NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single technology appraisal (STA)

Specification for manufacturer/sponsor submission of evidence

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Instructions for manufacturers and sponsors

This is the specification for submission of evidence to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. It shows manufacturers and sponsors what information NICE requires and the format in which it should be presented. NICE acknowledges that for medical devices manufacturers particular sections might not be as relevant as they are for pharmaceuticals manufacturers. When possible the specification will refer to requirements for medical devices, but if it hasn't done so, manufacturers or sponsors of medical devices should respond to the best of their ability in the context of the question being addressed.

Use of the specification and completion of appendices 1 to 13 (sections 10.1 to 10.13) are mandatory (when applicable), and the format should be followed whenever possible. Reasons for not following this format must be clearly stated. Sections that are not considered relevant should be marked 'N/A' and a reason given for this response. The specification should be completed with reference to the NICE document 'Guide to the methods of technology appraisal' (www.nice.org.uk), particularly with regard to the 'reference case'. Users should see NICE's 'Guide to the single technology appraisal (STA) process' (www.nice.org.uk) for further details on some of the procedural topics referred to only briefly here.

If a submission is based on preliminary regulatory recommendations, the manufacturer or sponsor must advise NICE immediately of any variation between the preliminary and final approval.

A submission should be as brief and informative as possible. It is expected that the main body of the submission will not usually exceed 100 pages excluding the pages covered by the template. The submission should be sent to NICE electronically in Word or a compatible format, and not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level

of detail requested, but that is considered to be relevant to the submission. Appendices are not normally presented to the Appraisal Committee. Any additional appendices should be clearly referenced in the body of the submission and should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the clinical-effectiveness section with ‘see appendix X’. Clinical trial reports and protocols should not be submitted, but must be made available on request.

Trials should be identified by the first author or trial ID, rather than by relying on numerical referencing alone (for example, ‘Trial 123/Jones et al.[126]’ rather than ‘One trial[126]’).

For information on submitting cost-effectiveness analysis models, disclosure of information and equality and diversity, users should see ‘Related procedures for evidence submission’, section 11.

If a patient access scheme is to be included in the submission, please refer to the patient access scheme submission template available on request. Please submit both documents and ensure consistency between them.

Executive summary

Key points

GIST is the most common sarcoma in the gastrointestinal tract, occurring most frequently in the stomach and small intestine.[32] It accounts for up to 3% of all reported primary gastrointestinal tumours.[35] The incidence of GIST is estimated to be between 9 and 14.5 per million population.[36] The mainstay of treatment for localised, primary GIST is surgical resection[2,6,8,35] and around two-thirds of GIST are deemed to be resectable. [35,38]

The appropriate management of GIST requires an accurate diagnosis and an assessment of risk. The use of surgery alone is rarely curative and, after resection of GIST, as many as 1 in every 2 patients is at risk of recurrence.[3,8,35,39,40] According to current UK guidelines, all patients should be assessed to determine their risk for disease recurrence using the Miettinen 2006 criteria and patients at high risk of recurrence should be considered for adjuvant imatinib treatment, following surgical resection of the tumour.[6,34] This is estimated to be 164 patients per year in England and Wales.

Other than imatinib, there are no effective treatments available in the adjuvant setting for GIST. The clinical need motivated clinicians to set up independent, randomised, controlled trials to evaluate the efficacy and safety of imatinib in the adjuvant setting. The results from both these trials have shown that adjuvant imatinib improves recurrence-free survival; importantly, the longer treatment duration of 3 years provides overall survival benefits. Imatinib represents a step-change innovation for the adjuvant treatment of GIST patients, addressing a hitherto unmet clinical need. Compared with no treatment, the ICER for adjuvant one year imatinib was £3,509 per QALY gained. The ICER for 3 year adjuvant imatinib compared with no treatment was £8,390. The impact on the NHS budget of using imatinib in the adjuvant setting is limited due to the small number of eligible patients and restricted duration of treatment.

Summary of treatment characteristics, economic evaluation and budget impact

The treatment to be appraised

Imatinib (Glivec®) was the first licensed treatment for gastro-intestinal stromal tumours (GIST). Prior to its introduction, prognosis was poor because traditional treatments are not effective in this tumour type. Cytotoxic agents have proved ineffective against GIST,[2,6,7,38] whilst these tumours appear resistant to radiotherapy.[6,35,41]

The first imatinib licence in the GIST setting was granted in 2002 for patients who had unresectable and/or metastatic disease. However, clinicians realised that, if imatinib were taken immediately following resection surgery (adjuvantly), it had the potential to delay or avoid recurrence. Consequently, three separate clinician-led groups initiated independent trials to investigate the use of adjuvant imatinib:

- American College of Surgeons Oncology Group (ACOSOG)
- Scandinavian Sarcoma Group and the Sarcoma Group of the Arbeitsgemeinschaft Internistische Onkologie (SSGXVIII/AIO)
- European Organisation for Research and Treatment of Cancer (EORTC)

Although started at a similar time to the trials in the metastatic setting, the adjuvant data have necessarily taken time to mature. In Europe, imatinib was approved in 2009 for one year of adjuvant treatment of adult patients who are at significant risk of relapse following resection of KIT (CD117)-positive gastrointestinal stromal tumours (GIST). Patients who have a low or very low risk of recurrence should not receive adjuvant treatment.[1] The licence was subsequently amended in 2012 to extend the imatinib treatment duration from one to three years. The recommended dose of imatinib as an adjuvant treatment is 400 mg orally, once daily.[4] Imatinib remains the only licensed treatment for use in the adjuvant GIST setting and thus represents a step-change innovation in the management of these patients.

Although imatinib is licensed for patients at *significant* risk of tumour recurrence, the EMA did not specify what this should encompass. As a result, the definition has been interpreted differently, according to the various available guidelines. Given that NICE guidance applies to England and Wales, this submission focusses on the

recommendations of the UK guidelines; that is, patients at high risk of disease recurrence, as defined by the Miettinen criteria.

Data from both the ACOSOG and SSGXVII/AIO trials were made available to Novartis for regulatory purposes.

- The initial EMA approval, covering a one-year treatment duration of adjuvant imatinib therapy for use in patients at significant risk of relapse following resection of KIT-positive GIST, was based on evidence from the ACOSOG Z9001 trial, designed in 2000. This study assessed 1 year of imatinib adjuvant therapy (400 mg/day) versus placebo and included patients from all risk categories.[8] It was stopped early when a planned interim analysis demonstrated a compelling effect for adjuvant imatinib compared with no treatment. Indeed, an analysis of data for high-risk patients defined according to Miettinen risk criteria revealed a greater difference in 1-year RFS between treatment groups (98.7% for imatinib versus 56.1% for placebo).[12]

- The inclusion of a three-year treatment duration in the licence followed the results of the SSGXVIII/AIO trial. This trial compared imatinib adjuvant therapy (400 mg/day) for 3 years post-resection versus therapy taken for 1 year post-resection in patients at high risk of recurrence.[9,10] In the Miettinen high-risk patients, OS was statistically significantly longer in the 3-year group compared with the 1-year group (HR 0.39; 95% CI 0.19 to 0.79; p = 0.007). At 5 years, OS rates were 74.2% for the 1-year group and 89.5% for the 3-year group (HR 0.39; 95% CI 0.19 to 0.79, p = 0.007).[9]

The results of these two RCTs consistently demonstrate an improvement in RFS for adjuvant imatinib therapy in patients at high risk of recurrence. Further, the SSG trial shows that longer imatinib treatment durations are associated with benefits in overall survival. These data are further supported by preliminary results from the EORTC 62024 study and the results reported for non-RCTs identified by a systematic literature review.[8-25]

Across the RCTs and non-RCTs assessing adjuvant imatinib therapy, it has been observed that long-term daily treatment with 400 mg/day is well tolerated. No notable increase in adverse events (AEs) occurred during 3 years of treatment when

compared with 1 year of treatment, suggesting that the risk–benefit profile of adjuvant therapy is good and that patient health-related quality of life is unlikely to be negatively impacted by treatment, even if of longer duration.

Economic evaluation

An economic analysis has been conducted from the perspective of the NHS in England and Wales to evaluate the cost effectiveness of one and three years of imatinib compared to no treatment for the adjuvant treatment of GIST patients at high risk of recurrence. A Markov process was used to model patients at high-risk of recurrence from GIST following tumour resection over a lifetime horizon (50 years). Discount rates of 3.5% were applied to both benefits and costs, as per the NICE reference case.

The probability of moving from one health state to another (transition probabilities) was estimated from clinical data from the pivotal phase III trials of adjuvant imatinib (ACOSOG Z9001 and SSGXVII/AIO) and supplemented with published evidence for transitions from post-recurrence health states. The baseline risk of disease progression for patients treated with surgical resection only is based on data from the placebo arm of the ACOSOG Z9001 trial. The treatment effect was estimated for two distinct periods: the period patients received adjuvant imatinib ("*on treatment*" period) and the period immediately after cessation of adjuvant imatinib ("*off-treatment*" period).

The treatment effect for patients receiving 1-year or 3-year adjuvant imatinib during the "off treatment" period (i.e. after cessation of adjuvant imatinib) compared with placebo (no treatment) was estimated from an "indirect comparison" between placebo vs. 1 year of adjuvant treatment, and 1 year of adjuvant vs. 3 years of adjuvant therapy.

Quality of life is captured by utility values, which are assigned for patients in different phases of disease – recurrence-free, recurrent GIST (first recurrence), recurrent GIST (second recurrence) and best supportive care. Utility weights used in the economic model were identified through a systematic review of the literature and based on assumption when appropriate.

To measure the resource use associated with the different disease states, the current UK guidelines were used to determine the frequency of visits and tests. Costs associated with outpatient attendance, CT scans, blood counts, liver function tests, surgery for recurrence and adverse events requiring hospitalisation were estimated from the NHS reference costs. The frequency and types of adverse events included were based on the most frequently reported grade 3/4 adverse events in the SSG trial. As imatinib is an oral therapy there are no costs associated with its administration.

The results of the cost-effectiveness analysis are shown in the following table. Compared with no treatment, the ICER for adjuvant one year imatinib was £3,509 per QALY gained. The ICER for 3 year adjuvant imatinib compared with no treatment was £8,390.

	Total Per Patient:				**Incremental:**				**ICERs (compared with no treatment)**		**ICERs (incremental analysis)**	
	Costs	**QALYs**	**LYs**		**Costs**	**QALYs**	**LYs**		**Cost/ QALY Gained**	**Cost/LY Saved**	**Cost/ QALY Gained**	**Cost /LY Saved**
No treatment	£47,292	3.83	5.08									
Adjuvant imatinib 1 yr tx	£55,136	6.07	7.71		£7,844	2.24	2.63		£3,509	£2,984	£3,509	£2,984
Adjuvant imatinib 3 yr tx	£78,068	7.50	9.46		£22,931	1.43	1.75		£8,390	£7,021	£16,006	£13,071

One-way sensitivity analyses indicated that the results for both comparisons were robust to all the changes in key parameters considered. The Cost Effectiveness Acceptability Curves (CEACs) demonstrate that the likelihood of 1 year and 3 years of imatinib treatment being cost effective at a threshold of £20,000 per QALY is 41.7% and 58.3%, respectively, and at a threshold of £30,000 per QALY is 30.0% and 69.1%, respectively. Adjuvant imatinib given for 1 year or 3 years in patients with GIST at high risk of recurrence therefore represents an efficient use of NHS resources.

Budget impact

The annual incidence of GIST is estimated to be around 14.5 per million population,[26] which equates to 826 GIST patients in England and Wales in 2014. Of these164 are high risk patients who are potentially eligible for adjuvant imatinib therapy. The additional drug costs associated with prescribing adjuvant imatinib is likely to be partly offset by the cost-savings from the reduced number of recurrences. The net budget impact is therefore estimated to be relatively low, starting at £1.9 million in 2014 and slowly increasing to £4.6 million in 2018 for three year imatinib treatment.

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR]), and a (draft) technical manual for devices should be provided (see section 10.1, appendix 1).

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Brand name: Glivec®
Approved name: Imatinib mesylate
Therapeutic class: Protein-tyrosine kinase inhibitor
Anatomical Therapeutic Chemical (ATC) code: L01XE01

1.2 What is the principal mechanism of action of the technology

Imatinib is a signal-transduction inhibitor designed to selectively inhibit certain classes of tyrosine kinase, including the receptor for stem cell factor coded for by the c-KIT proto-oncogene and the platelet-derived growth factor receptors alpha and beta (PDGFRA-alpha and PDGFRA-beta).[1] Gastrointestinal stromal tumours (GIST) are distinct mesenchymal tumours[27] [originating from pacemaker cells in the intestine (interstitial cells of Cajal [ICC])],[28] 90% of which express a tyrosine kinase with an activating KIT mutation,[29] which plays a key role in the pathogenesis and growth of KIT (CD117)-positive tumours.[30] Imatinib binding to c-KIT alters cell signal transduction, inhibiting cell proliferation and inducing apoptosis.[1]

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give

the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Imatinib was approved (European Medicines Agency [EMA] authorisation on 29 April 2009) for adjuvant treatment of adult patients who are at significant risk of relapse following resection of KIT (CD117)-positive GIST. Patients who have a low or very low risk of recurrence should not receive adjuvant treatment.[1]

The imatinib Summary of Product Characteristics (SmPC) in relation to adjuvant treatment of adult patients following resection of GIST notes that optimal treatment duration is not yet established but the length of treatment in the clinical trial supporting this indication was 36 months.[1]

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the marketing authorisation).

The main issues which were discussed by the EMA related to:[31]

- the identification of subgroups for risk of recurrence;
- the provision of follow-up data;
- the details of a risk-management programme;
- the response of patients in the advanced setting following previous adjuvant treatment.

Use of imatinib was restricted to patients at significant risk of relapse, whilst those at low or very low risk were expressly excluded from the licence.

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

Imatinib is indicated for the adjuvant treatment of adult patients who are at significant risk of relapse following resection of KIT (CD117)-positive GIST. Patients who have a low or very low risk of recurrence should not receive adjuvant treatment.

