3%) Fatigue: 102/124 (82.3%) Dyspnoea: 30/124 (24.2%) Infection: 20/124 (16.1%) Nausea: 82/124 (66.1%) Leucopenia: 56/121 (46.3%) Neutropenia: 49/121 (40.5%) Thrombocytopenia: 7/121 (5.8%) Anaemia: 119/121 (98.3%)

Study ID	Participants	Intervention(s) and comparators	Outcomes summary
	n *(%) with site(s) of active disease at study entry in*:		***n* (%) with adverse event reporting decreased severity after crossover:**
	Site of primary tumour: 50 (38%)		Oedema: 25/99 (25.3%)
	Liver: 96 (72%)		Skin rash: 23/45 (51.1%)
	Lung: 16 (12%)		Fatigue: 21/102 (20.6%)
	Ascites: 12 (9%)		Dyspnoea: 8/30 (26.7%)
	Pleura: 4 (3%)		Infection: 9/20 (45.0%)
	Bone: 3 (2%)		Nausea: 38/82 (46.3%)
	Skin: 3 (2%)		Leucopenia: 25/56 (44.6%)
	n *(%) receiving previous treatment of*:		Neutropenia: 30/49 (61.2%)
	Surgery: 116 (87%)		Thrombocytopenia: 4/7 (57.1%)
	Radiotherapy: 6 (5%)		Anaemia: 15/119 (12.6%)
	Chemotherapy: 51 (38%)		***n* (%) with adverse event reporting increased severity after crossover:**
			Oedema: 33/99 (33.3%)
			Skin rash: 19/45 (42.2%)
			Fatigue: 47/102 (46.1%)
			Dyspnoea: 14/30 (46.7%)
			Infection: 9/20 (45.0%)
			Nausea: 26/82 (31.7%)
			Leucopenia: 16.56 (28.6%)
			Neutropenia: 13/49 (26.5%)
			Thrombocytopenia: 2/7 (28.6%)
			Anaemia: 51/119 (42.9%)
			***n* (%) with adverse event achieving increased severity to grade 3- to grade-4 level:**
			Oedema: 7/99 (7.1%)
			Skin rash: 2/45 (4.4%)
			Fatigue: 10/102 (9.8%)
			Dyspnoea: 1/30 (3.3%)
			Infection: 1/20 (5.0%)
			Nausea: 3/82 (3.7%)
			Leucopenia: 0/56 (0.0%)
			Neutropenia: 0/49 (0.0%)
			Thrombocytopenia: 0/7 (0.0%)
			Anaemia: 17/119 (14.3%)

NA, not available.

Appendix 9

Quality assessment of the individual full-text studies

TABLE 24 Quality assessment of the non-randomised studies (comparative studies and case series)

	Study ID			
Quality criteria	Blanke 2008[39] (B2222)	Blanke 2008[41] (S0033)	Park 2009[79]	Zalcberg 2005[44]
Q1: Were participants a representative sample selected from a relevant patient population?	?	?	?	?
Q2: Were the inclusion/exclusion criteria of participants clearly described?	+	+	+	+
Q3: Were participants entering the study at a similar point in their disease progression?	+	+	+	?
Q4: Was selection of patients consecutive?	–	–	–	–
Q5: Was data collection undertaken prospectively?	+	+	+	+
Q6: Were the groups comparable on demographic characteristics and clinical features?	*N/A*	*N/A*	*N/A*	*N/A*
Q7: Was the intervention (and comparison) clearly defined?	+	+	+	+
Q8: Was the intervention undertaken by someone experienced at performing the procedure?	?	?	?	?
Q9: Were the staff, place and facilities where the patients were treated appropriate for performing the procedure? (e.g. access to back-up facilities)	?	?	?	?
Q10: Were all the important outcomes considered?	–	–	–	–
Q11: Were objective (valid and reliable) outcome measure(s) used?	+	+	+	+
Q12: Was the assessment of main outcomes blind?	–	–	–	–
Q13: Was follow-up long enough to detect important effects on outcomes of interest?	+	+	?	+
Q14: Was information provided on non-respondents, dropouts?	–	+	?	?
Q15: Were participants lost to follow-up likely to introduce bias? (e.g. high dropout rate; differential dropout; no description of those lost)	+	?	?	?
Q16: Was length of follow-up similar between comparison groups?	*N/A*	*N/A*	*N/A*	*N/A*
Q17: Were important prognostic factors identified?	?	?	+	–
Q18: Were the analyses adjusted for confounding factors?	?	?	–	–

+, yes; –, no; ?, unclear; N/A, not applicable (items specific to comparative studies).

TABLE 25 Quality assessment at trial entry if study itself is randomised

	Study ID			
Quality criteria	Blanke 2008 (B2222)[39]	Blanke 2008 (S0033)[81]	Park 2009[79]	Zalcberg 2005[44]
Was the allocation sequence adequately generated?	?	+	N/A	+
Was allocation adequately concealed?	?	?	N/A	–

+, yes; –, no; ?, unclear; N/A, not applicable (items specific to comparative studies).

Appendix 10

Search strategies for review of economic analysis studies, cost-effectiveness analysis

MEDLINE (2000 – October, week 4 2009), EMBASE (2000–9, week 44), MEDLINE In-Process (3 November 2009)

Ovid Multifile Search URL: https://shibboleth.ovid.com/

1. Gastrointestinal Stromal Tumors/use mesz
2. Gastrointestinal Stromal Tumor/use emez
3. gastrointestinal neoplasms/use mesz
4. exp digestive system tumor/use emez
5. gist.tw.
6. ((gastro$or gastric) adj3 stromal).tw.
7. (3 or 4) and (kit or cd117 or cd 117).tw.
8. (3 or 4) and (stromal or connective or mesenchymal).tw.
9. or/1-2,5-8
10. exp "costs and cost analysis"/
11. exp economic evaluation/use emez
12. economics/
13. exp economics,hospital/
14. exp economics,medical/
15. economics,pharmaceutical/
16. exp budgets/
17. exp models, economic/
18. exp decision theory/
19. ec.fs. use mesz
20. monte carlo method/
21. markov chains/
22. exp technology assessment, biomedical/
23. cost$.ti.
24. (cost$adj2 (effective$or utilit$or benefit$or minimis$))
25. economics model$.tw.
26. (economics$or pharmacoeconomic$or pharmo-economic$).ti.
27. (price$or pricing$).tw.
28. (financial or finance or finances or financed).tw.
29. (value adj2 (money or monetary)).tw.
30. markov$.tw.
31. monte carlo.tw.
32. (decision$adj2 (tree? or analy$or model$)).tw.
33. or/10-32
34. 9 and 33
35. limit 34 to yr="2000 -Current"
36. quality of life/

37. quality adjusted life year/
38. "Value of Life"/use mesz
39. health status indicators/use mesz
40. health status/use emez
41. sickness impact profile/use mesz
42. disability evaluation/use mesz
43. disability/use emez
44. activities of daily living/use mesz
45. exp daily life activity/use emez
46. cost utility analysis/use emez
47. rating scale/
48. questionnaires/
49. (quality adj1 life).tw.
50. quality adjusted life.tw.
51. disability adjusted life.tw.
52. (qaly? or qald? or qale? or qtime? or daly?).tw.
53. (euroqol or euro qol or eq5d or eq 5d).tw.
54. (hql or hqol or h qol or hrqol or hr qol).tw.
55. (hye or hyes).tw.
56. health$year$equivalent$.tw.
57. (hui or hui1 or hui2 or hui3).tw.
58. (health adj3 (utilit$or disutili$)).tw.
59. (health adj3 (state or status)).tw.
60. (sf36 or sf 36 or short form 36 or shortform 36).tw.
61. (sf6 or sf 6 or short form 6 or shortform 6).tw.
62. (sf12 or sf 12 or short form 12 or shortform 12).tw.
63. (sf16 or sf 16 or short form 16 or shortform 16).tw.
64. (sf20 or sf 20 or short form 20 or shortform 20).tw.
65. willingness to pay.tw.
66. standard gamble.tw.
67. trade off.tw.
68. conjoint analys?s.tw.
69. discrete choice.tw.
70. or/36-69
71. 9 and 70
72. limit 71 to yr="2000 -Current"
73. 35 or 72

Science Citation Index (2000, 3 November 2009)

Web of Knowledge URL: http://wok.mimas.ac.uk/

1 TS=gist
2 TS=((gastric or gastro*) SAME stromal)
3 TS=((gastric or gastro*) SAME (kit or cd117 or cd 117))
4 TS=((gastric or gastro*) SAME mesenchymal)
5 #1 or #2 or #3 or #4
6 #5 and TS=economic*
7 #5 and TS=cost*
8 #5 and TS=(price* or pricing)
9 #5 and TS=(financial or finance*)
10 #5 and TS=(decision* SAME (tree* OR analy* or model*))

11 #5 and TS=markov*
12 #5 and TS=monte carlo
13 #5 and TS=conjoint analys*
14 #5 and TS=discrete choice*
15 #5 and TS=standard gamble
16 #5 and TS=trade off
17 #5 and TS=willingness to pay
18 #5 and TS=(health SAME (indicator* or status or utilit*))
19 #5 and TS=quality of life
20 #5 and TS=quality adjusted life
21 #5 and TS=disability adjusted life
22 #5 and TS=(qaly* or qald* or qale* or qtime* or daly*)
23 #5 and TS=(euroqol* or euro qol* or eq5d or eq 5d)
24 #5 and TS=(hql or hqol or h qol or hrqol or hr qol)
25 #5 and TS=(hye or hyes)
26 #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6
#27 #26 CPCI-S Timespan=2000–2009

Health Management Information Consortium (September 2009)

Ovid Multifile Search URL: http://gateway.ovid.com/athens

1. gist.tw.
2. ((gastro$or gastric$) adj3 stromal).tw.
3. gastrointestinal cancer/94
4. 3 and (kit or CD117 or cd 117).tw.
5. 3 and (stromal or connective or mesenchymal).tw.
6. or/1-2,4-5