The recommended dose of imatinib for adjuvant treatment for adult patients who are at significant risk of relapse following resection of KIT (CD117)-positive GIST is 400 mg once daily. The optimal treatment duration is not yet established but the length of treatment in the clinical trial supporting this indication was 36 months.

This appraisal submission considers the evidence available in support of a role for adjuvant imatinib therapy for patients at high risk of relapse (high risk as defined by the Miettinen 2006 criteria)[32] following diagnosis and resection of KIT (CD117)-positive GIST. The decision to restrict the submission to the high-risk sub-group, as defined by Miettinen, is based on the recommendations in the UK guidelines. It also reflects the need to use data from two different trials (ACOSOG and SSG) and to ensure that the populations from these were as similar as possible in terms of risk of recurrence.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

Additional evidence on imatinib as long-term adjuvant therapy for patients at high risk of relapse following resection of KIT (CD117)-positive GIST is not anticipated, either from completed or from ongoing studies as described in section 6, in the next 12 months.

There are two clinical studies listed on clinicaltrials.gov that are ongoing or recruiting and which may provide some additional data on long-term use of adjuvant imatinib in patients at significant risk of recurrence following resection of primary GIST, although it is not clear whether the results of these studies will be available in the next 12 months.

Study NCT00867113 is a phase II, non-randomised, open-label, multicentre, US study to evaluate the use of long-term (5-year) adjuvant imatinib therapy in 91 patients at significant risk of recurrence following complete resection of primary GIST. This study has an estimated completion date of May 2018.

Study NCT01172548 is a phase II, non-randomised, open-label study that will assess the safety and efficacy of 2 years of adjuvant imatinib therapy compared with historical data and has an estimated primary completion date of March 2014.[33]

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

The technology has been launched.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Imatinib has received regulatory approval for the adjuvant treatment of adult patients who are at significant risk of relapse following resection of KIT (CD117)-positive GIST in 25 countries, including approval for use in the European Union (EU) (April 2009), Australia (June 2009) and the USA (December 2008).

On 31 January 2012, the US Food and Drug Administration (FDA) granted imatinib regular approval for use in adult patients following surgical removal of KIT (CD117)-positive GIST, based on an increase in overall patient survival when treatment is taken for 3 years rather than 1 year. This regular approval was an update to the accelerated approval granted in 2008.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Previous health technology assessment (HTA) submissions in the UK

A Single Technology Assessment (STA) entitled “The clinical and cost effectiveness of imatinib as adjuvant treatment for adult patients who are at significant risk of relapse following resection of KIT-positive gastrointestinal stromal tumours” was submitted to NICE in November 2009. This original submission was based on a single randomised controlled trial (RCT) – the American College of Surgeons Oncology Group (ACOSOG) Z9001 study – that investigated adjuvant imatinib therapy given for 1 year, together with data from four ongoing clinical trials.

In their conclusions (TA196 August 2010) the appraisal committee did not recommend the use of adjuvant imatinib for GIST.

The Scottish Medicines Consortium (SMC) also reviewed imatinib as adjuvant treatment for patients at significant risk of relapse following resection of KIT (CD117)-positive GIST, following a submission made in December 2009 (584/09). Like the original NICE submission,

the SMC 584/09 submission was based on data relating to adjuvant therapy with imatinib for 1 year. The SMC decided that the economic analysis in submission 584/09 was insufficiently robust. Subsequently, in September 2010, following a resubmission that focused on patients at high risk of relapse, the SMC permitted restricted use of imatinib as adjuvant therapy of adult patients at high risk of relapse following resection of KIT (CD117)-positive GIST. The committee noted that, up to that point in time, the economic case for adjuvant therapy had been demonstrated only for 1 year of treatment.

A further resubmission was made to the SMC in 2011, which focused on a 3-year treatment duration of adjuvant therapy in patients classified as being at high risk of recurrence according to the Miettinen 2006 criteria. Based on that resubmission, the SMC have approved imatinib for restricted use within NHS Scotland for the treatment of patients at high risk of recurrence (Miettinen 2006 criteria) following complete resection of GIST. The committee noted that adjuvant imatinib therapy given for 3 years compared with 1 year, significantly improved the recurrence-free survival (RFS) in adult patients at significant risk of relapse following resection of GIST. They concluded that the clinical effectiveness and cost-effectiveness had been demonstrated for adjuvant imatinib therapy administered for a 3-year period.

A submission has also been made to the All Wales Medicines Strategy Group (AWMSG), at their request, and summarises the currently available evidence regarding both short-term (1-year) and longer-term (3-year) adjuvant imatinib therapy in patients classified as being at high risk of recurrence (Miettinen 2006 criteria) following primary resection of GIST.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table A-1 Unit costs of technology being appraised

Pharmaceutical formulation	Film-coated tablets
Acquisition cost (excluding VAT)	£1724.39 (30 x 400 mg); £862.19 (60 x 100 mg)
Method of administration	Oral
Doses	400 mg
Dosing frequency	Once daily
Average length of a course of treatment	Treatment is continuous with durations of either 1 or 3 years.
Average cost of a course of treatment	Cost per year £20,692.68 (3 years, £62,078.04)
Anticipated average interval between courses of treatments	Treatment is continuous, not course-based
Anticipated number of repeat courses of treatments	Treatment is continuous, not course-based
Dose adjustments	Not anticipated

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

There are no additional investigations associated with the use of adjuvant imatinib beyond those for current clinical practice for diagnosis (KIT/CD117 immunohistochemistry) and management of patients with GIST. Imatinib is indicated as adjuvant therapy in patients considered at significant risk of relapse after GIST resection. Stratification of GIST into risk categories is recommended by current UK guidelines,[6,7,34] and is achieved by a review of tumour size and location (from imaging), and tumour mitotic count (from standard pathological examination), in order to assess the prognosis following surgery.

The SmPC recommends that therapy with imatinib should be initiated by a physician who has experience in the treatment of malignant sarcomas,[1] and UK GIST guidelines recommend the management of patients with GIST through a multidisciplinary team with knowledge and experience of GIST.[6,7] Imatinib is administered orally and hence there are no particular resources required relating to administration.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

Complete blood counts must be performed regularly during therapy with imatinib, and liver function (transaminases, bilirubin, alkaline phosphatase) should also be monitored regularly.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

No other therapies are likely to be administered at the same time as imatinib in the adjuvant setting.

.

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Management of primary/localised GIST

GIST is the most common sarcoma in the gastrointestinal tract, occurring most frequently in the stomach and small intestine,[32] and accounts for up to 3% of all reported primary gastrointestinal tumours.[35] The incidence of GIST is estimated to be between 9 and 14.5 per million population.[36]

The appropriate management of GIST requires an accurate diagnosis and an assessment of risk, using tumour size, site and mitotic count.[6,7] A suspected diagnosis of GIST may be confirmed by immunostaining for c-KIT (CD117) using an anti-c-KIT antibody, with around 95% of GISTs being found to be positive for c-KIT.[37] According to current UK guidance, all patients with a localised GIST diagnosis should be assessed to determine their risk for disease recurrence using the Miettinen 2006 criteria.[6,34]

The mainstay of treatment for localised, primary GIST is surgical resection.[2,6,8,35] Patients are evaluated to determine whether they have resectable or unresectable disease, based on their stage of disease and fitness for surgery.[6] Around two-thirds of GIST are deemed resectable.[35,38]

Risk of recurrence: the context for adjuvant imatinib therapy

The context for adjuvant imatinib therapy is based upon the knowledge that the use of surgery alone is rarely curative and, after resection of GIST, as many as 1 in every 2 patients is at risk of relapse or recurrence.[3,8,35,39,40]

For patients undergoing resection of a GIST with high risk of recurrence, with no adjuvant treatment, up to 90% would be expected to have an adverse outcome (namely recurrence, metastasis or GIST-related death),[35] and in these patients the median time to recurrence may be less than 2 years following complete resection, with a 5-year RFS of 20%.[3,8]

Current clinical guidelines[5-7,34] recommend stratifying patients as having very low, low, moderate or high risk of recurrence based on the Miettinen 2006 criteria, and support the use of adjuvant imatinib in patients at moderate to high risk or at high risk of recurrent disease following primary resection. The UK guidelines recommend the use of adjuvant imatinib in patients at high risk of recurrence.[6]

The use of post-surgical adjuvant chemotherapy is not recommended because cytotoxic agents have proved ineffective against GIST.[2,6,7,38] The reported median survival of patients treated with cytotoxic chemotherapy is generally less than 2 years (range, 14 to 18 months).[2] There is no precedent for the use of radiation therapy in the management of GIST, not only because it is difficult to spare any adjacent, healthy tissue but because these tumours appear resistant to radiotherapy.[6,35,41]

Risk stratification

Determination of a patient's risk category is imperative, as this aids the accurate identification of patients at risk of relapse post-resection, and these patients may therefore be eligible for post-surgical adjuvant treatment with imatinib.[6,42] Risk stratification should be performed in all patients.[2,6]

The risk of GIST recurrence varies according to factors such as the site and size of the tumour and the tumour mitotic count.[3,32,43] Today, it is recommended that patient risk is determined based on the system proposed by Miettinen et al. in 2006, which was derived from assessing patient data and outcomes.[32] This system forms the basis of the risk stratification systems of the National Comprehensive Cancer Network (NCCN) and the Armed Forces Institute of Pathology (AFIP),[2] and is also recommended in current UK GIST guidelines.[6,7,34] This system of risk stratification takes into account the location of the tumour, its size and mitotic count to stratify patients into the following risk categories: very low, low, moderate or high risk. These are shown in Table A-2.[2]

Table A-2. Risk stratification of primary GIST by mitotic count, size and site

Tumour parameters		Risk of developing progressive disease or metastases during long-term follow-up (%)			
Tumour size	**Mitotic count**	**Tumour location**			
		Gastric	**Jejunal/ileal**	**Duodenal**	**Rectal**
≤ 2 cm	≤ 5/50 HPF	None (0)	None (0)	None (0)	None (0)
> 2 to ≤ 5 cm		Very low (1.9)	Low (4.3)	Low (8.3)	Low (8.5)
> 5 to ≤ 10 cm		Low (3.6)	Moderate (24)	NA[b]	NA[b]
> 10 cm		Moderate (10)	**High (52)**	**High (34)**	**High (57)[a]**
≤ 2 cm	> 5/50 HPF	None (0)[a]	**High (50)[a]**	NA[b]	**High (54)**
> 2 to ≤ 5 cm		Moderate (16)	**High (73)**	**High (50)**	**High (52)**
> 5 to ≤ 10 cm		**High (55)**	**High (85)**	**NA[b]**	**NA[b]**
> 10 cm		**High (86)**	**High (90)**	**High (86)**	**High (71)**

Demetri et al 2010[2]

HPF, high-power fields; [a]Very small case numbers; [b]Insufficient data

It should be noted that several new factors have been, or are being investigated additionally for estimating risk of recurrence, including:

- rupture of tumour, age at diagnosis and gender[44]
- traditional exon and PDGFRA mutation testing
- a prognostic scoring scheme using genes related to mitosis and chromosome management, called the Complexity Index in Sarcomas (CINSARC)[45]
- the *aurora kinase A* gene (AURKA) overexpression testing[46,47]

At present, it is not clear whether these are independent of the risk factors that are the basis of the recommended stratification scheme (ie, Miettinen 2006 criteria of tumour size, location and mitotic count). There is also no evidence of their use in informing the decision to use adjuvant therapy.

In the 2012 publication by Joensuu et al., tumour rupture (hazard ratio [HR] 1.65, 95% confidence interval [CI] 1.10 to 2.46; $p = 0.015$) and gender (HR 1.38, 95% CI 1.07 to 1.77; $p = 0.013$) were independently associated with RFS, in addition to tumour size, site and mitosis count ($p < 0.001$ for each). However, although tumour rupture (either spontaneously or at surgery) is associated with a high risk of recurrence, whether it is an independent risk factor is controversial.[44]

It is also not clear whether risk levels, as determined by any of these new schemes, overlap with each other or, indeed, the Miettinen 2006 criteria.

Mutations, such as in KIT exon 11 at codons 557 to 558, and many tumour biological factors, are associated with unfavourable outcomes. However, they are not considered established independent risk factors and are not included in the current risk-stratification schemes, Joensuu et al. note that this is "probably because a few hundred different single mutations have been identified in GIST and large enough series with adequate follow-up to address their effect on outcome are lacking".[44]

Considering the literature and available evidence, the predictive value of mutation alone in recurrent GIST has not been proven. About 68% of GIST harbour a KIT exon 11 mutation and, therefore, depending on the prevalence of the exons under investigation, a significant sample size would be required to provide enough data for other genotypes (in order to assess the possibility of a differential treatment effect). It is not clear what would be required in order to validate the CINSARC scoring scheme or AURKA overexpression testing.[45-47] Even if a risk stratification scheme was developed using the above methods for analysing mutations (other than KIT exon 11), it has not been demonstrated how this could be used to guide treatment decisions, particularly in the adjuvant setting.

In practice, mutational testing seems to have been interpreted as a means of determining the dose of adjuvant imatinib treatment, rather than the decision to treat, per se. However, there are no data within the adjuvant setting for doses above 400 mg and, since this is outside of the licence for imatinib, it will not be covered in the submission. Although not recommended by NICE, doses above 400 mg have been tested in the metastatic setting .[48] Limited data exist on the effect of dose increases from 400 mg to 600 mg or 800 mg in patients progressing at the lower dose.[1]

Given this high degree of uncertainty and the lack of robust data, this submission focuses on patients at high risk of recurrence as identified by the current standard of risk stratification, the Miettinen 2006 criteria.

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

The incidence of GIST is estimated to be between 9 and 14.5 per million population.[6,36] In England and Wales, this suggests that 820 new cases occur per year (based on mid-2012 population data and the upper range of incidence [14.5 per million population]). The incidence

of GIST is considered more pertinent to this submission than prevalence, because only newly diagnosed (and surgically resected) patients are eligible for adjuvant imatinib therapy.