NHS Economic Evaluation Database (October 2009), HTA Database (October 2009)

NHS Centre for Reviews and Dissemination URL: http://nhscrd.york.ac.uk/welcome.htm

1 MeSH Gastrointestinal Stromal Tumors EXPLODE 1 2 3
2 gist
3 (gastric OR gastro*) AND (kit OR cd117 OR cd AND 117)
4 (gastric OR gastro*) AND (stromal OR connective OR mesenchymal)
5 #1 or #2 or #3 or #4

IDEAS (October 2009)

RePEC URL: http://ideas.repec.org/

Gist or gastrointestinal stromal

Conference proceedings

International Society for Pharamoeconomics and Outcomes Research

9th Annual European Congress, Copenhagen, October 2006

10th Annual European Congress, Dublin, October 2007
11th Annual European Congress, Athens, November 2008
12th Annual European Congress, Paris, October 2009
11th Annual International Meeting, Philadelphia, May 2006
12th Annual International Meeting, Arlington, May 2007
13th Annual International Meeting, Toronto, May 2008
14th Annual International Meeting, Orlando, May 2009

Websites consulted (accessed October 2009)

Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland
URL: www.augis.org/

Department of Health
URL: www.dh.gov.uk/en/index.htm

GIST Support International
URL: www.gistsupport.org/

Glivec
URL: www.glivec.com/index.jsp

Medicines and Healthcare products Regulatory Agency (MHRA)
URL: www.mhra.gov.uk/

National Cancer Institute
URL: www.cancer.gov/

National Comprehensive Cancer Network
URL: www.nccn.org/index.asp

National Institute for Health and Clinical Excellence
URL: www.nice.org.uk/nice-web/Cat.asp?c=20

NHS Evidence
URL: www.library.nhs.uk/Default.aspx

NHS Knowledge Network Scotland
URL: www.knowledge.scot.nhs.uk/home.aspx

Novaritis UK
URL: www.novartis.co.uk/

Pfizer UK
URL: www.pfizer.co.uk/Pages/Home.aspx

Scottish Sarcoma Network
URL: www.ssn.scot.nhs.uk/

Appendix 11

Summary of the included economic analysis and economic evaluation studies

Study identification	Author and year	Chabot 2008[95]
	Intervention studied/ comparators	BSC vs sunitinib for imatinib-resistant or -intolerant patients
	Hypothesis/question	Examine the challenges to undertake cost-effectiveness study in oncology using crossover trial, and presented the submission to the CDR of a cost-effectiveness evaluation of sunitinib vs BSC for treatment of GIST in patients who are imatinib resistant or intolerant
Key features of the study	Type of study	Descriptive, and a full economic evaluation (cost-effectiveness analysis)
	Target population/sample population	Patients who failed or are intolerant to imatinib
	Context/settings	Canada, hypothetical population at provincial level
	Date to which the data of the study relate	2005
	Source of effectiveness data	Clinical effectiveness from Phase III clinical trials (NCT00075218)[52] Health outcome – QALY-based utility measured by EQ-5D questionnaire administered on clinical trial patients
	Modelling	Markov modelling
	Link between effectiveness and costs data	Costs in the model include costs of sunitinib acquisition, and health-care resource use for BSC, cost of routine follow-up for patients receiving sunitinib, cost of adverse events, and end-life costs. Information on health-care resource use and corresponding unit costs were derived from published literature, medical oncologist and Canadian Government Schedule
Information on the clinical evidence and effectiveness – main outcome of the study	Sample patients/study sample/ patient groups	Cohort population in the model
	Study design	Modelling for cost–utility analysis
	Effectiveness analysis	The following trial end points were used for the valuation of the outcomes (effectiveness): (a) PFS, defined as the time from randomisation to the point when the tumour progressed or death was due to GIST (b) OS (c) utility, measured by the EQ-5D (d) treatment-related adverse events

	Effectiveness measures and results/outcome measures	Sunitinib compared with BSC for the patients who failed or did not respond to imatinib and found sunitinib more effective than BSC – in terms of OS, PFS, LYG, LYS and QALY
	Primary end points/outcome and secondary end points/outcome	Mean survival sunitinib group,1.6 years; mean progression-free health state, 0.5 years; and 1.1 years with PD
		Patients in BSC group spent on average 0.2 years in the progression-free health state and 0.7 years with PD; and had mean survival of 0.9 years
		Sunitinib treatment resulted in 0.7 LYG, and 0.4 QALYs compared with BSC
	Statistical precision of these outcomes	Utilities associated with sunitinib:
		No progression during 4 weeks' sunitinib: 0.712 ± 0.2
		Next 2 weeks' utility improvement: 0.081 ± 0.02
		No progression BSC: 0.781 ± 0.2
		Progression: $0.577 + 0.3$
	Clinical recommendations and conclusion	The initial CDR recommendation based on the economic evaluation was 'not to reimburse' sunitinib in Canada. This was reversed owing to the fact that patients who are resistant to imatinib have no other treatment options. Based on review of the quality, safety and efficacy data, Health Canada concluded that sunitinib had favourable risk–benefit profile for the treatment of GIST after failure or intolerance of imatinib treatment
Economic analysis	Measures of health outcome/ benefits used in the economic analysis	QALY based on EQ-5D from UK study[55]
	Direct costs and its components	*Cost per 6-week cycle*
	Prospective or retrospective (depend on study design)	Sunitinib treatment standard dose: C$6947.99
	Whether values were imputed in for certain cases	Sunitinib treatment reduced dose for adverse event management: C$5210.99
	How hospital stay was defined, and whether any classifications were used or not	Sunitinib treatment medical follow-up: cycle 1 C$2275.13, cycle 2 726.47, cycle 3+ 1072.11
	Costing of complications or side effects	Terminal phase – end-of-life cost C$3752. Cost of serious adverse event with sunitinib $42.84
	Estimations of unit costs and source/methods	
	Indirect costs and its components	
	Cost of productivity, cost of volunteer care and support for the patient	Not considered
	Currency, year prices	C$, at 2005 prices
	Statistical analysis/cost	Mean and standard deviation of the progression and progression-free time
	Sensitivity analysis	Univariate sensitivity analysis was conducted by varying the most influential model parameters, namely utility of progression and no progression, OS (HR), PFS, PET at initiation of sunitinib treatment, the cost of palliative care and the cost of PET. The model assumed the cost of acquisition of sunitinib is certain and did not vary this in sensitivity analysis. The sensitivity analysis suggests that results of the economic evaluation were most sensitive to health-state utility value and rate of OS and PFS

Results/major findings	Benefits results from the economic evaluation	Mean QALYs: Sunitinib 0.97 BSC 0.54 ICER ($/LYS) 49,826 ICUR ($/QALYs) 79,884 These (ICER, ICUR lies between an estimated thresholds boundary of $26,433–132,166)
	Costs results used in the economic evaluation	*Mean costs in C$*
	Cost of treatment, costs to health sector (cost to NHS)	Sunitinib $46,125 BSC $11,632
	Major determinants of costs, the principle costs drivers	
	Synthesis of costs and benefits	*Cost-effectiveness of sunitinib vs BSC*
	Any attempt to consider the uncertainty surrounding estimates of effects	ICER ($/LYS) 49,826 ICUR ($/QALYs) 79,884 Sensitivity analysis – sensitivity uncertainty in the OS advantage for sunitinib? As patients were allowed to cross over
	Author conclusion/ recommendations	Sunitinib cost-effective The decision of approval for sunitinib from Health Canada was based on the recognition of sunitinib's clinical benefits for the imatinib-intolerant group. The paper suggests reliance on cost-effectiveness methodology is unsatisfactory Guidance is needed on how better to reconcile the best available clinical trial data with the cost-effectiveness requirements and the objectives of prompt access to oncology medicine

CDR, Canadian Drug Review; ICUR, incremental cost–utility ratio.

Study identification	Author and year	Contreras-Hermandez 2008[96]
	Intervention studied/ comparators	Sunitinib 50 mg/day, imatinib 800 mg/day and BSC
	Hypothesis/question	Examine the cost-effectiveness to compare the alternatives (imatinib 800 mg/day, sunitinib 50 mg/day) as second line of treatment for those who failed or became intolerant with imatinib 400 mg/day. The study examined whether it is worth it for the Mexican insurance system to reimburse for sunitinib or higher dose of imatinib
Key features of the study	Type of study	Model-based (Markov) full economic evaluation (cost-effectiveness analysis)
	Target population/sample population	Twenty-one advanced GIST patients who were treated at Hospital de Oncología IMSS, Mexico. Treatment examined over 5 years
	Context/settings	Mexico, 21 advanced GIST patients who were treated at Hospital de Oncología IMSS
	Dates to which the data of the study relate	January 2005 to 31 December 2007
	Source of effectiveness data	Clinical trial and published literature Motzer *et al.* 2006[104] – sunitinib Phase III study and study by Demetri *et al.* 2006[52] mainly from survival data and 21 advanced GIST patients who were treated at Hospital de Oncología IMSS
	Modelling	Markov model. Model utilised the effectiveness data from Motzer *et al.* 2006[104] (review of sunitinib treatment) – sunitinib Phase III study and study by Demetri *et al.* 2006[52]
	Link between effectiveness and costs data	All costs used in the model (except for the cost of sunitinib) were based on the information from IMSS pricing and reimbursement procedures. For cost of sunitinib, as it was not available in the Mexican market at the time of the analysis, the cost information was provided by Pfizer Laboratories. Costs included cost of mean number of visits to the oncologist, laboratory examinations, and radiology procedures, and cost of mean length of stay