Imatinib is also indicated for treatment of:[1]

- adult patients with KIT (CD117)-positive, unresectable and/or metastatic malignant GIST
- adult and paediatric patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplant is not considered as first-line treatment
- adult and paediatric patients with Ph+ CML in the chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis
- adult and paediatric patients with newly diagnosed Ph+ acute lymphoblastic leukaemia (ALL) integrated with chemotherapy
- adult patients with relapsed/refractory Ph+ ALL as monotherapy
- adult patients with myelodysplastic/myeloproliferative diseases associated with PDGFR gene rearrangements
- adult patients with advanced hypereosinophilic syndrome and/or chronic eosinophilic leukaemia with FIP1L1-PDGRFα rearrangement
- adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and recurrent and/or metastatic DFSP who are not eligible for surgery.

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

The life expectancy following surgical resection of a primary GIST without metastases depends on a patient's risk category. Historical reports suggest a 5-year disease-specific survival of 54% with a median of 66 months for patients with primary localised and resected GIST, as a whole.[2]

After complete resection, most GIST recurrences take place within the first 5 years of follow-up, which may underline the importance of longer adjuvant treatment within this period to avoid future recurrences.[44]

For patients undergoing resection and considered as being at high risk of recurrence, up to 90% have an adverse outcome – recurrence, metastasis or GIST-related death[35] – and in these patients the median time to recurrence may be less than 2 years following complete resection, with a 5-year RFS of 20%.[3,8]

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

As described above, the NICE TA196, issued in August 2010, concluded at that time that there was not enough evidence from clinical trials to assess the efficacy and cost-effectiveness of adjuvant imatinib treatment in patients at moderate to high risk of recurrence. (TA196 considered data relating to patients at moderate to high risk of recurrence and assessed adjuvant treatment given for 1 year). The appraisal committee did not recommend the use of adjuvant imatinib for GIST.

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

Current treatment recommendations

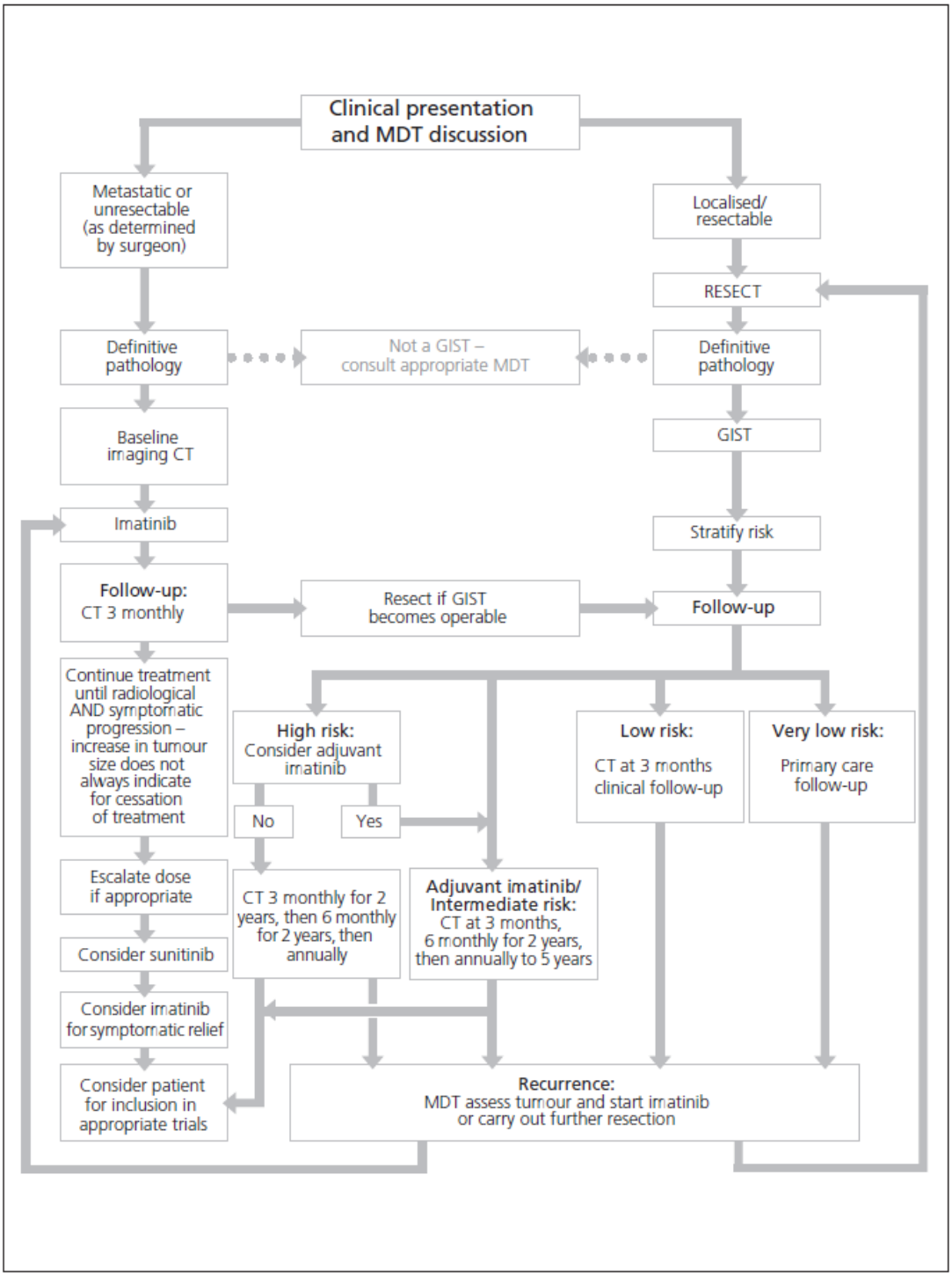
There are a number of current guidelines that focus on the management and treatment of patients with resectable GIST, including those published by the European Society for Medical Oncology (ESMO), sets of guidelines from the UK and Scotland, and guidance from the US NCCN.[2,5-7,49]

Each of these guidelines recommend stratifying patients as at very low, low, moderate or high risk of recurrence. However, the criteria for considering a patient at high risk of recurrence differ somewhat between guidelines.[2,5-7,49]

The NCCN guidelines of 2013 recommend using adjuvant imatinib for resectable GIST in patients with negative margins who are at risk of significant morbidity, as well as supporting imatinib treatment in patients with unresectable and/or metastatic GIST.[49] Adjuvant therapy with imatinib for 3 years is considered by current ESMO guidelines to be standard treatment for patients with a high risk of relapse, and imatinib is also a recommended therapy for patients with locally advanced inoperable and metastatic GIST.[5] The most recent UK guidelines, published in 2009, recommend adjuvant therapy with imatinib for patients at high risk of recurrence, after primary resection, or imatinib for the treatment of patients with unresectable and/or metastatic disease, whilst Scottish guidelines also recommend adjuvant

imatinib for patients at moderate risk or recurrence.[6,7] The most applicable guidelines to this submission are the set from the UK because they apply directly to England and Wales. The treatment algorithm for the management of GIST recommended by these UK guidelines is summarised in Figure A-1.

Figure A-1. Treatment algorithm for GIST



CT, computed tomography; MDT, Multidisciplinary team; PET-CT, position emission tomography-computed tomography

There is a discrepancy between the current standard of care, as depicted in Figure A-1, and the decision reached by TA196, which does not recommend imatinib as an adjuvant treatment for people after surgical removal of a GIST.

2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Current UK clinical guidelines support the use of adjuvant imatinib in patients with c-KIT (CD117)-positive GIST at high risk of recurrent disease.[6,7] ESMO guidelines support this practice and recommend 3 years of adjuvant therapy; the UK guidelines do not define duration.[5,6]

Another developing area is the risk classification systems for patients with GIST following surgical resection. A brief overview of risk assessment tools and their historic application, as well as the data reviewed and presented in support of adjuvant imatinib therapy following primary GIST resection, is pertinent to this submission. This is because the two RCTs which provide the best currently available evidence on adjuvant imatinib therapy differ in the criteria that were used to define patients' risk of relapse or recurrence (as will be described in section 6). The ACOSOG Z9001 study[8] was designed before there was either agreement or good evidence on how best to stratify patients according to their likely risk for disease recurrence, whilst the later SSGXVIII/AIO study defined high risk using modified US National Institutes of Health (NIH) consensus criteria.[10]

Several risk classification systems have been developed for patients with GIST following surgical resection.[42] The first widely accepted risk classification was the US NIH Consensus Criteria developed in 2002 (referred to as the Fletcher 2002 criteria), which used two risk factors, tumour size and tumour mitotic count as determined per 50 high power fields (HPF) of the microscope, to assign risk category.[50]

The Miettinen 2006 criteria (see Table A-2) categorise patients according to three independent predictors of RFS: tumour size, mitotic count and tumour location.[32] The addition of primary tumour location to the risk assessment was based on evidence from studies that demonstrated that gastric GISTs are generally associated with better outcomes than intestinal GISTs.[32,41,51] The Miettinen 2006 risk stratification system forms the basis of the NCCN and AFIP risk stratification systems.[2,37]

Current UK clinical guidelines recommend that at diagnosis, all patients with c-KIT (CD117)-positive GIST are stratified as being at very low, low, moderate or high risk of recurrence according to Miettinen 2006 criteria.[6,7]

In this submission, in addition to presenting the original findings reported from ACOSOG Z9001[8] and SSGXVIII/AIO trials,[10] unpublished data from these studies will be presented for subgroups of patients with GIST at high risk of recurrence as defined by Miettinen 2006 criteria. Not only is this in line with UK guidelines, it also allows for more consistency when considering the combined evidence base across the two studies.

As noted above in section 2.1, several other factors may contribute to the way risk of recurrence is determined and, in time, may come to supplement the currently recommended Miettinen 2006 criteria. However, given the high degree of uncertainty and the lack of robust data to support treatment decisions, this submission cannot consider these methods.

2.7 Please identify the main comparator(s) and justify their selection.

There is no currently accepted alternative to imatinib as adjuvant therapy for patients at significant risk of relapse following resection of primary GIST.

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

No specific therapies are recommended to manage adverse reactions associated with adjuvant imatinib therapy.

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Patients at high risk of relapse following resection of c-KIT (CD117)-positive GIST and treated with oral adjuvant imatinib would be managed and followed-up in the same way as intermediate risk patients who do not receive adjuvant imatinib. Therefore, there are no anticipated additional locations, staff usage, administration costs, monitoring or tests related to use of the therapy.

2.10 Does the technology require additional infrastructure to be put in place?

No additional infrastructure is required for the use of imatinib as adjuvant therapy given long-term to adults at high risk of relapse following resection of KIT (CD117)-positive GIST.

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3 Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

3.1 *Identification of equality issues*

3.1.1 Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

1.1.1 Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

There are no issues identified by Novartis that relate to equity or equalities.

3.1.2 How has the analysis addressed these issues?

Not applicable.

4 Innovation

4.1.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

Imatinib is an innovative therapy that targets a key pathological driver in GIST. Imatinib is a signal-transduction inhibitor designed to selectively inhibit certain classes of tyrosine kinase,[52] including the receptor for stem cell factor coded for by the c-KIT proto-oncogene, which is expressed in more than 90% of GIST tumours.[29,30] Imatinib binding to c-KIT protein that affects cell signalling, inhibits proliferation and induces apoptosis.

After complete resection, most of GIST recurrences take place within the first 5 years of follow-up. The use of adjuvant imatinb in patients at high risk of relapse offers RFS and OS advantages to patients who would otherwise be offered no post-surgical therapy and for whom the risk of relapse can be substantial.[5-7]

"Adjuvant imatinib is pointing to a significant improvement in survival with a high quality of life for the additional years for those patients at the highest risk of a relapse. Its value has been recognised worldwide with the ready adoption of the adjuvant approach."[53]

Current clinical guidelines that reviewed the short-term outcome data from studies of imatinib therapy recognised the RFS benefits of therapy given for 1 year and recommended that this treatment be used in high-risk patients, and that patients be considered for enrolment in clinical trials of adjuvant imatinib therapy.[5-7] The availability of longer-term follow-up data and evidence regarding the use of adjuvant imatinib treatment given for more than 1 year and up to 3 years, now support the benefits of continued treatment, and should allow imatinib to be recognised as offering a step change in the management of patients known to be at a significant and high risk of disease recurrence after surgery.

4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

The purpose of a primary resection of a C-KIT (CD117)-positive GIST is to remove the tumour, leaving no margins, with the objective of rendering the patient disease-free and able to enjoy as near to normal health-related quality of life (HRQoL) as possible.

The benefit of the adjuvant therapy is to extend the period of time the patient remains disease free, thereby also extending overall survival.

These benefits are captured in the model by the higher utility value assigned to remission and the longer survival time compared with disease progression and subsequent death. However, adjuvant imatinib therapy may also be expected to improve patients' sense of wellbeing knowing they are receiving a therapy known to target the tumour and improve their chances for longer recurrence free survival.

4.1.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

Please see Section 2.

5 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address.

This appraisal evaluates the evidence supporting adjuvant imatinib therapy given long-term (3-years) to adults at high risk of disease recurrence following diagnosis and resection of C-KIT (CD117)-positive GIST. A summary statement of the decision problem is provided in Table A-3.

Table A-3. Statement of the decision problem

	Final scope issued by NICE	**Decision problem addressed in the submission**
Intervention	**Imatinib (Glivec)**	**Imatinib (Glivec)**
Population	Adults who are at significant risk of relapse following resection of c-KIT (CD117)-positive GIST.	Adults who are at high risk of relapse following resection of c-KIT (CD117)-positive GIST.
Comparator(s)	Observation after surgery (no adjuvant therapy)	Observation after surgery (no adjuvant therapy) via indirect comparison for 3 years' duration
Outcomes	The outcome measures to be considered include: • overall survival • recurrence-free survival • adverse effects of treatment • health-related quality of life	The outcome measures to be considered include: • overall survival • recurrence-free survival • adverse effects of treatment • health-related quality of life
Economic Analysis	The reference case stipulates that the cost-effectiveness of treatment should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical effectiveness and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcome between the technologies being compared. Costs will be considered from	Cost-effectiveness will be expressed in terms of incremental cost per quality-adjusted life year. A lifetime time horizon has been chosen to capture all relevant outcomes and costs over the lifetime of patients with GIST. Recurrent disease may lead to death from GIST and patients who receive adjuvant treatment have a reduced probability of recurrence. Therefore, this potential survival benefit is accrued over the remaining patient lifetime. Costs have been considered

	an NHS and Personal Social Services perspective. Where appropriate, costs of any additional biomarker testing required for this treatment should be considered in the economic analysis.	from an NHS and Personal Social Services perspective.
Other considerations	If evidence allows, subgroup analysis by baseline risk of relapse and tumour genetic mutational status should be considered. Consideration should be given to number of treatment cycles and continuation rules for treatment if clinically appropriate. Guidance will only be issued in accordance with the marketing authorisation.	A retrospective analysis of patient baseline risk has been used, based upon the Miettinen 2006 criteria. The subgroup of patients who are at high-risk of disease recurrence is considered in this submission. For the purposes of the economic evaluation, adjuvant treatment with imatinib is assumed to be up to 3 years' duration This is taken from the maximum adjuvant treatment duration in the studies that are covered by the SmPC. The model is based on the licence for imatinib in the adjuvant setting.
Related NICE recommendations	Related Technology Appraisals: Technology Appraisal No. 196, August 2010, 'Imatinib for the adjuvant treatment of gastrointestinal stromal tumours'. Currently under review. Related Cancer Service Guidance: Cancer Service Guidance, March 2006 'Improving outcomes for people with sarcoma' Cancer Service Guidance, March 2004 'Improving supportive and palliative care for adults with cancer'	Related Technology Appraisals: Technology Appraisal No. 196, August 2010, 'Imatinib for the adjuvant treatment of gastrointestinal stromal tumours'. Currently under review. Related Cancer Service Guidance: Cancer Service Guidance, March 2006 'Improving outcomes for people with sarcoma' Cancer Service Guidance, March 2004 'Improving supportive and palliative care for adults with cancer'

Section B – Clinical and cost effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal' – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	**Reference case**	**Section in 'Guide to the methods of technology appraisal'**
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12
HRQL, health-related quality of life; NHS, National Health Service; PSS, personal social services; QALY(s), quality-adjusted life year(s)		

6 Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3 and 5.3.1 to 5.3.8.

6.1 Identification of studies

6.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.2, appendix 2.

No manufacturer-initiated clinical study programme was developed to assess adjuvant imatinib therapy in patients following resection of c-KIT (CD117)-positive GIST. Rather, the principal available RCT evidence regarding adjuvant imatinib therapy comes from independent and investigator-initiated studies. These studies were founded upon an interest in investigating adjuvant therapy given that, while two-thirds of GIST are resectable,[38] post-surgery as many as 1 in every 2 patients with GIST are at risk of disease recurrence.[8,35]

The first RCT of adjuvant imatinib therapy (the ACOSOG Z9001 trial) was initiated and undertaken by a group of surgeons and is described in detail in sections 6.3 and 6.5. This study was unblinded early after an interim efficacy analysis demonstrated the benefits of adjuvant imatinib therapy. The ACOSOG Z9001 trial provides evidence that 1 year of adjuvant imatinib (400 mg/day) following surgical resection is superior to placebo treatment in terms of 1-year RFS. It was observed in the ACOSOG Z9001 trial that, among patients with a high risk of relapse (described in that study as a greater than 50% chance of recurrence at 2 years in the absence of adjuvant therapy), the RFS benefits of adjuvant imatinib therapy seemed particularly relevant.[8] Following a request from the EMA to match patients to the currently accepted risk stratification scheme (Miettinen 2006 criteria as described in section 2 and Table A-2), Novartis was granted access to the mitotic data collected by the ACOSOG Z9001 study, which permitted a retrospective analysis of the impact of risk status on outcomes. Evidence from this study thus formed the basis of the regulatory submission made by Novartis for adjuvant imatinib therapy and supported the approval of imatinib 400 mg/day as adjuvant treatment of adult patients who are at significant risk of relapse following resection of c-KIT (CD117)-positive GIST. It should be noted that "significant" risk is not a defined category from any of the risk stratification schemes.

A further RCT initiated by the SSGXVIII/AIO investigated adjuvant imatinib therapy (400 mg/day) in patients deemed to be at high risk of relapse (according to a modified NIH consensus criteria) after primary resection of c-KIT (CD117)-positive GIST.[10] This study, like the ACOSOG Z9001 trial, was conducted independently of the manufacturer and was not part of any clinical trial programme. The primary outcome data from the SSGXVIII/AIO study have been published and Novartis has been allowed access to the dataset. Data from the SSGXVIII/AIO study appear in the current imatinib SmPC in support of the 3-year adjuvant treatment duration.

Collectively, the data from these two RCTs provide the best currently available evidence on adjuvant imatinib therapy following primary GIST resection. In design and methodologically the studies differ, as will be described in section 6.3. A key area of difference lies in the criteria used to define patients' risk of relapse or recurrence. The ACOSOG Z9001 study was designed before there was either agreement or good evidence on how best to stratify patients according to their likely risk for disease recurrence, whilst the later SSGXVIII/AIO study defined high-risk using modified US NIH Consensus Criteria.

Systematic review

In order to identify all studies reporting on the clinical effectiveness and safety of imatinib in the adjuvant setting of GIST, a systematic literature review covering the period 2009 to April 2013 was performed. The review was an update of the original NICE submission (2010); consequently, similar search terms and sources were used (see section 10).

Systematic review methodology

Databases searched were EMBASE, MEDLINE and the Cochrane Library. Although the electronic databases contain information from a number of relevant conferences, these were supplemented by an electronic review of abstracts from the American Society of Clinical Oncology (ASCO), ESMO and the European Crohn's and Colitis Organisation conferences for 2010 to June 2013.

6.2 Study selection

6.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

In order to be included in this systematic review, studies had to meet the inclusion and exclusion criteria detailed in Figure B-2. This process was fully compliant with the 2009 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines for the reporting of systematic reviews and meta-analyses.

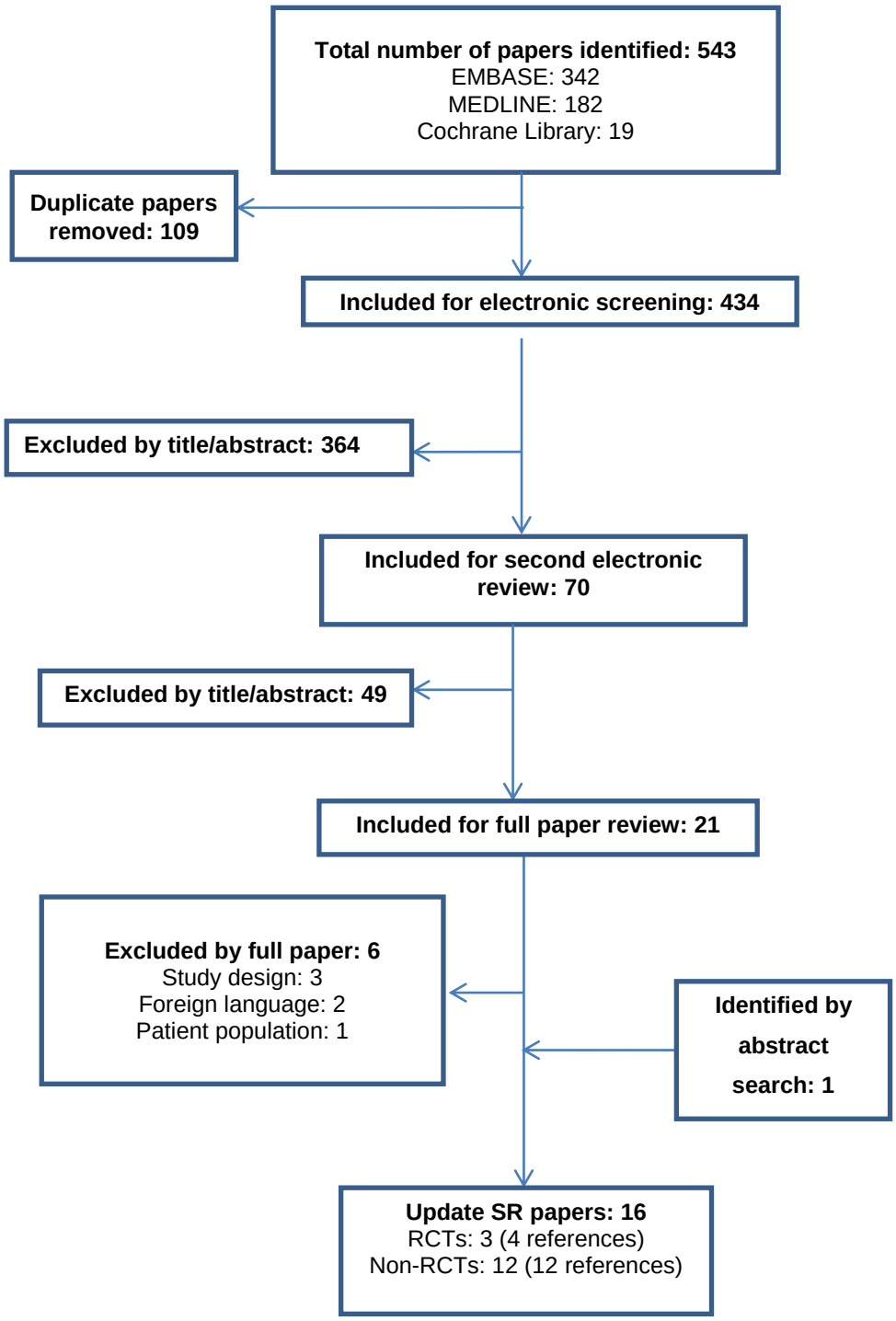
6.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 6.2.4.

The database searches were run on 08 April 2013 and the supplementary abstract search was run on 21 June 2013.

An analyst screened articles for inclusion and a second researcher performed a random quality check of 30% of all articles selected. A third researcher resolved any disputes. All publications that met the inclusion criteria, based on titles and abstracts, were obtained as full documents and reassessed against the inclusion criteria. Data from relevant articles were subsequently extracted. All data extraction was fully validated by a second reviewer.

A flow diagram of the studies included and excluded at each stage is provided in Figure B-2.

Figure B-2. PRISMA diagram of included and excluded studies in the systematic review



PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; RCT, randomised controlled trial; SR, systematic review

6.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

The 543 articles initially identified were reduced to 15 publications that were suitable for inclusion in the systematic review. One further abstract was identified through the supplementary abstract search, giving a total of 16 publications. The searches identified three potentially relevant RCTs[8,10,11,54] (Table B-4) and 12 non-RCTs. [14-25]

Complete list of relevant RCTs

6.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

Three potentially relevant RCTs were identified and are listed in Table B-4.

The ACOSOG Z9001 trial: a randomised, double-blind, placebo-controlled RCT that compared adjuvant imatinib (400 mg/day) therapy given for 1 year following surgical resection with placebo, and included patients at any level of risk of recurrence.[8,54]

The SSGXVIII/AIO study: a randomised, open-label, prospective study that compared adjuvant imatinib (400 mg/day) therapy given for 1 year following surgical resection with imatinib therapy given for 3 years post-resection, in patients with high risk of recurrence of GIST.[10] In this study patients were categorised as at high risk of recurrence based on modified US NIH Consensus Criteria.

The European Organisation for Research and Treatment of Cancer (EORTC) 62024 trial: a randomised, controlled, observational, open-label study that compared 2 years of imatinib (400 mg/day) therapy following surgical resection with observation only (no treatment), and included patients with intermediate- or high-risk GIST as defined by the NIH consensus criteria. Only preliminary results of this study are available as an abstract; these data were presented at ASCO 2013.[11]

Table B-4. List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
ACOSOG Z9001	Imatinib 400 mg/day for 1 year	Placebo for 1 year	Adult patients with complete resection of c-KIT (CD117)-positive GIST at least 3 cm in size	Dematteo RP et al.,[8] *Lancet* 2009; 373:1097–104 Secondary reference: Corless CL *et al*.,[54] 2010
SSGXVIII/AIO	Imatinib 400 mg/day for 1 year	Imatinib 400 mg/day for 3 years	Adult patients with c-KIT (CD117)-positive GIST removed at open surgery	Joensuu H et al.,[10] *JAMA* 2012;307: 1265–72
EORTC 62024	Imatinib 400 mg/day	No other therapy after surgery	Localised, surgically resected GIST of high-/intermediate-risk of recurrence	Casali PG et al.,[11] *J Clin Oncol* 2013;31 (Suppl):Abs 10500
ACOSOG, American College of Surgeons Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; GIST, gastrointestinal stromal tumour; RCT, randomised controlled trial; SSGXVIII/AIO, Scandinavian Sarcoma Group and the Sarcoma Group of the Arbeitsgemeinschaft Internistische Onkologie DeMatteo et al. 2009;[8] Corless et al. 2010;[54] Joensuu et al. 2012;[10] Casali et al. 2013.[11]				

6.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

The ACOSOG Z9001 trial and the SSGXVIII/AIO study are relevant to the decision problem. The ACOSOG Z9001 trial provides data on adjuvant imatinib (400 mg/day) therapy given for 1 year following surgical resection versus placebo, and included patients at any level of risk of recurrence.[8,54] Unpublished data are available for a subgroup of patients with Miettinen high-risk GIST,[12] and unpublished long-term (5-year) follow-up data are also available for this subgroup.[13] The SSGXVIII/AIO study compared adjuvant imatinib (400 mg/day) therapy given for 1 year following surgical resection with imatinib therapy given for 3 years post-resection, in patients with high risk of recurrence of GIST.[10] In this study patients were categorised as at high risk of recurrence based on modified US NIH Consensus Criteria. Unpublished data are available for a subgroup of patients with Miettinen high-risk GIST.[9]

The EORTC 62024 trial data are preliminary and published only in abstract form, without the ability to determine which patients might be classified as high-risk. In addition, this study used an endpoint of imatinib failure-free survival (IFS) (changed from OS 5 years into the study) as a surrogate for OS in this study. This endpoint has not been used in other studies of adjuvant GIST (see Figure B-8).

6.2.6 further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

In addition to the EORTC 62024 trial being unavailable in peer-reviewed format, the manufacturer has no access to the dataset.

List of relevant non-RCTs

6.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 6.8 and key details should be presented in a table; the following is a suggested format.