Information on the clinical evidence and effectiveness, main outcome of the study	Sample patients/study sample/patient groups	Twenty-one advanced GIST patients who were treated at Hospital de Oncología IMSS and hypothetical cohort of 1000 patients for modelling exercise
	Study design	Observation study based on 21 patients and Markov modelling with a follow-up period of 5 years
	Effectiveness analysis	PFMs, PFS, LYG
	Effectiveness measures and results/outcome measures	
	Primary end points/outcome and secondary end points/ outcome	PFMs 5.64 and 1.4 LYG (95% CI 1.3 to 1.6) for sunitinib
		Imatinib – PFM = 5.28 and 1.31 LYG (95% CI 1.1 to 1.4)
		BSC – PFM = 2.52 and 1.08 LYG (95% CI 1.0 to 1.3)
	Statistical precision of these outcomes	
	Clinical recommendations and conclusion	Sunitinib as second line of treatment for those who failed with 400 mg
Economic analysis	Measures of health outcome/ benefits used in the economic analysis	PFMs
		LYGs
	Direct costs and its components	Direct costs estimated from treatment follow-up, health systems perspective
		Imatinib higher dose: expected costs per patient US$35,225 (SD US$1253)
		Sunitinib: expected costs per patient US$17,805 (SD US$694.83)
		BSC: expected cost per patient US$2071.86 (SD US$472.88)
		Using IMSS data, the estimated annual cost per patient for medical consultation, hospitalisation, laboratory examination and radiology procedures was $2424.32, $2657.57, $566.99 and $2392.67, respectively
	Indirect costs and its components	
	Cost of productivity, cost of volunteer care and support for the patient	Not taken into consideration
	Currency, year prices	US$, at 2006 prices
	Statistical analysis/cost (whether parametric or non-parametric bootstrap used to generate the CIs around each difference in costs and differences in total costs	Standard deviation of the mean costs, and mean life-years saved, and CI of the mean life-years saved
	Sensitivity analysis: one way or two way	Monte Carlo second order sensitivity analysis, probabilistic sensitivity analysis conducted
		Results from the sensitivity analysis were used to develop the acceptability curve
Results/major findings	Benefits results from the economic evaluation	Sunitinib resulted in mean PFMs of 5.64, and 1.4 LYG
		For imatinib, PFM = 5.28, and 1.31 LYG
		For BSC, PFM = 2.52, and 1.08 LYG
		Incrementally, sunitinib yielded 0.32 LYG when compared with BSC
		ICER: sunitinib vs BSC
		$15,734.23 per patient treated with sunitinib and $56,612.55 per year of PFS and $46,108.89 per LYG
	Costs results used in the economic evaluation	Imatinib higher dose: expected cost per patient US$35,225 (SD US$1253)
		Sunitinib: expected cost per patient US$17,805 (SD US$694.83)
		BSC: expected cost per patient – US$2071.86 (SD US$472.88)
		Using IMSS data, the estimated annual cost per patient for medical consultation, hospitalisation, laboratory examination and radiology procedures was $2424.32, $2657.57, $566.99 and $2392.67, respectively
	Author conclusion/ recommendations	Reimbursing sunitinib over high dose of imatinib would deliver cost savings to the IMSS and greater survival benefits

IMSS, Instituto Mexicano del Seguro Social.

Study identification	Author and year	Mabasa 2008[98]
	Intervention studied/ comparators	Imatinib vs no imatinib (BSC) in GISTs
	Hypothesis/question	Examine the cost-effectiveness of imatinib
Key features of the study	Type of study	Full economic evaluation (cost-effectiveness analysis)
	Target population/sample population	Patients in British Columbia, BCCA patients with advanced GIST who received imatinib or historical treatment
	Context/settings	BCCA-registered patients with advanced GIST, British Columbia, Canada
	Dates to which the data of the study relate	1996–2001 for non-imatinib cases 2002–5 imatinib cases. Follow-up periods: 60 months and 44 months, respectively
	Source of effectiveness data	Data derived from medical records of the patients
	Modelling	No modelling, patient-level data used for CEA
	Link between effectiveness and costs data	All costs used were based on the information on the BCCA patients followed and included on an intention-to-treat basis. The mean and median duration of follow-up for the imatinib group were significantly longer than for the historical group Costs of treatment include cost of drugs, cost per cycle of 1 month, cost of labour and supply (not clearly specified what it includes) and cost of counselling Costing was based on BCCA registry: ■ ICER imatinib vs no imatinib per median LYG (incremental cost per LYG) ■ ICER imatinib vs no imatinib per progression survival
Information on the clinical evidence and effectiveness – main outcome of the study	Sample patients/study sample/ patient groups	46 imatinib group 47 no imatinib (historical) group
	Study design	Retrospective follow up case–control study based on medical records
	Effectiveness analysis	Kaplan–Meier estimates of OS and imatinib and historical groups
	Effectiveness measures and results/outcome measures	
	Primary end points/outcome and secondary end points/ outcome Statistical precision of these outcomes	*Median OS (months)* Imatinib 66.7 No imatinib 7.7 *Median PFS (months)* Imatinib 45.3 No imatinib 5.6 *OS at 1 year* Imatinib 95.4% No imatinib 32.6% *PFS at 1 year* Imatinib 81.4% No imatinib 17.4%
	Clinical recommendations and conclusion	Patient receiving imatinib had significantly longer median OS and median PFS, and higher 1-year OS and 1-year PFS than the historical group

Economic analysis	Measures of health outcome/ benefits used in the economic analysis	OS, PFS and life-year gained
	Direct costs and its components	*Details provided in methods section on actual cost of drugs, labour and supply, but no results given*
	Prospective or retrospective (depend on study design)	Mean costs per patient: $79,829 imatinib; $1743 no imatinib
	Whether values were imputed in for certain cases	Costs of surgery or radiotherapy not included (though similar in both arms)
	How hospital stay was defined, and whether any classifications were used or not	
	Costing of complications or side effects	Did not include the cost of side effects, cost of health-care visits, or supportive care
	Estimations of unit costs and source/methods	Cost of drugs presumably include cost of side effects treatment
	Indirect costs and its components	
	Cost of productivity, cost of volunteer care and support for the patient	Not included
	Currency, year prices	C$, 2006 prices
	Sensitivity analysis	Conducted univariate sensitivity analysis to examine the impact of upper and lower values of the cost of the drugs, the cost of treatment, the utilities of successful treatment and PD, the time horizon, and the annual rate of discount. They used imatinib at a 600 mg/day dose to examine the impact of results variation as an alternative scenario for the sensitivity analysis
Results/major findings	Benefits results from the economic evaluation	Mean OS from imatinib 66.7 months, and historical control group 7.7 months
		Mean PFS – 45.3 months vs 5.6 months
	Costs results used in the economic evaluation	Cost of treatment, costs to health sector (cost to NHS)
		Major determinants of costs, the principle costs drivers
	Synthesis of costs and benefits	Conducted the sensitivity analysis
	Author conclusion/ recommendations	Imatinib cost-effective in treatment of GIST with an ICER of $15,882

BCCA, British Columbia Cancer Agency.

Study identification	Author and year	Paz-Ares 2008[99]
	Intervention studied/ comparators	Sunitinib (50 mg/day) with BSC and BSC alone
	Hypothesis/question	Assess cost-effectiveness of sunitinib vs BSC as second line of treatment
Key features of the study	Type of study	Full economic evaluation (cost-effectiveness analysis)
	Target population/sample population	Hypothetical cohort of Spanish population with GIST after progression with imatinib. Perspective – Spanish national health system
	Context/settings	Patients with advanced unresectable GIST, intolerant to or with diseases progressing during treatment with imatinib
	Dates to which the data of the study relate	Used Demetri *et al.* 2006 study[52]
	Source of effectiveness data	Used Demetri *et al.* 2006 study[52]
		Expert panel, three pathology experts, three health economists
	Modelling	Markov model
	Link between effectiveness and costs data	Data reported by expert panel on number of visits to oncology clinic, laboratory tests, CT scans, nurse visits, visits to palliative units and analgesic drugs. QoL obtained from EQ-5D scores of A6181004 (Demetri study population)

Information on the clinical evidence and effectiveness – main outcome of the study	Sample patients/study sample/ patient groups	Hypothetical cohort of patients with advanced unresectable GIST, intolerant to or with disease progressing during treatment with imatinib (same as Demetri study??)
	Study design	Decision model analysis, based on the trial[52]
	Effectiveness analysis	LYG, QALY
		Progression-free life-years
		Total mean cost per patient
		Cost per QALY gained
		ICER
	Effectiveness measures and results/outcome measures	
	Primary end points/outcome and secondary end points/ outcome	OS, LYG
		PFS
	Statistical precision of these outcomes	Incidence and treatment of adverse effects
	Clinical recommendations and conclusion	According to oncology thresholds for oncology patients, sunitinib is considered better
Economic analysis	Measures of health outcome/ benefits used in the economic analysis	QoL obtained from EQ-5D scores
	Direct costs and its components	*Total mean costs/patient*
		€23,259 in sunitinib group (including costs of adverse events) as against €1622 for BSC
	Indirect costs and its components	
	Cost of productivity, cost of volunteer care and support for the patient	Not included
	Currency, year prices	€, 2007 prices
	Statistical analysis/cost (whether parametric or non-parametric boot strap used to generate the CIs around each difference in costs and differences in total costs	Deterministic
	Sensitivity analysis	Univariate sensitivity analysis

Results/major findings	Benefits results from the economic evaluation	Patients benefits in LYG: 1.59 (for sunitinib + BSC) vs 0.88 (BSC)
		Progression-free life-years: 0.50 (sunitinib) vs 0.24 (BSC)
		QALY 1 vs 0.55
	Costs results used in the economic evaluation	Total mean costs/patients:
		€23,259 vs €1622
	Synthesis of cost and benefits	Treatment with sunitinib vs BSC resulted in patients' benefits of 0.26 progression-free life-years, 0.71 LYG and 0.45 QALYs gained with the cost difference of €21,637/per patient between both treatments
		ICER of sunitinib vs BSC:
		i. per LYG €30,242
		ii. per month of PFS €4090
		iii. per QALY gained €49,090
		Univariate sensitivity analysis
		The most important variables:
		OS HR
		Cost of sunitinib
		Utility value during active treatment and after progression
	Any attempt to consider the uncertainty surrounding estimates of effects	Yes, considered the uncertainty surrounding estimates of effects
		Considering ± 25% variation on the OS, the parameter most influencing the model results, the ICER/QALY gained would oscillate between €39,201 and €62,806
	Author conclusion/ recommendations	Sunitinib can be considered cost-effective vs BSC with acceptable cost per LYG and QALY gained
		Notes the limitation in using an extrapolated survival curve

Study identification	Author and year	Huse 2007[97]
	Intervention studied/ comparators	Imatinib in the treatment of advanced GIST
	Hypothesis/question	Estimated the cost-effectiveness of imatinib mesylate in treatment of unresectable GIST using trials data elsewhere and using them in US context
Key features of the study	Type of study	Cost-effectiveness modelling for decision analysis
	Target population/sample population	Advanced GIST patients
	Context/settings	USA, imatinib mesylate treatment vs no treatment of advanced hypothetical GIST population in USA
	Dates to which the data of the study relates to	Mostly trial data used: Demetri *et al.* 2002[38] trial data and Blanke trial[39,103,117] data and Phase II clinical trial data
	Source of effectiveness data	Demetri *et al.* 2002[38] trial data and Blanke trial[39,103,117] data
	Modelling	Decision modelling
	Link between effectiveness and costs data	Imatinib cost: *Pharmacy's Fundamental Reference*. Montvale, NJ: Thomson Health Care; 2005, and *Physicians' Desk Reference 2005*. Montvale, NJ: Thomson PDR; 2005
		Cost of medical management for pancreatic cancer was used in absence of data for GIST management
		Cost data for diseases specific
		For palliative care – as GIST-specific palliative care data not available, information on palliative care for pancreatic cancer was used

Information on the clinical evidence and effectiveness – main outcome of the study	Sample patients/study sample/ patient groups	Hypothetical cohort population with advanced GIST
	Study design	Decision model
	Effectiveness analysis	QALY
	Effectiveness measures and results/outcome measures	Used from UK study (Wilson *et al.*[55])
	Primary end points/outcome and secondary end points/ outcome	Utilities
		0.875 for PD (lower bound 0.75 to 1.00 upper)
	Statistical precision of these outcomes	0.935 for successful treatment (0.4 to 1.00)
	Clinical recommendations and conclusion	Imatinib is cost-effective in advanced GIST patients
Economic analysis	Measures of health outcome/ benefits used in the economic analysis	QALY, OS, cost, cost per LYG and cost per QALY gained
	Indirect costs and its components	
	Cost of productivity, cost of volunteer care and support for the patient	Not included
	Currency, year prices	US$, 2005 prices
	Sensitivity analysis	One-way sensitivity analysis
Results/major findings	Benefits results from the economic evaluation	Effectiveness QALYs – 4.15 for imatinib, 2.23 for untreated
		Difference (treated – untreated) 1.92
		The net discounted cost of achieving the survival benefit of 2.2 QALY (PV of 1.9 QALY) is US$74,369 per imatinib-treated patient
		CER – US$38,723
	Costs results used in the economic evaluation	Imatinib treatment US$416,255
		Untreated US$341,886
	Cost of treatment, costs to health sector (cost to NHS)	Weekly cost of imatinib: $US685 (685 to 1028)
		Weekly costs of care successfully treated patients: US$359 (226 to 492)
	Major determinants of costs, the principle costs drivers	Weekly cost of care for PD: US$2575 (1700 to 3450)
		Utilities of successful treatment and PD: 0.935, 0.875, respectively
		Time horizon (years): 10, 20 in sensitivity analysis
		Major cost drivers – cost of drugs
	Synthesis of cost and benefits	The cost-effectiveness ratio was most sensitive to variation in the cost estimates and time horizon for the analysis
	Any attempt to consider the uncertainty surrounding estimates of effects	CER ratios were estimated for the upper and lower bound of the parameters
	Author conclusion/ recommendations	Over 10 years' time horizon, imatinib treatment increases mean quality-adjusted survival from 2.4 to 4.6 QALYs, this gain of 2.2 QALYs (undiscounted) with PV of 1.92 QALYs. Net undiscounted cost of achieving this survival benefit is US$74,369 per imatinib-treated patient, yielding a cost-effectiveness ratio of US$38,723 per QALY

PV, present value.

Study identification	Author and year	Teich 2009[100]
	Intervention studied/ comparators	Sunitinib vs imatinib 800 mg/day, and BSC for those who failed with imatinib 400 mg/day
	Hypothesis/question	What is the cost-effectiveness of sunitinib vs imatinib in second-line treatment for GIST in Brazil
Key features of the study	Type of study	Model analysis
	Target population/sample population	Cohort population failed with imatinib 400 mg/day
	Dates to which the data of the study relate	Not specified, 2005 prices used
	Modelling	Markov model
	Link between effectiveness and costs data	Cost per LYGs, cost per progression-free life-years
		ICER
Information on the clinical evidence and effectiveness – main outcome of the study	Sample patients/study sample/ patient groups	Cohort population number 1000
	Study design	Modelling
	Effectiveness analysis	In comparison with BSC sunitinib increases life-years and progression-free life-years by 0.3 and 0.26 years, respectively
		With incremental costs of R$86,756 (US$61,968, PPP 2005)
		In comparison with imatinib, sunitinib was more effective and cost-effective with increased life-year of 0.02 and progression-free LYG of 0.47, and less costly over 6 years
Results/major findings	Author conclusion/ recommendations	Sunitinib is cost-effective when compared with imatinib 800 mg/day and BSC

Study identification	Author and year	Wilson 2005[55]
	Intervention studied/ comparators	Cost-effectiveness of imatinib in the treatment of unresectable and/or metastatic KIT-positive GIST relative to current standard practice
	Hypothesis/question	Assess the clinical effectiveness and cost-effectiveness of imatinib in the treatment of unresectable and/or metastatic KIT-positive GIST relative to current standard practice
Key features of the study	Type of study	Systematic review of clinical effectiveness and economic evaluation
	Target population/sample population	Hypothetical cohort population with unresectable GIST in UK
	Context/settings	UK NHS perspective
	Dates to which the data of the study relates to	2004?
	Source of effectiveness data	Trials
		Novartis model from clinical trial
	Modelling	Markov modelling
		Reporting results from two modelling works
		1. Novartis model
		2. Birmingham model
	Link between effectiveness and costs data	ICER, cost per QALY

Information on the clinical evidence and effectiveness – main outcome of the study	Sample patients/study sample/ patient groups	Trial patients – 147 patients with malignant unresectable and/or metastatic GISTs with median follow-up 25 months
		Modelled for 10 years
	Study design	Open-label multicentre trial compared two imatinib doses: 400 or 600 mg/day
	Effectiveness analysis	The survival rate was 88% after 1 year and 78% after 2 years
	Clinical recommendations and conclusion	The survival rate was 88% after 1 year and 78% after 2 years
Economic analysis	Measures of health outcome/ benefits used in the economic analysis	QALYs from ECOG performance of the trial patients
	Direct costs and its components	
	Prospective or retrospective (depend on study design)	Prospective as trial data
	Whether values were imputed in for certain cases	Values were not imputed as patients' data were used from trials
	How hospital stay was defined, and whether any classifications were used or not	
	Costing of complications or side effects	Costs of side effects were available from patients' data
	Estimations of unit costs and source/methods	*From Novartis model*
		Drug cost of imatinib £20,000
		Costs of outpatient visits £440 per year
		Cost of CT scan £656 for imatinib patients and £82 for patients with PD
		Cost of GP visits £40 per year
		Cost of management of adverse events £159 per year (range £127.20–190.80)
		Costs discounted at 6% (sensitivity – 3% and 6%)
		QALY discounted at 1.5% (sensitivity – 1.5–3%)
		Birmingham model developed for this report
		4 weeks
		Cost of adverse event £12.23
		Cost of imatinib 400 mg £1453.54
		Cost of imatinib 600 mg £1874.49
		Costs of no treatment (BSC) £43.23
		Cost of terminal disease (death) £2730
		Discounted rate for cost 0.0046154
		Discounted rate for QALY 0.0011538
		Other costs for imatinib-treated patients £87.38
		Utility for imatinib 0.935
		Utility for progressive state 0.875
		Using incidence rate used by Novartis (15 per million population) and assuming 10–30% of all GIST patients expected to have metastatic and/or unresectable disease, the number of patients treated with metastatic and/or unresectable disease would be between 80 and 240, and the budgetary impact on the NHS is estimated at between £2.4M and £11.8M per year. The costs to the NHS per patient at £20,400 per year
	Indirect costs and its components	Not included
	Currency, year prices	£, 2004 prices

Results/major findings	Benefits results from the economic evaluation	The cost per QALY ranged from £51,515 to £98,889 after 2 years and from £27,331 to £44,236 after 5 years and from £21,404 to £33,976 after 10 years
		Results from Birmingham model
		ICER changes depending whether Weibull or exponential distribution is used
		Weibull ICER – £26,427
		Exponential ICER £21,707
	Costs results used in the economic evaluation	*From Novartis model*
		Drug cost of imatinib £20,000
	Cost of treatment, costs to health sector (cost to NHS)	Costs of outpatient visits £440 per year
		Cost of CT scan £656 for imatinib patients and £82 for patients with PD
	Major determinants of costs, the principle costs drivers	Cost of GP visits £40 per year
		Cost of management of adverse events £159 per year (range £127.20–190.80)
		Weekly cost of imatinib (pooled trial data) £420.38 (£420.38–370.38; 400 mg per day start dose)
		Other costs per imatinib-treated patients £1136 (£1786–570)
		Others costs per PD patients £562 (£1498–233)
		Utilities:
		Imatinib treated 0.935 (0.900–0.935)
		Progressive 0.875 (0.875)
		Birmingham model developed for this report
		4 weeks
		Cost of adverse event £12.23
		Cost of imatinib 400 mg £1453.54
		Cost of imatinib 600 mg £1874.49
		Costs of no treatment (BSC) £43.23
		Cost of terminal disease (death) £2730
		Discounted rate for cost 0.0046154
		Discounted rate for QALY 0.0011538
		Other costs for imatinib-treated patients £87.38
		Utility for imatinib 0.935
		Utility for progressive state 0.875
	Synthesis of cost and benefits	Yes costs, discount rate, cost for acquisition of drugs
	Any attempt to consider the uncertainty surrounding estimates of effects	
	Author conclusion/ recommendations	The Novartis model suggested that the costs per QALY gained ranged from £51,515 to £98,889 after 2 years, from £27,331 to £44,236 after 5 years and from £21,404 to £33,976 after 10 years. This range of estimates may still not reflect the uncertainty, as the estimates after 2 years are mainly based on mathematical extrapolation beyond observed data. The results from the Birmingham model confirm the findings of the Novartis model
		Because there were no directly controlled trials the results for the model cannot be very conclusive owing to the uncertainties