Twelve relevant non-RCTs were identified and are summarised in Table B-16. Eight comparative studies were identified: six compared adjuvant imatinib therapy with no treatment or historical controls (who received no treatment);[14-17,20,24] one compared long-term (2 years or more) with short-term (6 months to 2 years) adjuvant therapy with imatinib;[19] and one compared RFS for patients with R0 versus R1 resection in patients receiving adjuvant imatinib therapy with those receiving placebo.[22] Four studies were prospective single-arm studies of adjuvant imatinib therapy given for 1 or 2 years.[18,21,23,25]

6.3 Summary of methodology of relevant RCTs

6.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (**www.consort-statement.org**). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.

Methods

6.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of

follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

A summary of the methods used in the RCTs is provided in Table B-5 and fuller descriptions of each study and their methodologies are given below. A summary of patient eligibility criteria are provided in
Table B-6 and baseline characteristics of patients in the RCTs are given in Table B-7.

Table B-5. Comparative summary of methodology of the RCTs

Trial no. (acronym)	**ACOSOG Z9001[8]**	**SSGXVIII/AIO[10]**	**EORTC 62024[11]**
Location	USA and Canada	Sweden, Norway, Germany and Finland	Australia, Belgium, France, Germany, Italy, Netherlands, Poland, Spain, UK
Design	Randomised, phase 3, double-blind, placebo-controlled, multicentre trial (230 institutions)	Randomised, phase 3, prospective, open-label, multicentre (24 institutions)	Randomised, phase 3, controlled (no other post-surgical treatment), observational, open-label
Duration of study	57 months	82 months	2 years
Method of randomisation	Computer-generated random numbers were used (stratified biased coin design)	Computer-generated random numbers were used	Not stated
Method of blinding (care provider, patient and outcome assessor)	Study was double-blind; imatinib and placebo capsules looked alike and patients and investigators were blinded to the group that the patient was assigned Patients were unblinded when tumour recurrence was reported No further information provided	None, study was open-label	None, study was open-label
Intervention(s) (n =) and comparator(s) (n =)	Imatinib 400 mg/day for 1 year (n = 359) Placebo for 1 year (n = 354)	Imatinib 400 mg/day for 1 year (n = 199) Imatinib 400 mg/day for 3 years (n = 198)	Imatinib 400 mg/day for 2 years (n = 454) Observation (n = 454)
Primary outcomes (including scoring methods and timings of assessments)	Overall survival[a] (time from patient registration to death from any cause) Recurrence-free survival[b] (time from patient registration to the development of tumour recurrence or death from any cause)	Recurrence-free survival (time period from the date of randomisation to the date of first documentation of recurrence)	Imatinib-failure-free survival (changed from overall survival 5 years into the study)

Secondary outcomes (including scoring methods and timings of assessments)	Safety	Safety Overall survival (time period from the date of randomisation to death) GIST-specific survival (time period from the date of randomisation to the date of death considered to be caused by GIST)	Overall survival, progression-free survival, progression-free interval
Duration of follow-up	19.7 months (median)	54 months (median)	4.7 years (median)
ACOSOG, American College of Surgeons Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; GIST, gastrointestinal stromal tumour; RCT, randomised controlled trial; SSGXVIII/AIO, Scandinavian Sarcoma Group and the Sarcoma Group of the Arbeitsgemeinschaft Internistische Onkologie DeMatteo et al. 2009;[8] Joensuu et al. 2012;[10] Casali et al. 2013.[11]			

The ACOSOG Z9001 trial[8]

Objective

The objective of the ACOSOG Z9001 trial was to test the benefit of 1 year of adjuvant imatinib therapy, compared with placebo, on RFS in patients undergoing resection for GIST.

Methods and study design

The ACOSOG Z9001 trial was a randomised, phase 3, double-blind, placebo-controlled, RCT conducted in the USA and Canada that compared adjuvant imatinib (400 mg/day) therapy, given for 1 year after surgical resection, with placebo, and included patients at any level of risk of recurrence.

Following recurrence, patients were unblinded. Patients randomised to placebo or those who had completed the 1 year of imatinib treatment could then receive imatinib 400 mg, whereas patients who experienced recurrence whilst still on imatinib (400 mg) could receive imatinib 800 mg. Following an interim efficacy analysis that showed the results had crossed the boundary for RFS, accrual was stopped and the whole was study unblinded. At this point, patients randomised to placebo who had not yet had a recurrence were able to cross over and receive imatinib therapy for 1 year.

Participants

Eligible participants (see
Table B-6) were adults with c-KIT (CD117)-positive, localised primary GIST greater than or equal to 3 cm in size, with an Eastern Cooperative Oncology Group (ECOG) status of greater than 2 who were tumour free within 28 days of trial entry. Eligible patients were required to have adequate renal, haematological and hepatic function, and a negative serum pregnancy test when applicable. Patients were excluded if they had a history of previous imatinib use, chemotherapy, radiation therapy or other investigational treatment after surgery. Additional exclusion criteria were presence of active infection

requiring antibiotics within 14 days of trial registration, pregnant or breastfeeding women, presence of New York Heart Association class 3 or 4 cardiac disease, and requirement for full dose warfarin.

The ACOSOG Z9001 trial was designed in 2000, before the concept of risk stratification had been introduced for GIST. Patients were stratified according to tumour size, the only known risk factor for recurrence at the time.[39] However, tumour specimens were also collected and this has allowed for a retrospective analysis of mitotic count and an unpublished assessment of risk according to Miettinen criteria.

Baseline characteristics

Baseline characteristics are summarised in Table B-7.

The SSGXVIII/AIO study[10]

Objective

To investigate the role of imatinib as adjuvant treatment in patients with GIST at high risk of recurrence after surgery, and specifically, to compare the outcomes in patients treated for 1 year with those for patients treated for an extended period of 3 years post-resection.

Methods and study design

The SSGXVIII/AIO study was a randomised, phase 3, open-label, prospective study that compared adjuvant imatinib (400 mg/day) therapy given for 1 year with adjuvant imatinib therapy given for 3 years in patients at high risk of recurrence of GIST. The study was conducted in 24 centres in Sweden, Norway, Germany and Finland.

Patients were randomised 1:1 to receive imatinib 400 mg once daily for either 1 year (n = 200) or 3 years (n = 200). Patients were required to take four capsules of imatinib 100 mg once a day with food. Dose modifications were permitted to manage toxicities: doses were reduced to 300 mg once daily if patients experienced recurrence of grade 2 non-haematological toxicity, a grade 3 or 4 non-haematological toxicity or a persistent (greater than 2 weeks' duration) grade 3 or 4 haematological toxicity.

Participants

Participants in the SSGXVIII/AIO trial were adults with c-KIT (CD117)-positive GIST that had been removed by open surgery 1 to 12 weeks prior to randomisation and were considered to be at high risk of recurrence based on modified US NIH Consensus Criteria (see Table B-6). In brief, NIH high-risk was defined based on tumour site (gastric GIST has a lower risk of recurrence than non-gastric tumours of the same size and mitotic count) and whether or not the tumour had ruptured (tumour rupture confers increased risk). Patients were required to have at least

one of the following: longest tumour diameter greater than 10.0 cm, mitotic count greater than 10 mitoses/50 HPF of the microscope, tumour diameter greater than 5.0 cm and mitotic count greater than 5 mitoses/50 HPF, or tumour rupture before or at surgery.

Patients were excluded if they had inoperable, metastatic or recurrent GIST; a history of congestive heart failure or myocardial infarction within 6 months of enrolment or other severe or uncontrolled medical disease; invasive cancer within 5 years of enrolment; human immunodeficiency virus infection; were pregnant or breastfeeding; had been receiving either chemotherapy or neoadjuvant imatinib for GIST prior to randomisation; or had operable intra-abdominal GIST metastases (this latter item was added to the exclusion criteria from October 2006 onward).

The criteria used in this study to select patients at high risk of tumour recurrence were based on tumour size, mitotic count, whether tumour rupture into the abdominal cavity had occurred or the presence of confirmed or suspected microscopic infiltration. Thus the definition of high-risk used in this study can be considered to be a modified version of the NIH consensus criteria.

The Miettinen 2006 criteria, which additionally include tumour location to assess risk,[32] were not used in this study because they had not been published at time of conception of the study. However, tumour location was recorded during the study, which allowed data to be analysed *post hoc* using the Miettinen 2006 criteria. Using these criteria, patients were deemed to be at high risk of recurrence if they had a non-gastric tumour of greater than 10 cm in diameter irrespective of the mitotic count, or if they had a tumour of any size or location with a mitotic count of greater than 5 mitoses/50 HPF (with the exception of a gastric tumour of 5 cm or less in diameter).

Baseline characteristics

Baseline characteristics are summarised in Table B-7.

Participants

6.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

Table B-6. Eligibility criteria in the RCTs

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
ACOSOG Z9001[8]	Aged ≥ 18 years c-KIT (CD117)-positive, localised, primary GIST ≥ 3 cm ECOG status ≤ 2 Tumour free within 28 days of trial entry Adequate renal, haematological and hepatic function Negative serum pregnancy test when applicable	Previous imatinib therapy or use of chemotherapy, radiation therapy or investigational treatment after surgery Active infection requiring antibiotics within 14 days of trial registration Women who were pregnant or breastfeeding NYHA class 3 or 4 cardiac disease Full dose warfarin
SSGXVIII/AIO[10]	Aged ≥ 18 years c-KIT (CD117)-positive GIST removed at open surgery between 1 and 12 weeks prior to randomisation High estimated risk of recurrence, based on US NIH Consensus Criteria: • the longest tumour diameter greater than 10.0 cm • mitotic count greater than 10 mitoses per 50 HPFs of the microscope • tumour diameter greater than 5.0 cm and mitotic count over 5 mitoses per 50 HPFs of the microscope, or • tumour rupture before surgery or at surgery ECOG status ≤ 2 Adequate renal, hepatic and bone marrow function	Inoperable, metastatic, or recurrent GIST CHF or myocardial infarction within 6 months of enrolment or other severe or uncontrolled medical disease Invasive cancer within 5 years of enrolment Pregnant or breastfeeding HIV infection Received either chemotherapy or neoadjuvant imatinib for GIST prior to randomisation Operable intra-abdominal GIST metastases (only an exclusion criterion from October 2006 onward)
EORTC 62024[11]	Age > 18 years Localised c-KIT (CD117)-positive GIST Intermediate or high-risk based on NIH consensus criteria R0 or R1 surgical margins No previous medical therapy	Not stated

ACOSOG, American College of Surgeons Oncology Group; CHF, congestive heart failure; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; GIST, gastrointestinal stromal tumour; HPF, high-power fields; HIV, human immunodeficiency virus; NIH, National Institutes of Health; NYHA, New York Heart Association; R0, complete resection; R1, microscopic residual tumour suspected; RCT, randomised controlled trial; SSGXVIII/AIO, Scandinavian Sarcoma Group and the Sarcoma Group of the Arbeitsgemeinschaft Internistische Onkologie
DeMatteo et al. 2009;[8] Joensuu et al. 2012;[10] Casali et al. 2013.[11]

6.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Patient characteristics of participants in the RCTs show that patients were well balanced between the respective study arms in any given study, but highlight some slight differences between the studies in terms of patient baseline features. For example, fewer subjects in the ACOSOG Z9001 study had R1 resection margins (7–10%) than patients in either the SSGXVIII/AIO (15–19%) or the EORTC 62024 studies (15–16%). An R1 resection means that on histopathological examination of the excised tumour the excision margin contains tumor cells.[5] Further, the proportion of patients in the ACOSOG Z9001 study with an ECOG status of 0 was slightly lower (75–78%) than in the SSGXVIII/AIO (85–86%) or the EORTC 62024 studies (84–88%).[8,10,11]

Table B-7. Characteristics of participants in the RCTs across randomised groups

Trial no. (acronym) **Baseline characteristic**	**Randomised group X**	**Randomised group Y**
ACOSOG Z9001[8] **(n = 713)**	**Imatinib 400 mg/day, 1 year** (n = 359)	**Placebo, 1 year** (n = 354)
Age, median (range), years	59 (18 to 88)	58 (18 to 91)
Female sex	189 (52.6)	163 (46.0)
ECOG status		
0	281 (78.3)	265 (74.9)
1	74 (20.6)	81 (22.9)
2	4 (1.1)	8 (2.3)
Margins		
R0	325 (90.5)	330 (93.2)
R1	34 (9.5)	23 (6.5)
Not available	0	1 (0.3)
Tumour origin		
Stomach	209 (58.2)	235 (66.4)
Small intestine	125 (34.8)	102 (28.8)
Rectum	5 (1.4)	5 (1.4)
Other	18 (5.0)	12 (3.4)
Not available	2 (0.6)	0
Tumour size, cm		
≥ 3 to < 6	143 (39.8)	149 (42.1)
≥ 6 to < 10	123 (34.3)	119 (33.6)
≥ 10	93 (25.9)	86 (24.3)
SSGXVIII/AIO[10] **(n = 397)**	**Imatinib 400 mg/day, 1 year** (n = 199)	**Imatinib 400 mg/day, 3 years** (n = 198)
Age, median (range), years	62 (23 to 84)	60 (22 to 81)
Female sex	95 (48)	101 (51)

ECOG status		
0	169 (85)	170 (86)
1	26 (13)	27 (14)
2	2 (1)	0
Not available	2 (1)	1 (1)
Resected intra-abdominal metastases	13 (7)	11 (6)
Margins		
R0	169 (85)	160 (81)
R1	29 (15)	37 (19)
Not available	1 (1)	1 (1)
Tumour origin		
Stomach	97 (49)	105 (53)
Small intestine	74 (37)	62 (31)
Colon or rectum	16 (8)	19 (10)
Other	11 (6)	11 (6)
Not available	1 (1)	1 (1)
Primary tumour diameter, median (range), cm	9 (2 to 35)	10 (2 to 40)
< 5.1	29 (15)	18 (9)
5.1 to 10.0	91 (46)	81 (41)
> 10.0	78 (39)	98 (50)
Not available	1 (1)	1 (1)
Modified Consensus Classification Risk Group		
High	178 (89)	181 (91)
Intermediate	15 (8)	8 (4)
Low	2 (1)	3 (2)
Very low	0	0
Not available	4 (2)	6 (3)
EORTC 62024[11]	**Imatinib 400 mg/day, 2 years** (n = 454)	**Observation, 2 years** (n = 454)
Age, median (range), years	58.8 (17.9 to 85.6)	58.2 (20.0 to 88.8)
Female sex	222 (48.9)	220 (48.5)
ECOG status		
0	399 (87.9)	380 (83.7)
1	54 (11.9)	74 (16.3)
2	1 (0.2)	0
Margins		
R0	381 (83.9)	381 (83.9)
R1	70 (15.4)	72 (15.9)
R2	1 (0.2)	1 (0.2)
Unknown	2 (0.4)	0
Tumour origin		
Gastric	250 (55.1)	253 (55.7)
Other	204 (44.9)	201 (44.3)

Risk category (NIH consensus criteria) review diagnosis		
Very low	0	2 (0.4)
Low	19 (4.2)	13 (2.9)
Intermediate	162 (35.7)	150 (33.0)
High	168 (37.0)	168 (37.0)
Not reviewed	105 (23.1)	121 (26.7)

Data provided as n (%) unless otherwise stated.
ACOSOG, American College of Surgeons Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; ECOG, Eastern Cooperative Oncology Group; R0, complete resection/negative microscopic margins; R1, microscopic residual tumour suspected/positive microscopic margins; R2, macroscopic residual tumour suspected/positive macroscopic margins; RCT, randomised controlled trial; SSGXVIII/AIO, Scandinavian Sarcoma Group and the Sarcoma Group of the Arbeitsgemeinschaft Internistische Onkologie
DeMatteo et al. 2009;[8] Joensuu et al. 2012;[10] Casali et al. 2013.[11]

Outcomes

6.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL), and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

The primary and secondary outcomes of the RCTs are summarised in Table B-8 and described below. Table B-9 summarises the statistical analyses in the RCTs.

Table B-8. Primary and secondary outcomes of the RCTs

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
ACOSOG Z9001[8]	OS RFS (became primary endpoint 6 months before the first planned efficacy interim analysis)	RFS is considered to be the most relevant endpoint for assessing the efficacy of adjuvant therapy for GIST OS is also a relevant endpoint although this endpoint can be influenced by treatments given on relapse	Safety	N/A
SSGXVIII/ AIO[10]	RFS	RFS is considered to be the most relevant endpoint for assessing the efficacy of adjuvant therapy for GIST	Safety OS GIST-specific survival	OS and GIST-specific survival are relevant endpoints in this indication although the latter can be influenced by treatments given on relapse
EORTC 62024[11]	Imatinib-failure-free survival (IFS) (changed from OS 5 years in to study)	IFS is used as a surrogate for OS in this study. However, this is not a generally recognised endpoint and has not been used in other studies of adjuvant GIST	Overall survival Progression-free survival Progression-free interval	Progression-free survival and OS are considered to be the most relevant endpoints for assessing the efficacy of adjuvant therapy for GIST
ACOSOG, American College of Surgeons Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; GIST, gastrointestinal stromal tumour; OS, overall survival; RCT, randomised controlled trial; RFS, recurrence-free survival; SSGXVIII/AIO, Scandinavian Sarcoma Group and the Sarcoma Group of the Arbeitsgemeinschaft Internistische Onkologie DeMatteo et al. 2009;[8] Joensuu et al. 2012;[10] Casali et al. 2013.[11]				

The ACOSOG Z9001 trial[8]

Study assessments

During the study, patients were assessed at weeks 1, 2, 4, 6, 8, 12, 16, 20 and 24, then every 3 months until year 2 and then every 6 months until year 5 with physical examination, complete blood count with differential count, other laboratory parameters and assessment of adverse events (AEs). Contrast computer tomography (CT) or magnetic resonance imaging (MRI) scans of the abdomen and pelvis were performed at 3-month intervals for the first and second years and at 6-month intervals thereafter for 3 years.

Outcomes

The original primary endpoint in the ACOSOG Z9001 trial was OS. This was changed 6 months before the planned first interim analysis to RFS on the basis of discussions with the Cancer Therapy Evaluation Program and the US FDA. This reflected the fact that it became apparent that the actual mortality would be markedly lower than that described in the original statistical design; this was because imatinib was also being evaluated in recurrent GIST and had proved efficacious in that setting, so the crossover design permitted patients on placebo who experienced progression to receive imatinib. Consequently, the trial was grossly underpowered to demonstrate a difference in OS between adjuvant imatinib therapy started immediately after surgery and starting imatinib therapy on recurrence. The revised statistical plan assumed that the putative median RFS for placebo would be 3.5 years, based on historical data. The intended accrual was increased from 380 to 803 patients with a minimum follow-up of 3 years. This yielded 90% power to detect a 40% improvement in RFS at a 0.025 one-sided significance level in the imatinib group, which corresponded to a median RFS of 4.9 years in the imatinib group, with an HR of 0.71.

Statistical analysis

Analyses of the full population (intention-to-treat) were used for both RFS and OS. Both endpoints were estimated with the Kaplan–Meier method. Differences in RFS and OS between the randomised treatment groups were assessed using a one-sided log-rank test stratified by tumour size. HRs and 95% CIs were reported on the basis of a Cox proportional hazards regression model, which was also stratified by tumour size for RFS. An unstratified Cox model was used for OS because of the few recorded deaths. The placebo group was used as the HR denominator, so that HRs of less than 1 favour imatinib. The proportionality assumption of the Cox model was tested with Schoenfeld residuals, and was valid for all the analyses. All patients who received one or more doses of their assigned treatment were included in the safety analysis.

The SSGXVIII/AIO study[10]

Assessments

Contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen and pelvis, and CT of the chest or chest X-ray were mandatory staging examinations, and were required within 28 days prior to the first dose of the study drug. CT or MRI of the abdomen and pelvis were carried out at 6-month intervals in both groups during treatment and follow-up. Blood cell counts and chemistries were performed at 2- to 12-week intervals during the first 3 years of the study, and subsequently at 6-month intervals. Physical examinations were performed at 4 weeks after study entry, at approximately 3-month intervals until 3 years after study entry and subsequently at 6-month intervals.

Outcomes

The primary endpoint of the study was RFS, defined as the time period from the date of randomisation to the earliest date of recurrence (first date at which the physician suspected GIST recurrence leading to cytological or histological confirmation or radiological evidence of recurred GIST) or death from any cause. Between treatment difference was assessed using a log-rank test to compare RFS between the two groups. Kaplan–Meier estimates were plotted along with quartile estimates (25% quartile, median and 75% quartile) of time to RFS with 95% CI. The HR for RFS and its corresponding 95% CI were calculated using the Cox proportional hazards regression model, with treatment group as the only factor in the model. The primary RFS analysis was based on the full population (intention-to-treat population, ie, all patients with signed consent). RFS was also determined for patients assessed to be at high risk of recurrence according to the Miettinen 2006 criteria (referred to as the Miettinen high-risk population). Additional subgroup analyses of RFS were performed on the full population using the following variables: age, tumour site, tumour size, local and central mitotic count, tumour rupture, completeness of surgery and tumour mutation site.

OS, defined as the time period from the randomisation date to death from any cause plus 1 day, was a secondary endpoint. OS was analysed by an unstratified log-rank test and Cox proportional hazards regression model (with treatment group as the only factor in the model) to test for a treatment effect at the two-sided 5% level of significance. Kaplan–Meier estimates were plotted and the HR with corresponding 95% CI was calculated. OS was determined for the full population and the Miettinen high-risk population.

Statistical analysis

The final study sample size was estimated by simulating log-rank tests assuming a HR of 0.44 in favour of the 3-year group. At least 110 events were required in the efficacy population (patients with confirmed GIST and who did not have metastatic disease at study entry) to achieve a power of 80% with 160 patients in each group using a two-sided significance level of 0.05. Assuming a drop-out rate of 20%, 200 patients were planned to be randomised to each group.

Patients were followed up until a final analysis date, a date when all randomised patients had completed their first visit following 1 year of adjuvant imatinib treatment or at least 110 events had been recorded. After the final analysis date, patients were monitored for approximately 5 years.

Statistical analysis and definition of study groups

6.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took

account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT

Table B-9. Summary of statistical analyses in RCTs

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
ACOSOG Z9001[8]			
To test the benefit of adjuvant imatinib therapy on RFS in patients undergoing resection for GIST	Both endpoints were estimated with the Kaplan–Meier method. The investigators analysed differences in RFS and OS between the groups with a one-sided log-rank test stratified by tumour size. HRs and 95% CIs were reported on the basis of a Cox proportion hazards regression model, which was also stratified by tumour size for RFS. An unstratified Cox model was used for OS because of the few recorded deaths. The investigators used the placebo group as the HR denominator, so that HRs of less than 1 favour imatinib. The proportionality assumption of the Cox model was tested with Schoenfeld residuals, and was valid for all the analyses. For the safety analysis, the investigators included all patients receiving one or more doses of their assigned treatment. They used $\chi 2$ tests to compare categorical variables between the two groups.	Initially, when overall survival was the primary outcome, the investigators planned to recruit 380 patients over a minimum of 3 years, which allowed the log-rank test to have 90% power to detect a minimum HR of 0.65 at a 0.05 one-sided level of significance. Based on the revised outcome (RFS), it was assumed that a total of 803 patients would be required with a minimum of 3 years of follow-up in order to yield 90% power, at a 0.025 one-sided level of significance, in order to detect a 40% improvement in RFS in the imatinib group over placebo. This corresponds to a median RFS of 4.9 years for the imatinib group and a HR of 0.71.	Intention-to-treat analyses were done for both RFS and OS (patients were analysed by randomised groups). Unclear how investigators dealt with missing data.
SSGXVIII/AIO[10]			
To investigate the role of imatinib administration duration as adjuvant treatment	Frequency tables were analysed using the $\chi 2$ test or Fisher exact test. Survival between	The final study sample size was estimated by simulating log-rank tests assuming an HR	Efficacy analyses are based on the efficacy population and the modified full

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
of patients who have a high estimated risk for GIST recurrence after surgery	groups was compared using the Kaplan–Meier life-table method and unstratified log-rank test (*p*-values) or an unstratified Cox proportional hazards model (HRs). The subgroup analyses were done similarly for each subgroup variable category at a time. Prognostic factors were analysed using a Cox model with forward selection and backward elimination. All *p*-values are two-sided and not adjusted for multiple testing.	of 0.44 in favour of the 3-year group. At least 110 events were required in the efficacy population to achieve a power of 80% with 160 patients in each group using a two-sided significance level of 0.05. Assuming a drop-out rate of 20%, the investigators planned to randomise 200 patients to each group.	population. The modified full population consisted of randomised patients who signed informed consent and the efficacy population of patients who signed informed consent, had centrally confirmed GIST, and did not have metastases resected prior to study entry. The safety population included patients who took at least one dose of the study medication. Patients lost to follow-up were censored on the date of the last follow-up visit.
EORTC 62024[11]			
Imatinib failure-free survival (IFS) in patients with localised GIST treated with adjuvant imatinib (IM):	Interim analysis HRs and *p*-values were adjusted for stratification factors (high- versus intermediate-risk; R0 versus R1; stomach versus others; institution	Not provided	

6.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

The manufacturer had access to the datasets of both the ACOSOG Z9001 study and the SSGXVIII/AIO study. This allowed for *post hoc* analysis of outcomes according to Miettinen 2006 criteria risk groups, as requested by the European regulatory authorities.

Participant flow

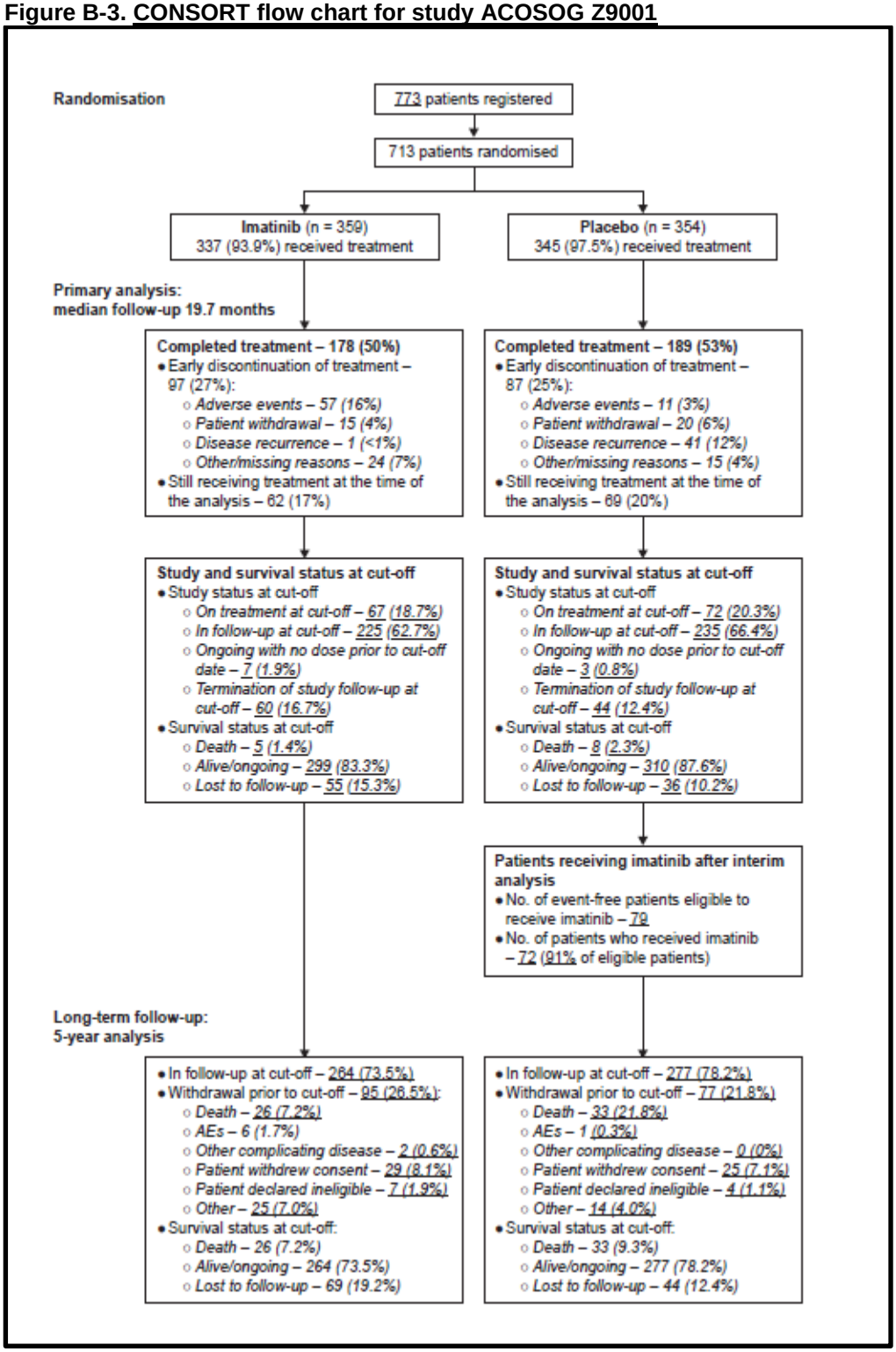
6.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

The disposition of patients in the ACOSOG Z9001 trial are summarised in the Consolidated Standards of Reporting Trials (CONSORT) flow chart (Figure B-3).