Study identification	Author and year	Reddy 2007[54]
	Intervention studied/ comparators	NA
	Hypothesis/question	NA
Key features of the study	Type of study	Systematic review to identify, summarise and evaluate published studies and abstracts describing the epidemiological, HRQoL and economic impact of GIST 2000–6 34 publications 29 provided data on epidemiology One provided cost data Three reported HRQoL One reported cost and HRQoL
	Target population/sample population	NA
	Context/settings	NA
Economic analysis	Measures of health outcome/ benefits used in the economic analysis	Performance stated was assessed using ECOG scale performance take from Demetri *et al.* study[52]
Results/major findings	Costs results used in the economic evaluation	The acquisition costs of imatinib were estimated at $18 per 100-mg tablet in the USA and €23 in France
	Cost of treatment, costs to health sector (cost to NHS)	Annual cost $32,850 in the USA and €41,975 in France (assuming 50% of patients each received 400 or 600 mg/day)
	Major determinants of costs, the principle costs drivers	UK study Annual drug cost £20,000 Outpatient visits including laboratory tests £440 GP visits £40 per year CT scans £656 for imatinib patients and £82 for patients with PD Management of adverse events: £159 (range £127–191) Another study (model base Wilson *et al.*[55]) Annual costs of imatinib were £18,896 and £24,368 for patients on 400 and 600 mg daily, respectively
	Synthesis of cost and benefits	Total costs with imatinib over 2 years £30,295 and for 10 years £47,521
	Any attempt to consider the uncertainty surrounding estimates of effects	BSC – £1949 at 2 years and £4047 at 10 years Cost QALY gained £85,224 after 2 years and £29,789 after 10 years Total costs were £31,160 at 2 years compared with £56,146 at 10 years with imatinib vs £1998 and £4230 at 2 and 10 years, respectively, with BSC The cost per QALY gain varied from £45,533 to £70,206 at 2 years and from £21,708 to £25,859 at 10 years

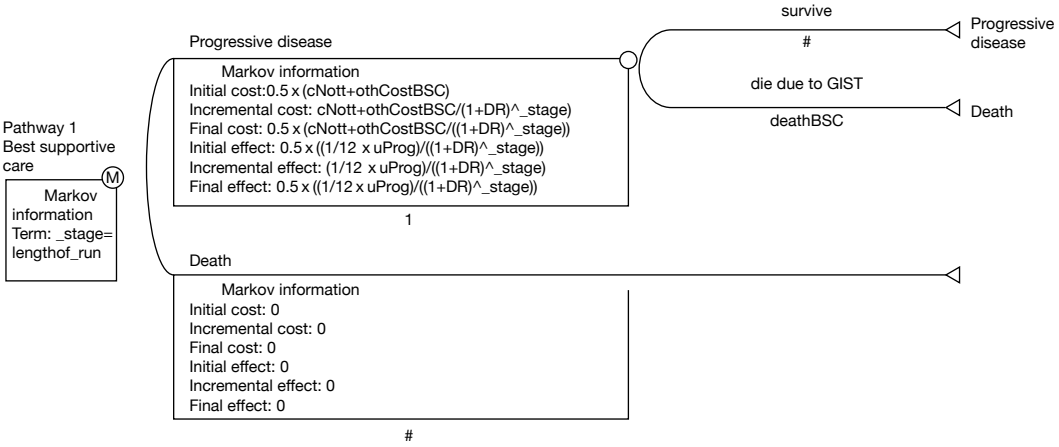
Study identification	Author and year	Hopkins 2008[101]
	Intervention studied/ comparators	Sunitinib and imatinib, and placebo (different studies reviewed)
	Hypothesis/question	Review the new developments in therapeutic cancer drugs
Key features of the study	Type of study	Review
	Target population/sample population	GIST patients, patients with diseases resistant to imatinib 800 mg/day or intolerant of imatinib
		Sample not applicable
	Context/settings	Settings of the clinical trials for sunitinib
		Three trials
		Phase III, 56 sites, Europe, America, Asia and Australia
	Dates to which the data of the study relate	2003, 2004, 2005 and 2009
	Source of effectiveness data	Reviewed from all the studies mentioned
	Modelling	Not applicable
	Link between effectiveness and costs data	Not relevant
Information on the clinical evidence and effectiveness – main outcome of the study	Sample patients/study sample/ patient groups	Maki[118] 2005 – 97
		Demetri 2006[52] – 207 and 105 (placebo)
		George[119] 2007 – 60
	Clinical recommendations and conclusion	Initial results for use of sunitinib are promising; however, too early to draw conclusion
		Important to consider the secondary resistance in GIST
		Mutational status should be determined before treatment in order to decide the initial dosage of kinase inhibitor
Economic analysis	Measures of health outcome/ benefits used in the economic analysis	Referred to SMC study[120]
	Direct costs and its components	
	Prospective or retrospective (depend on study design)	Not relevant – did not use or refer to studies with costing of the intervention
		Refer to SMC study[120]
	Whether values were imputed in for certain cases	Drug costs for one 6-week cycle of sunitinib 50 mg – £3304 for the 4–2 regimen – 4-cycle costing over £1300
	How hospital stay was defined, and whether any classifications were used or not	
	Costing of complications or side effects	
	Estimations of unit costs and source/methods	
	Indirect costs and its components	
	Cost of productivity, cost of volunteer care and support for the patient	Not considered
	Currency, year prices	Drug costs at 2006 prices
	Statistical analysis/cost	
	Sensitivity analysis	

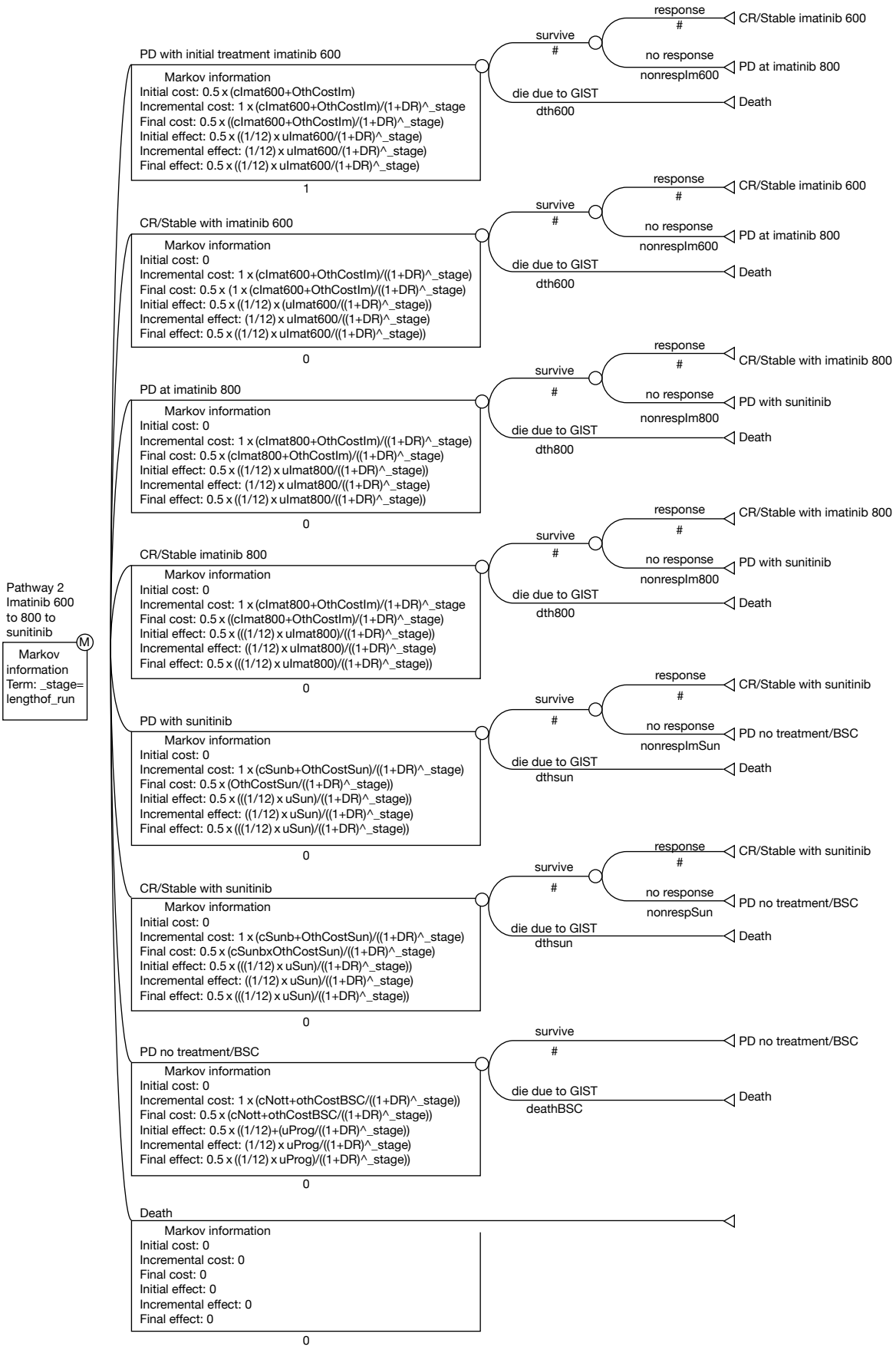
Results/major findings	Benefits results from the economic evaluation	
	Costs results used in the economic evaluation	Drugs costs – UK NHS
	Cost of treatment, costs to health sector (cost to NHS)	The total costs were not reported for the study reviewed. The costs are not from study reviewed
	Major determinants of costs, the principle costs drivers	
	Synthesis of cost and benefits:	There was not a complete economic evaluation either referred or modelled in this study
		So synthesising not relevant
	Any attempt to consider the uncertainty surrounding estimates of effects	No
	Author conclusion/ recommendations	No recommendation from economic evaluation

SMC, Scottish Medicines Consortium.