Following an interim efficacy analysis that showed the results had crossed the boundary for RFS, accrual was stopped and the study unblinded. At this point, patients randomised to placebo who had not yet experienced recurrence were able to receive imatinib therapy for 1 year. There were 79 patients who were still event-free and randomised to placebo and therefore eligible to receive imatinib treatment for 1 year. Seventy-two of these patients crossed over to receive imatinib treatment.

The disposition of patients in the SSGXVIII/AIO trial are summarised in the Consolidated Standards of Reporting Trials (CONSORT) flow chart (
Figure B-4).

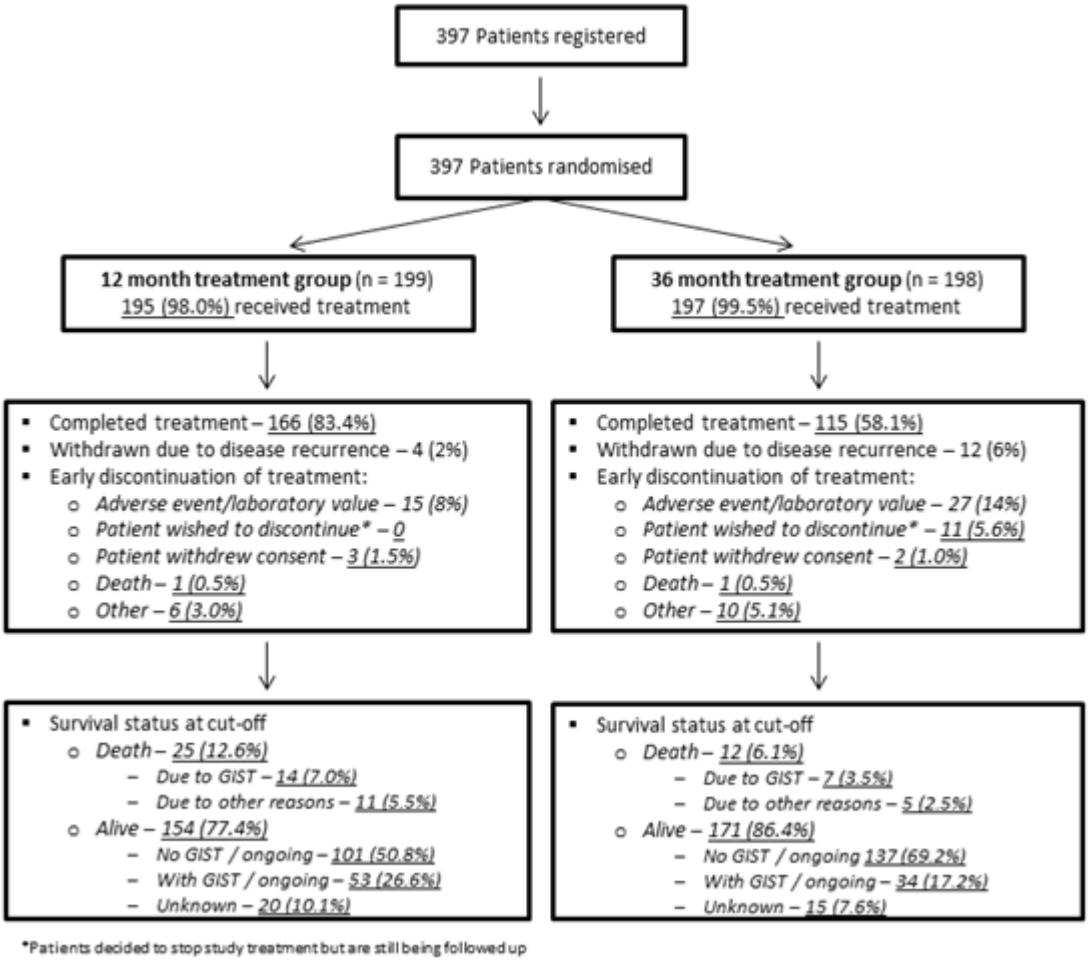
Figure B-3. CONSORT flow chart for study ACOSOG Z9001



ACOSOG, American College of Surgeons Oncology Group; AE, adverse event; CONSORT, Consolidated Standards of Reporting Trials

ACOSOG Z9001 study 5-year follow-up CSR;[13] ACOSOG Z9001 study primary analysis CSR.[55]

Figure B-4. CONSORT flow diagram for SSGXVIII/AIO study (full population)



*Patients decided to stop study treatment but were still being followed-up.
GIST, gastrointestinal stromal tumour; SSGXVIII/AIO, Scandinavian Sarcoma Group and the Sarcoma Group of the Arbeitsgemeinschaft Internistische Onkologie
Joensuu et al. 2011;[10] SSGXVIII/AIO study CSR.[9]

6.4 Critical appraisal of relevant RCTs

6.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

- Was the method used to generate random allocations adequate?
- Was the allocation adequately concealed?
- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?
- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

6.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 10.3, appendix 3 for a suggested format.

6.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

Table B-10 provides a quality assessment of the RCT evidence regarding adjuvant imatinib therapy following primary resection of GIST.

Table B-10. Quality assessment results for RCTs

Trial no. (acronym)	ACOSOG Z9001 study[8]	EORTC 62024 study[11]	SSGXVIII/AIO study[10]
Was randomisation carried out appropriately?	Yes	Not clear	Yes
Was the concealment of treatment allocation adequate?	Not clear	N/A	N/A
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	No	No
Were there any unexpected imbalances in drop-outs between groups?	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes Not clear	Not clear Not clear	Yes Yes
ACOSOG, American College of Surgeons Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; N/A, not applicable; RCT, randomised controlled trial; SSGXVIII/AIO, Scandinavian Sarcoma Group and the Sarcoma Group of the Arbeitsgemeinschaft Internistische Onkologie DeMatteo et al. 2009;[8] Joensuu et al. 2012;[10] Casali et al. 2013.[11]			

6.5 Results of the relevant RCTs

6.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale

for this should be given. **If there is more than one RCT, tabulate the responses.**

6.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.

6.5.3 For each outcome for each included RCT, the following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.
- Number of participants in each group included in each analysis and whether the analysis was by ‘intention to treat’. State the results in absolute numbers when feasible.
- When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.
- Discuss and justify definitions of any clinically important differences.
- Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

Table B-11 summarises the results of the RCTs.

Table B-11. Overview of relevant RCTs assessing imatinib therapy in the adjuvant setting of GIST

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics	Treatment regimens	Primary end-points (x versus y)
DeMatteo et al. 2009,[8] Corless et al.[54] ACOSOG Z9001 year primary analysis CSR[55]	ACOSOG Z9001: randomised, phase 3, double-blind, placebo-controlled, multicentre trial (230 institutions); duration of study 56 months (median duration of follow-up 19.7 months)	713[55] Mitotic data available retrospectively for 556, of whom 165 were classed as Miettinen high risk At 5-year follow-up, retrospective data were available for 627 patients in total, including 103 high-risk patients in the imatinib group and 98 patients in the placebo group.	Adult patients with complete resection of c-KIT (CD117)-positive GIST at least 3 cm in size with an ECOG status of at least 2 who were tumour free within 28 days of trial entry	Age: 59 versus 58 years % female: 53% versus 46% % ECOG status 0: 78% versus 75% % R0 margins: 91% versus 93% Tumour 10 cm or greater: 26% versus 24%	Imatinib 400 mg/day for 1 year (n = 359) or placebo for 1 year (n = 354)	OS (time from patient registration to death from any cause) RFS (time from patient registration to the development of tumour recurrence or death from any cause) – this became the primary endpoint 6 months before the first planned efficacy interim analysis Reported primary data: RFS Estimated 1-year RFS Imatinib: 98% (95% CI 96% to 100%) Placebo: 83% (95% CI 78% to 88%) HR 0.35; 95% CI 0.22 to 0.53; $p < 0.0001$ Deaths Imatinib: 5 (1%) Placebo: 8 (2%) OS HR 0.66; 95% CI 0.22 to 2.03; p = NS Long-term follow-up data through March 2011 Estimated 5-year RFS in full population: Imatinib: 72.8% (95% CI 67.1% to 78.4%) Placebo: 68.4% (95% CI 63.0 to 73.8%)[13] In high-risk (Miettinen 2006 criteria) patients 1-year RFS Imatinib 98.7% Placebo 56.1%

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics	Treatment regimens	Primary end-points (x versus y)
Joensuu et al. 2012;[10] SSGXVIII/ AIO study CSR[9]	SSGXVIII/AIO: randomised, phase 3, prospective, open-label, multicentre (24 institutions); duration of study 82 months (median duration of follow-up 54 months)	397, of whom 281 were classed as Miettinen high risk.	Adult patient with c-KIT (CD117)-positive GIST removed at open surgery 1 to 12 weeks prior to randomisation and considered at high risk of recurrence based on modified US NIH Consensus Criteria	Age: 62 versus 60 years % female: 48% versus 51% % ECOG status 0: 85% versus 86% % R0 margins: 85% versus 81% Tumour 10 cm or greater: 39% versus 50%	Imatinib 400 mg/day for 1 year (n = 199) or imatinb 400 mg/day for 3 years (n = 198)	RFS 5-year RFS 3-year imatinib: 65.6% 1-year: 47.9% HR 0.46; 95% CI 0.32 to 0.65; $p < 0.0001$[9] No significant difference in the hazard of GIST recurrence or death between the two groups during the first 1 year or 3 years after randomisation, but a substantial difference emerged during 12 to 2 years and 2 to 3 years after randomisation (HR 0.26; 95% CI 0.13 to 0.53; and HR 0.17; 95% CI 0.07 to 0.39, respectively) OS 5-year OS After 3 years of imatinib: 92.0% After 1 year of imatinib: 81.7% HR 0.45; 95% CI 0.22 to 0.89; $p = 0.02$ 5-year GIST-specific survival After 3 years of imatinib: 88.5% After 1 years of imatinib: 95.1% HR 0.46; 95% CI 0.19 to 1.14; $p = 0.09$ In high-risk groups (Miettinen 2006 criteria) RFS longer in the 3-year group compared with

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics	Treatment regimens	Primary end-points (x versus y)
						the 1-year group: HR 0.43 (95% CI 0.30 to 0.62; *p* < 0.0001) At 18 months: RFS 81.6% in the 1-year group and 93.4% in the 3-year group At 4 years: RFS 40.2% in the 1-year group and 72.0% in the 3-year group The median time to recurrence was 35.9 months in the 1-year adjuvant imatinib group and 71.8 months in the 3-year adjuvant imatinib group OS was longer in the 3-year group compared with the 1-year group; HR 0.39; 95% CI 0.19 to 0.79; p = 0.007). At 4 years: OS rate 83.0% (95% CI 73.8 to 89.1) for the 1-year group and 94.5% (95% CI 88.6 to 97.3) for the 3-year group. At 5 years, OS rates were 74.2% (1-year group) and 89.5% (3-year group).
Casali et al. 2013[11]	EORTC 62024: randomised, phase 3, controlled (no other post-surgical treatment), observational, open-label; duration of study 2 years	908	Localised, surgically resected GIST of high or intermediate risk of recurrence based on the NIH consensus criteria	Age: 59 versus 58 years % female: 49% versus 49% % ECOG status 0: 88% versus 84% % R0 margins: 84% versus 84%	Imatinib 400 mg/day for 2 years (n = 454) versus no other therapy after surgery or observation (n = 454)	IFS (changed from overall survival 5 years into the study) RFS 3-year RFS Imatinib: 84% Observation: 66% *p* < 0.001 5-year RFS Imatinib: 69%

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics	Treatment regimens	Primary end-points (x versus y)
	(median duration of follow-up 4.7 years)			% gastric tumour: 55% versus 56%		Observation: 63% $p < 0.001$ IFS 5-year IFS[a] Imatinib: 87% Observation: 84% HR, 0.80; 95% CI 0.51 to 1.26; $p = 0.23$ 5-year IFS[a] in high-risk patients (centrally reviewed pathology) Imatinib: 77% Observation: 73% $p = 0.44$ OS 5-year OS Imatinib: 100% Observation: 99%

ACOSOG, American College of Surgeons Oncology Group; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; GIST, gastrointestinal stromal tumour; HR, hazard ratio; IFS, imatinib failure-free survival; NIH, National Institutes of Health; OS, overall survival; R0, complete resection; R1, microscopic residual tumour suspected; RCT, randomised controlled trial; RFS, recurrence-free survival; SSGXVIII/AIO, Scandinavian Sarcoma Group and the Sarcoma Group of the Arbeitsgemeinschaft Internistische Onkologie

[a]IFS defined as first tyrosine kinase inhibitor (TKI) failure-free survival (ie, time to starting second TKI).