Appendix 12

Model structure




Pathway 2
Imatinib 600
to 800 to
sunitinib
M
Markov
information
Term: _stage=
lengthof_run
PD with initial treatment imatinib 600
Markov information
Initial cost: 0.5 x (cImat600+OthCostIm)
Incremental cost: 1 x (cImat600+OthCostIm)/(1+DR)^_stage
Final cost: 0.5 x ((cImat600+OthCostIm)/(1+DR)^_stage)
Initial effect: 0.5 x ((1/12) x uImat600/(1+DR)^_stage)
Incremental effect: (1/12) x uImat600/(1+DR)^_stage)
Final effect: 0.5 x ((1/12) x uImat600/(1+DR)^_stage)
1
survive
#
response
#
CR/Stable imatinib 600
no response
nonrespIm600
PD at imatinib 800
die due to GIST
dth600
Death
CR/Stable with imatinib 600
Markov information
Initial cost: 0
Incremental cost: 1 x (cImat600+OthCostIm)/((1+DR)^_stage)
Final cost: 0.5 x (1 x (cImat600+OthCostIm)/((1+DR)^_stage)
Initial effect: 0.5 x ((1/12) x (uImat600/((1+DR)^_stage))
Incremental effect: (1/12) x uImat600/((1+DR)^_stage)
Final effect: 0.5 x ((1/12) x uImat600/((1+DR)^_stage))
0
survive
#
response
#
CR/Stable imatinib 600
no response
nonrespIm600
PD at imatinib 800
die due to GIST
dth600
Death
PD at imatinib 800
Markov information
Initial cost: 0
Incremental cost: 1 x (cImat800+OthCostIm)/((1+DR)^_stage)
Final cost: 0.5 x (cImat800+OthCostIm)/((1+DR)^_stage)
Initial effect: 0.5 x ((1/12) x uImat800/((1+DR)^_stage))
Incremental effect: (1/12) x uImat800/((1+DR)^_stage)
Final effect: 0.5 x ((1/12) x uImat800/((1+DR)^_stage))
0
survive
#
response
#
CR/Stable with imatinib 800
no response
nonrespIm800
PD with sunitinib
die due to GIST
dth800
Death
CR/Stable imatinib 800
Markov information
Initial cost: 0
Incremental cost: 1 x (cImat800+OthCostIm)/(1+DR)^_stage
Final cost: 0.5 x ((cImat800+OthCostIm)/(1+DR)^_stage)
Initial effect: 0.5 x (((1/12) x uImat800)/((1+DR)^_stage))
Incremental effect: ((1/12) x uImat800)/((1+DR)^_stage)
Final effect: 0.5 x (((1/12) x uImat800)/((1+DR)^_stage))
0
survive
#
response
#
CR/Stable with imatinib 800
no response
nonrespIm800
PD with sunitinib
die due to GIST
dth800
Death
PD with sunitinib
Markov information
Initial cost: 0
Incremental cost: 1 x (cSunb+OthCostSun)/((1+DR)^_stage)
Final cost: 0.5 x (OthCostSun/((1+DR)^_stage))
Initial effect: 0.5 x (((1/12) x uSun)/((1+DR)^_stage))
Incremental effect: ((1/12) x uSun)/((1+DR)^_stage)
Final effect: 0.5 x (((1/12) x uSun)/((1+DR)^_stage))
0
survive
#
response
#
CR/Stable with sunitinib
no response
nonrespImSun
PD no treatment/BSC
die due to GIST
dthsun
Death
CR/Stable with sunitinib
Markov information
Initial cost: 0
Incremental cost: 1 x (cSunb+OthCostSun)/((1+DR)^_stage)
Final cost: 0.5 x (cSunbxOthCostSun)/((1+DR)^_stage)
Initial effect: 0.5 x (((1/12) x uSun)/((1+DR)^_stage))
Incremental effect: ((1/12) x uSun)/((1+DR)^_stage)
Final effect: 0.5 x (((1/12) x uSun)/((1+DR)^_stage))
0
survive
#
response
#
CR/Stable with sunitinib
no response
nonrespSun
PD no treatment/BSC
die due to GIST
dthsun
Death
PD no treatment/BSC
Markov information
Initial cost: 0
Incremental cost: 1 x (cNott+othCostBSC/((1+DR)^_stage))
Final cost: 0.5 x (cNott+othCostBSC/((1+DR)^_stage))
Initial effect: 0.5 x ((1/12)+(uProg/((1+DR)^_stage))
Incremental effect: (1/12) x uProg/((1+DR)^_stage)
Final effect: 0.5 x ((1/12) x uProg)/((1+DR)^_stage))
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survive
#
PD no treatment/BSC
die due to GIST
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Death
Death
Markov information
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Final cost: 0
Initial effect: 0
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Final effect: 0
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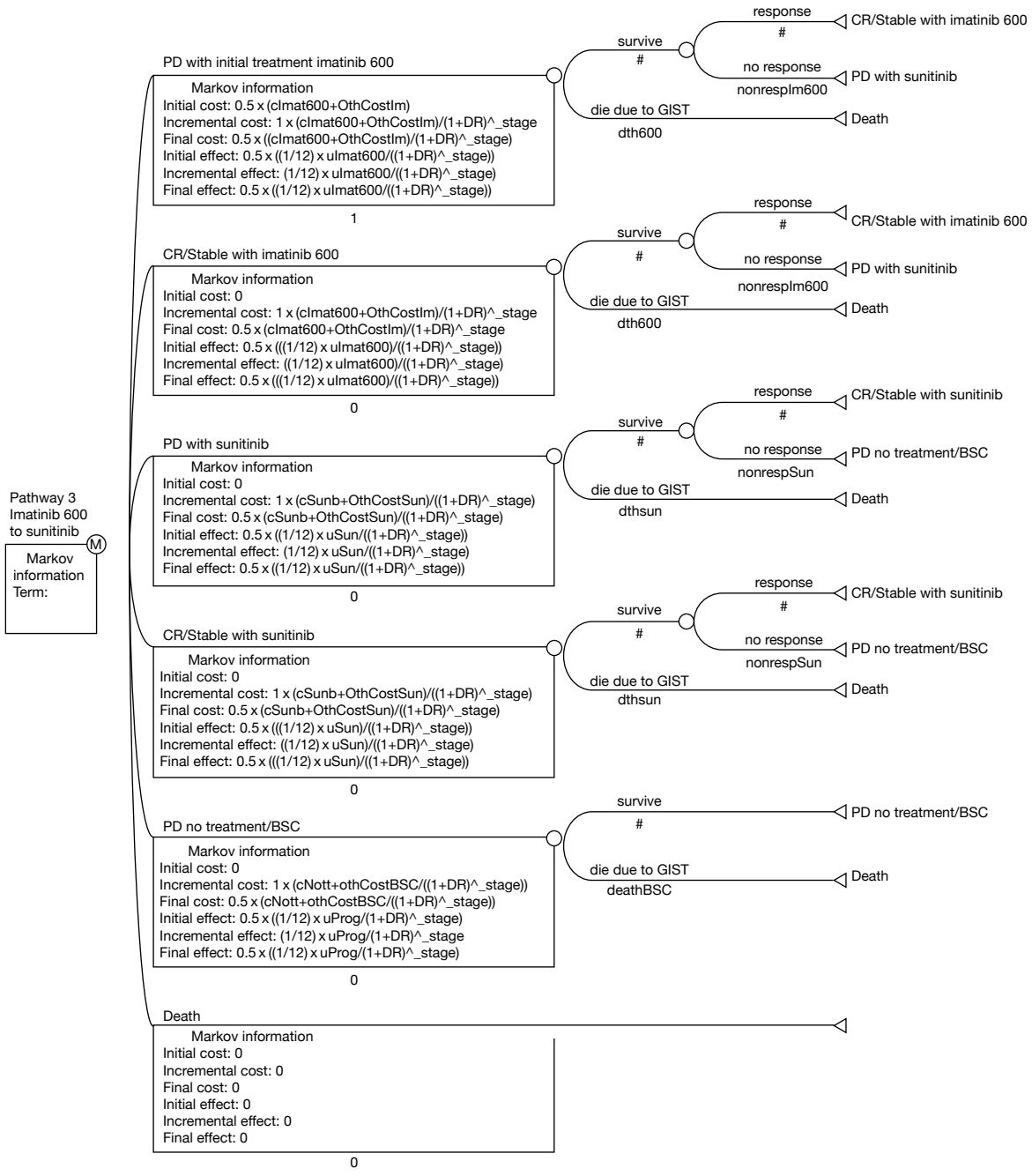

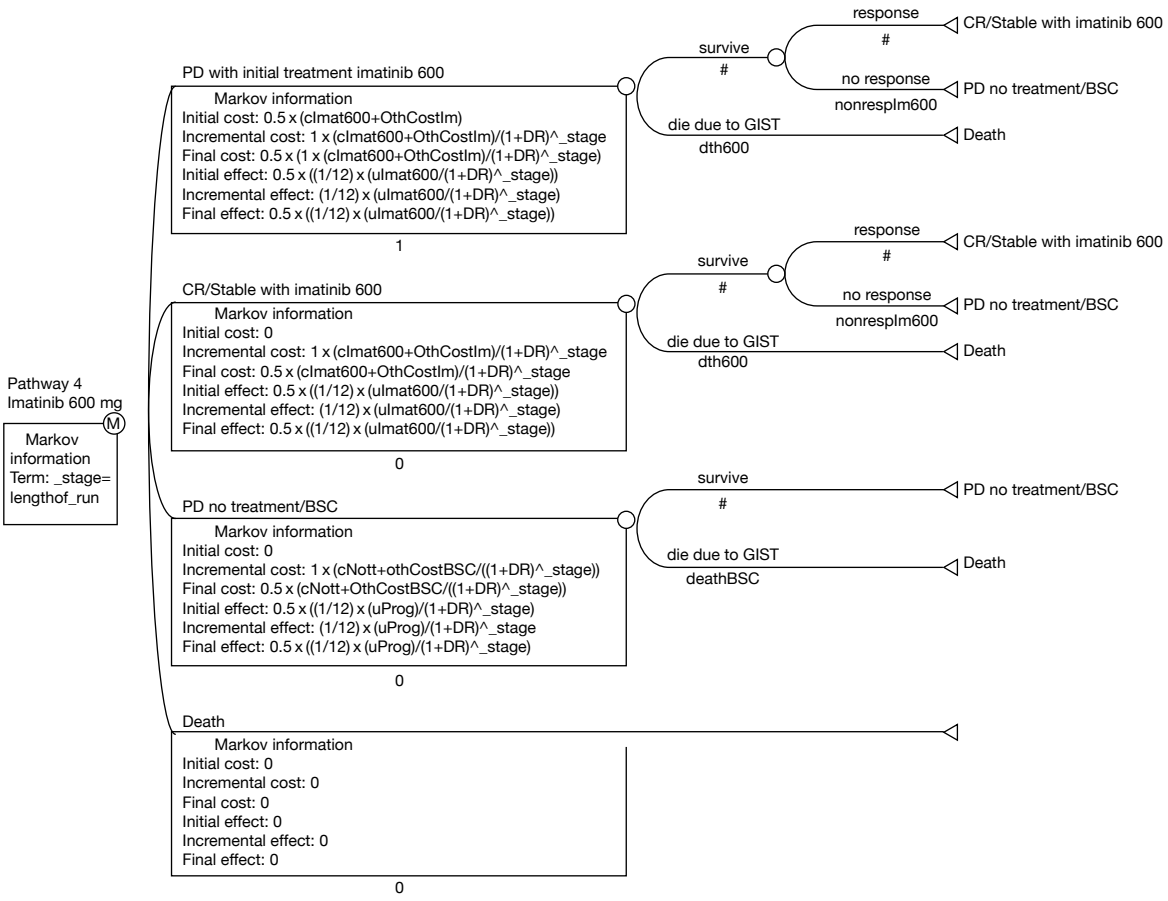
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Final cost: 0.5 x (1 x (cImat600+OthCostIm)/(1+DR)^_stage)
Initial effect: 0.5 x ((1/12) x (uImat600/(1+DR)^_stage))
Incremental effect: (1/12) x (uImat600/(1+DR)^_stage)
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1
survive
#
response
#
CR/Stable with imatinib 600
no response
nonrespIm600
PD no treatment/BSC
die due to GIST
dth600
Death
CR/Stable with imatinib 600
Markov information
Initial cost: 0
Incremental cost: 1 x (cImat600+OthCostIm)/(1+DR)^_stage
Final cost: 0.5 x (cImat600+OthCostIm)/(1+DR)^_stage
Initial effect: 0.5 x ((1/12) x (uImat600/(1+DR)^_stage))
Incremental effect: (1/12) x (uImat600/(1+DR)^_stage)
Final effect: 0.5 x ((1/12) x (uImat600/(1+DR)^_stage))
0
survive
#
response
#
CR/Stable with imatinib 600
no response
nonrespIm600
PD no treatment/BSC
die due to GIST
dth600
Death
PD no treatment/BSC
Markov information
Initial cost: 0
Incremental cost: 1 x (cNott+othCostBSC/((1+DR)^_stage))
Final cost: 0.5 x (cNott+OthCostBSC/((1+DR)^_stage))
Initial effect: 0.5 x ((1/12) x (uProg)/(1+DR)^_stage)
Incremental effect: (1/12) x (uProg)/(1+DR)^_stage
Final effect: 0.5 x ((1/12) x (uProg)/(1+DR)^_stage)
0
survive
#
PD no treatment/BSC
die due to GIST
deathBSC
Death
Death
Markov information
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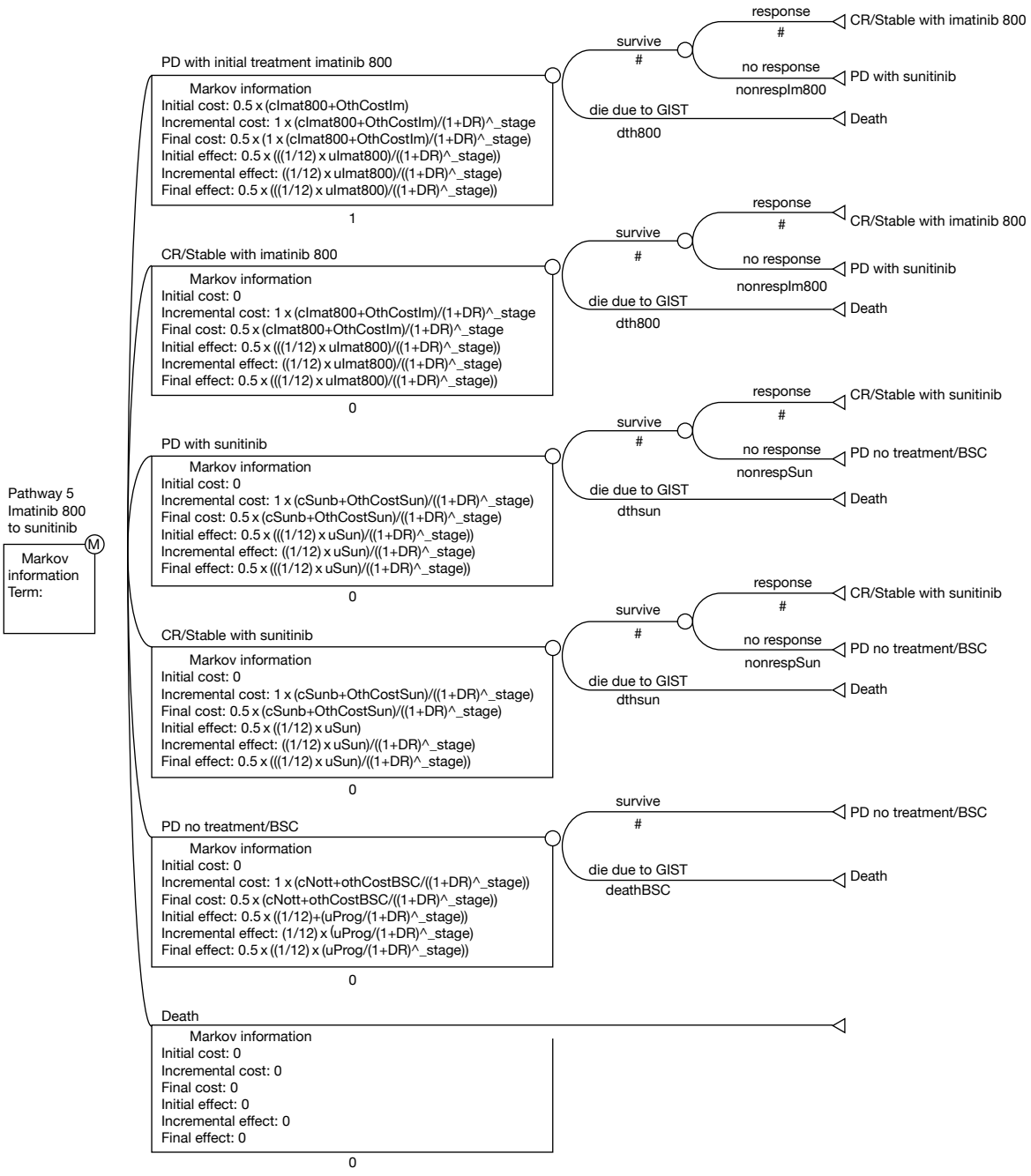

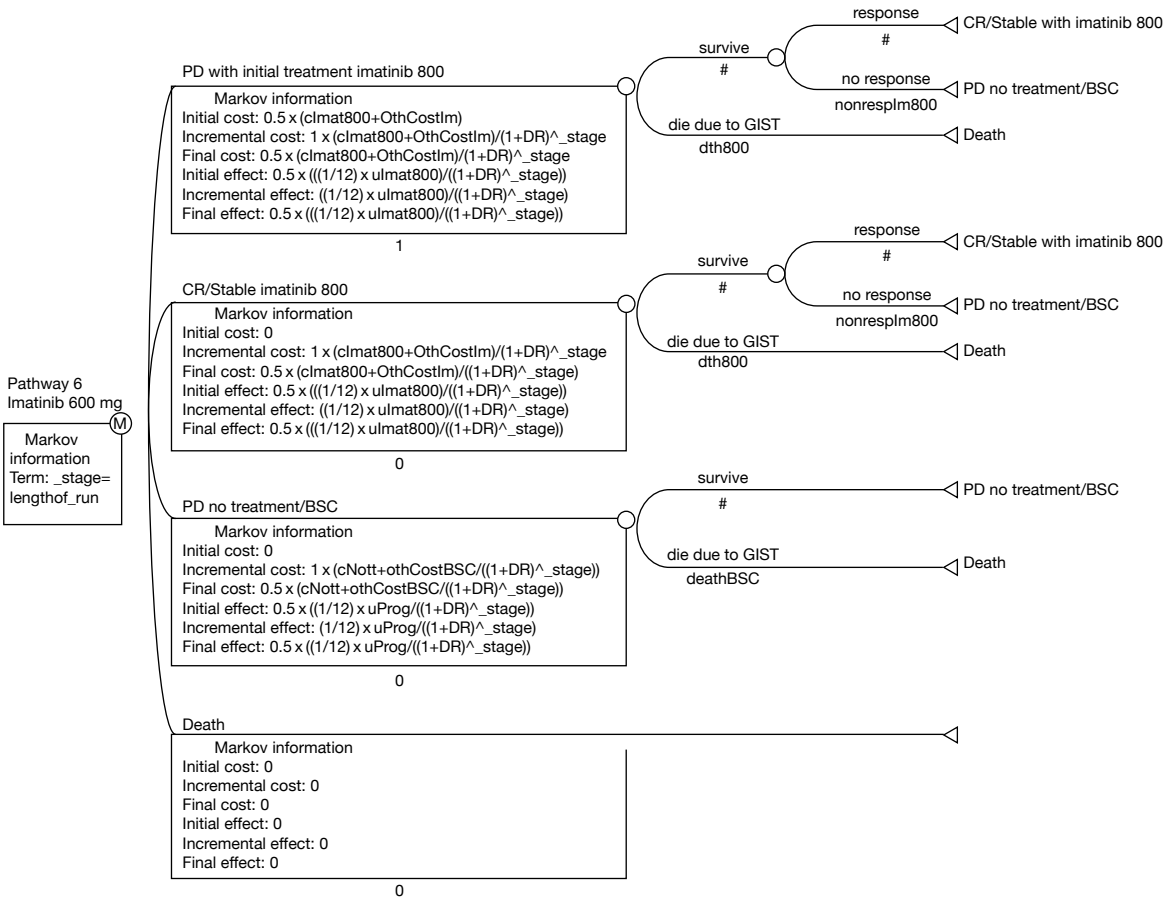
Pathway 6
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Markov information
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PD with initial treatment imatinib 800
Markov information
Initial cost: 0.5 x (cImat800+OthCostIm)
Incremental cost: 1 x (cImat800+OthCostIm)/(1+DR)^_stage
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Initial effect: 0.5 x (((1/12) x uImat800)/((1+DR)^_stage))
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nonrespIm800
PD no treatment/BSC
die due to GIST
dth800
Death
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Markov information
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PD no treatment/BSC
die due to GIST
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Death
Death
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Final effect: 0
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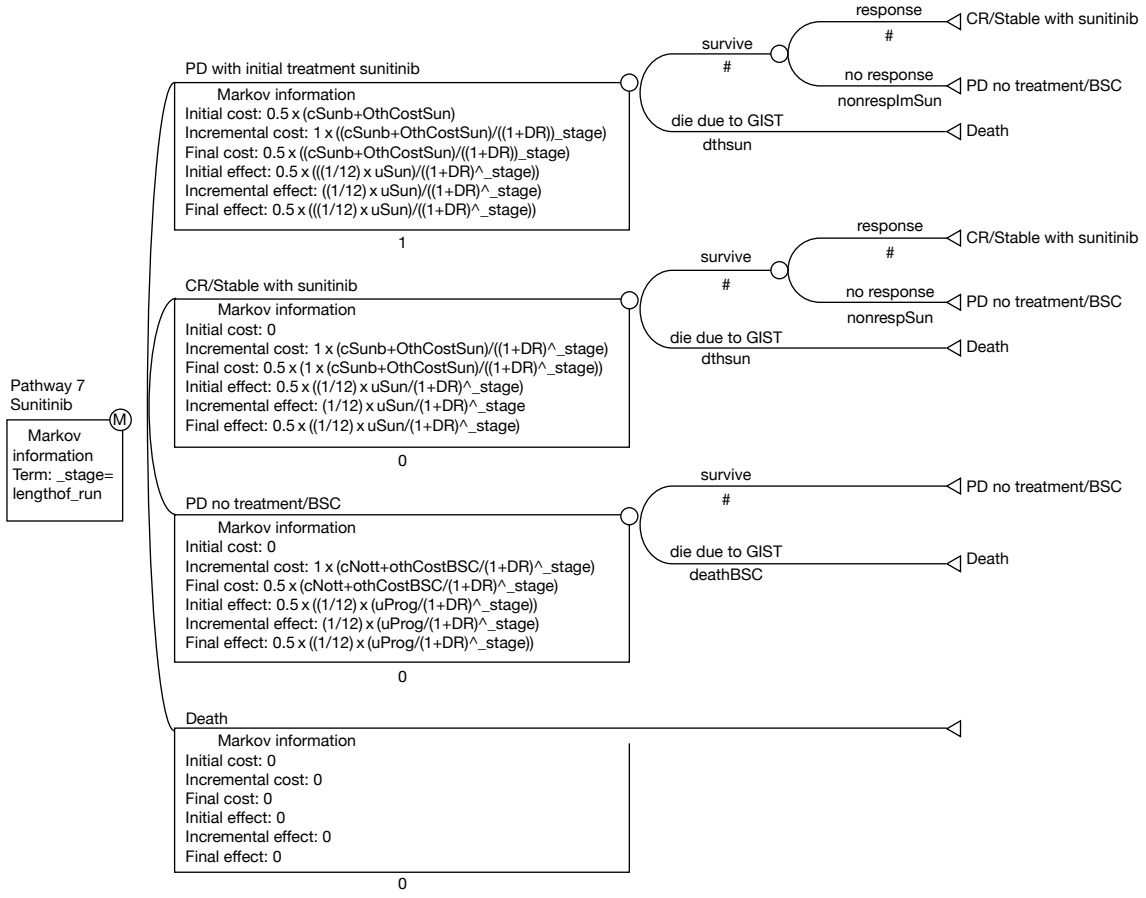
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Sunitinib
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Markov information
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Final cost: 0.5 x ((cSunb+OthCostSun)/((1+DR))_stage)
Initial effect: 0.5 x (((1/12) x uSun)/((1+DR)^_stage))
Incremental effect: ((1/12) x uSun)/((1+DR)^_stage)
Final effect: 0.5 x (((1/12) x uSun)/((1+DR)^_stage))
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nonrespImSun
PD no treatment/BSC
die due to GIST
dthsun
Death
CR/Stable with sunitinib
Markov information
Initial cost: 0
Incremental cost: 1 x (cSunb+OthCostSun)/((1+DR)^_stage)
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Incremental effect: (1/12) x uSun/(1+DR)^_stage
Final effect: 0.5 x ((1/12) x uSun/(1+DR)^_stage)
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no response
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PD no treatment/BSC
die due to GIST
dthsun
Death
PD no treatment/BSC
Markov information
Initial cost: 0
Incremental cost: 1 x (cNott+othCostBSC/(1+DR)^_stage)
Final cost: 0.5 x (cNott+othCostBSC/(1+DR)^_stage)
Initial effect: 0.5 x ((1/12) x (uProg/(1+DR)^_stage))
Incremental effect: (1/12) x (uProg/(1+DR)^_stage)
Final effect: 0.5 x ((1/12) x (uProg/(1+DR)^_stage))
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survive
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die due to GIST
deathBSC
Death
Death
Markov information
Initial cost: 0
Incremental cost: 0
Final cost: 0
Initial effect: 0
Incremental effect: 0
Final effect: 0
0

Appendix 13

Alternative best supportive care survival estimates

Source	Year	Definition of population for which survival outcome is given	No. in sample	Follow-up time	Median OS	Percentage surviving
Conlon[18]	1995	Those not having a complete resection	38	5 years		0
Dematteo[19]	2000	Metastatic (including 28/94 who had complete resection)	94	14 months	19 months	
de Mestier[121]/ Dematteo[19]	2005/2000	Those not having a complete resection	86	14 months	12 months	< 30 at 1 year
Demetri[52]	2006	Receiving placebo after median prior imatinib dose of 800 mg	105	7.2 months		62.5
Nilsson[26]	2005	Those with overtly malignant GISTs	29		1.4 years	5/29
Von Mehren[122]	2006	Those who had metastic GIST or recurrence after primary resection			6–18 months	
Plaat[123]	2000	Those with malignant GIST (18/26 had metastatic disease)	26		28 months	
				2 years		58.5
				5 years		13.0
Pidhorecky[124]	2000	Those undergoing palliative surgical procedure/biopsy	11	5 years	15 months	10
		Those with unresectable metastatic GIST			40 months	
Comandone[125]	2005	Metastatic GIST			6 months	
Pierie[107]	2001	Those with incomplete resection (41% had metastatic disease)	69	3 years		13
				5 years		9
Duffaud[126]	2003	Those with unresectable disease			10–20 months	
Cohen[127]	2002	Those with metastatic or recurrent disease			12–19 months	
Totman[128]/Van Oosterom[40]	2001	Those with unresectable or metastatic sarcoma (including GIST)			53 weeks	
Katz[129]	2008	Those who could not undergo complete resection			9–12 months	
Trent[130]	2003	Those with advanced/metastatic GIST treated with temozolomide, of which none responded	17	2 years	26.4 months	62[a]
Le Cesne[131]/ Verweij[42]	2009/2004	Those presenting with incurable advanced disease		2 years	10.25 months[a]	25
McGrath[106]	1987	Those with partial resection	21	5 years	9 months	10
		Those with distant metastases	28	5 years	10 months	0
Dougherty[112]	1991	Presenting with unresectable disease	15	2.167 years	12 months	3/15
				2.75 years		2/15
				4.167 years		1/15
Artinyan[113]	2008	Those with metastatic GIST	140	3 years	12 months	24
				3 years 11 months		21

a Data estimated from Kaplan–Meier curve within paper.

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We look forward to hearing from you.

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