DeMatteo et al. 2009;[8] Joensuu et al. 2012;[10] Corless et al. 2010;[54] Casali et al. 2013;[11] ACOSOG primary analysis CSR;[55] SSGXVIII/AIO study CSR.[9]

The ACOSOG Z9001 trial results [8]

The primary outcome data from the ACOSOG Z9001 trial were published at a median follow-up of 19.7 months,[8] and unpublished data are available for the subgroup of patients with high-risk disease (defined by the Miettinen 2006 criteria) for a follow-up corresponding to the primary analysis.[12] Further unpublished data are available for a 5-year follow-up of the total study population (corresponding to an overall median follow-up of 70 months) and for the subgroup with Miettinen high-risk disease .[13]

The full population consisted of 713 patients, of whom 359 were randomised to adjuvant imatinib therapy and 354 to placebo. At the time of the primary outcome analysis, approximately 50% of patients in both groups had completed 1 year of study treatment and approximately 25% had discontinued treatment early. The occurrence of AEs (16% of patients) was the most frequent reason for discontinuation from the imatinib group whereas disease recurrence (12% of patients) was the most frequent reason for early discontinuation in the placebo group. Dose reduction or interruption or both had occurred in 59 patients (16%) in the imatinib group and 17 patients (5%) in the placebo group, and was due to AEs in 52 (15%) and 10 (3%) patients, respectively.

At the 5-year follow-up analysis, approximately 75% of patients in both groups remained on study. The most frequent reasons for discontinuation from the study by this analysis were death, withdrawal of consent and other (imatinib group only). At the 5-year follow-up it was reported that, at study unblinding for the primary analysis (12 April 2007), 79 patients in the placebo arm were still recurrence-free. Seventy-two (72) of these 79 patients (i.e. 91%) opted to cross over to receive 1 year of treatment with imatinib. The 5-year data are analysed according to ITT and hence do not take into account the impact of these patients switching to receive imatinib.

Baseline demographic and pathological characteristics were similar between the imatinib and placebo groups (see Table B-7). The median age was 59 years (range: 18 to 88 years) in the imatinib group and 58 years (range: 18 to 91 years) in the placebo group. Most patients in each group (imatinib versus placebo) had an ECOG status of 0 (78.3% versus 74.9%), R0 margins (90.5% versus 93.2%) and the majority of tumours were in the stomach (58.2% versus 66.4%).[8]

The ACOSOG Z9001 trial was designed in 2000, before risk stratification schemes had been introduced for GIST. Patients were stratified according to tumour size, the only known risk factor for recurrence at the time.[8] However, tumour specimens were also collected and this has allowed for a retrospective analysis of mitotic count and an unpublished assessment of risk according to Miettinen 2006 criteria, which was used to support the presentation of the ACOSOG Z9001 trial findings to the regulatory authorities. At the time of the primary analysis, mitotic data were available retrospectively for 556 of the 713 randomised patients, and demographic characteristics and the duration of treatment exposure for those with mitotic data were found to be similar for the total full population. In total, 165 patients were classified as having Miettinen high-risk disease and these were evenly distributed between the two treatment groups; demographic and baseline disease characteristics for

this subgroup are summarised in Table B-12. By the time of the 5-year follow-up, retrospective data were available for a further 71 patients (ie, 627 in total) including 103 high-risk patients in the imatinib group and 98 patients in the placebo group (baseline demographic data not shown in Table B-14).

Table B-12. Baseline demographic and pathological characteristics of patients in the ACOSOG Z9001 trial as reported in the primary analysis (full population) and for primary analysis patients retrospectively identified as being high risk according to the Miettinen 2006 criteria

Characteristic	Full population		Miettinen high-risk population	
	Placebo n = 354	Imatinib n = 359	Placebo n = 81	Imatinib n = 84
Median age (range), years	58 (18 to 91)	59 (18 to 88)	56 (18 to 85)	56 (33 to 83)
Male, n (%)	191 (54.0)	170 (47.4)	44 (54.3)	45 (53.6)
ECOG performance status, n (%)				
0	265 (74.9)	281 (78.3)	52 (64.2)	64 (76.2)
1	81 (22.9)	74 (20.6)	24 (29.6)	19 (22.6)
2	8 (2.3)	4 (1.1)	5 (6.2)	1 (1.2)
Primary tumour site, n (%)				
Stomach	235 (66.4)	209 (58.2)	43 (53.1)	30 (35.7)
Small intestine	102 (28.8)	125 (34.8)	1 (1.2)	1 (1.2)
Rectum	5 (1.4)	5 (1.4)	1 (1.2)	3 (3.6)
Other	12 (3.4)	18 (5.0)	36 (44.4)	50 (59.5)
Not available	0	2 (0.6)	0	0
Median days between resection and randomisation (range)	59 (15 to 96)	57 (20 to 74)	54 (23 to 73)	57 (20 to 70)
Completeness of surgery, n (%)				
Complete resection (R0)	330 (93.2)	325 (90.5)	72 (88.9)	77 (91.7)
Microscopic residual tumour suspected (R1)	23 (6.5)	34 (9.5)	9 (11.1)	7 (8.3)
Not available	1 (0.3)	0	0	0
Tumour size range, cm				
≥ 3 to < 6, n (%)	149 (42.1)	143 (39.8)	7 (8.6)	13 (15.5)
≥ 6 to < 10.0, n (%)	119 (33.6)	123 (34.3)	22 (27.2)	30 (35.7)
≥ 10.0, n (%)	86 (24.3)	93 (25.9)	52 (64.2)	41 (48.8)

ACOSOG, American College of Surgeons Oncology Group; ECOG, Eastern Cooperative Oncology Group; R0, complete resection; R1, microscopic residual tumour suspected DeMatteo et al. 2009;[8] Data on file: ACOSOG Z9001 high-risk group analysis.[12]

The ACOSOG Z9001 trial primary analysis: adjuvant imatinib therapy given for 1 year significantly improved RFS compared with placebo after resection of primary GIST

At the primary outcome analysis, after a median follow-up of 19.7 months, 30 patients (8%) in the imatinib group had an event (tumour recurrence or death from any cause) compared with 70 (20%) in the placebo group.[8] The estimated 1-year RFS was 98% (95% CI 96 to 100) in the imatinib group and 83% (95% CI 78 to 88) in the placebo group, a difference that was highly statistically significant (HR 0.35 [0.22 to 0.53], $p < 0.0001$).

The ACOSOG Z9001 trial primary analysis: the improvement in RFS obtained with adjuvant imatinib therapy given for 1 year over placebo declined after treatment cessation

The effect of imatinib is greatest while patients are on treatment. In the full population, the improvements in RFS observed for adjuvant imatinib therapy were evident from 6 months after randomisation, being 99.3% (95% CI 98.4 to 100) for imatinib versus 90.7% (95% CI 87.4 to 94.1 for placebo) and continued through to the end of treatment at 1 year.[55] The difference between treatment groups was still evident at 30 months (84.2% versus 69.6%), but thereafter, the difference between treatment groups narrowed (Table B-13).

The ACOSOG Z9001 trial primary analysis: the benefit of 1 year of adjuvant imatinib therapy over placebo was particularly evident in patients with high-risk disease

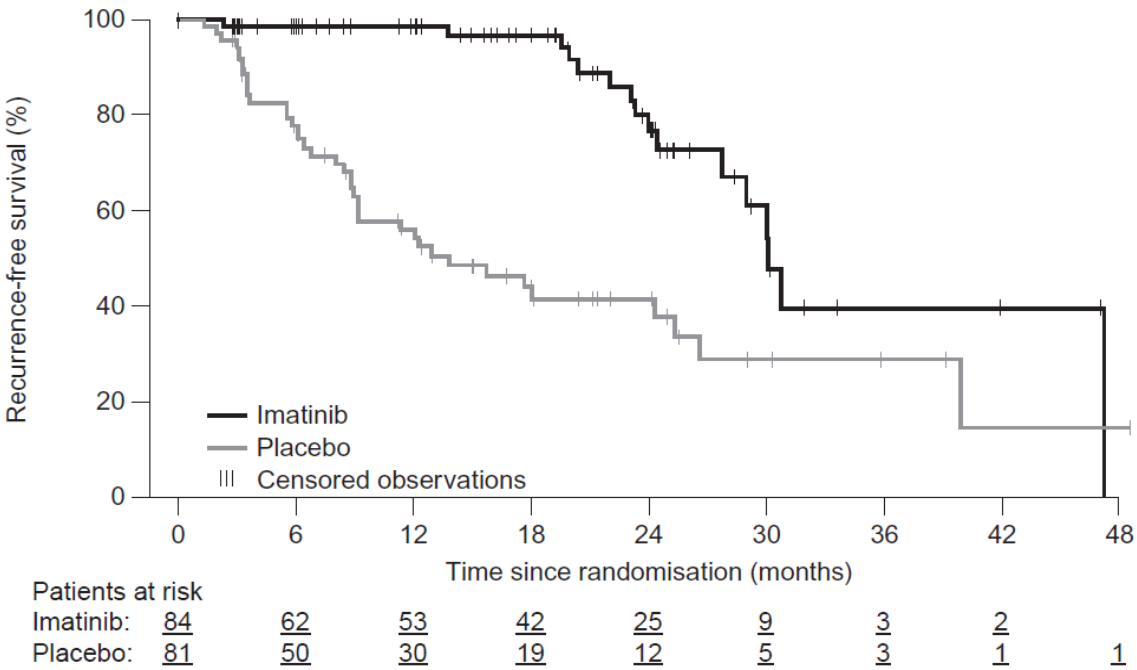
An analysis of RFS in patients categorised as high risk according to Miettinen 2006 criteria revealed that the benefit of adjuvant imatinib therapy was particularly evident for patients with high-risk disease. In this subgroup, the 1-year RFS was 98.7% in the adjuvant imatinib group versus 56.1% in the placebo group. As with the full patient population, the data for the high-risk patients revealed that the benefit of imatinib therapy was significant when compared with placebo, but showed that after 18 months from randomisation the effect on RFS began to wane, thus providing further evidence that the benefits of adjuvant imatinib therapy are likely to be increased by continuing the duration of therapy beyond 1 year (Table B-13 and Figure B-5).

Table B-13. Comparison of RFS probabilities (95% CI) (full and Miettinen high-risk population) based on the primary analysis of the ACOSOG Z9001 study

	Full population		**Miettinen high-risk population**	
Time period	**Imatinib (n = 359)**	**Placebo (n = 354)**	**Imatinib (n = 84)**	**Placebo (n = 81)**
6 months	99.3 (98.4 to 100.0)	90.7 (87.4 to 94.1)	98.7 (96.1 to 100.0)	77.9 (68.0 to 87.8)
1 year	97.7 (95.9 to 99.5)	82.3 (77.8 to 86.9)	98.7 (96.1 to 100)	56.1 (43.8 to 68.5)
1.5 years	95.7 (93.0 to 98.3)	76.5 (71.2 to 81.8)	96.7 (92.1 to 100.0)	43.9 (30.9 to 56.9)
2 years	90.8 (86.4 to 95.1)	73.5 (67.8 to 79.2)	79.9 (67.1 to 92.8)	41.5 (28.3 to 54.6)
3 years	75.9 (66.8 to 85.1)	69.6 (63.0 to 76.2)	39.5 (16.0 to 63.0)	28.7 (13.5 to 43.9)
4 years	65.3 (47.8 to 82.8)	66.4 (57.7 to 75.1)	0.0	14.4 (0.0 to 35.7)
5 years	65.3 (47.8 to 82.8)	66.4 (57.7 to 75.1)	0.0	0.0
HR (95% CI)	0.398 (0.259 to 0.610)		0.265 (0.148 to 0.477)	
p-value	<0.0001		< 0.0001	

Censoring time was defined as the last date that a patient was known to be alive and recurrence free. No. of patients with events/censoring: imatinib full population, 30/329; placebo full population, 70/284; imatinib high-risk population, 16/68; placebo high-risk population, 39/42
The HR was derived from a Cox proportional hazards model with treatment only in the model (unadjusted effect) and is for imatinib versus placebo. An HR less than 1 indicated a treatment effect in favour of imatinib.
ACOSOG, American College of Surgeons Oncology Group; CI, confidence interval; HR, hazard ratio; RFS, recurrence-free survival
ACOSOG Z9001 high-risk group analysis;[12] ACOSOG primary analysis CSR.[55]

Figure B-5. RFS rates for Miettinen high-risk population receiving imatinib or placebo in the ACOSOG Z9001 study based on the primary analysis (cut-off date 12 April 2007)



ACOSOG, American College of Surgeons Oncology Group; RFS, recurrence-free survival
ACOSOG Z9001 high-risk group analysis.[12]

Primary analysis: few deaths were observed in either treatment group at 2 years

The primary outcome analysis estimated the OS at 2 years in the full population to be 98.8% and 97.6% for the imatinib and placebo groups, respectively.[55] An analysis of OS for the subgroup of patients with Miettinen high-risk disease revealed no statistically significant difference between treatment groups overall (p = 0.0764); 2-year OS was 100% for the imatinib group versus 94.7% for the placebo group and the difference increased to 100% versus 90.9% for 4-year OS.

Five-year follow-up data: improvements in RFS were observed for imatinib over placebo and were particularly marked in patients with high-risk disease, in agreement with results for the primary analysis

Unpublished, 5-year follow-up data are available from the ACOSOG Z9001 trial to a cut-off date of 15 March 2011 and provide additional data on long-term outcomes, together with some insights into the confounding effects of patient crossover following study unblinding.[13] The 5-year follow-up provides a median duration of RFS follow-up for all patients of 46.3 months . The data are for the full population consisting of 359 patients originally assigned to adjuvant imatinib therapy and 354 to placebo, and for 103 patients (imatinib group) and 98 patients (placebo group) with high-risk disease as defined by the Miettinen 2006 criteria.

As for the primary analysis, an improvement in RFS was observed for the imantinib group compared with placebo (HR 0.718; 95% CI 0.531 to 0.971, *p* = 0.0305) and the difference between treatment groups was greatest at 18 months from randomisation (RFS: 95.4% versus 80.1%), decreasing thereafter (Table B-14). However, the overall treatment effect for imatinib was less than that observed in the primary analysis because the follow-up analysis is confounded by the majority of the placebo patients who were recurrence-free at the time of study unblinding opting to cross over to active treatment for one year. A supportive analyses which removed patients that crossed over from placebo to 1 year of imatinib treatment after 12 April 2007 reported an HR of 0.671 (0.491 to 0.919; *p* = 0.0123).

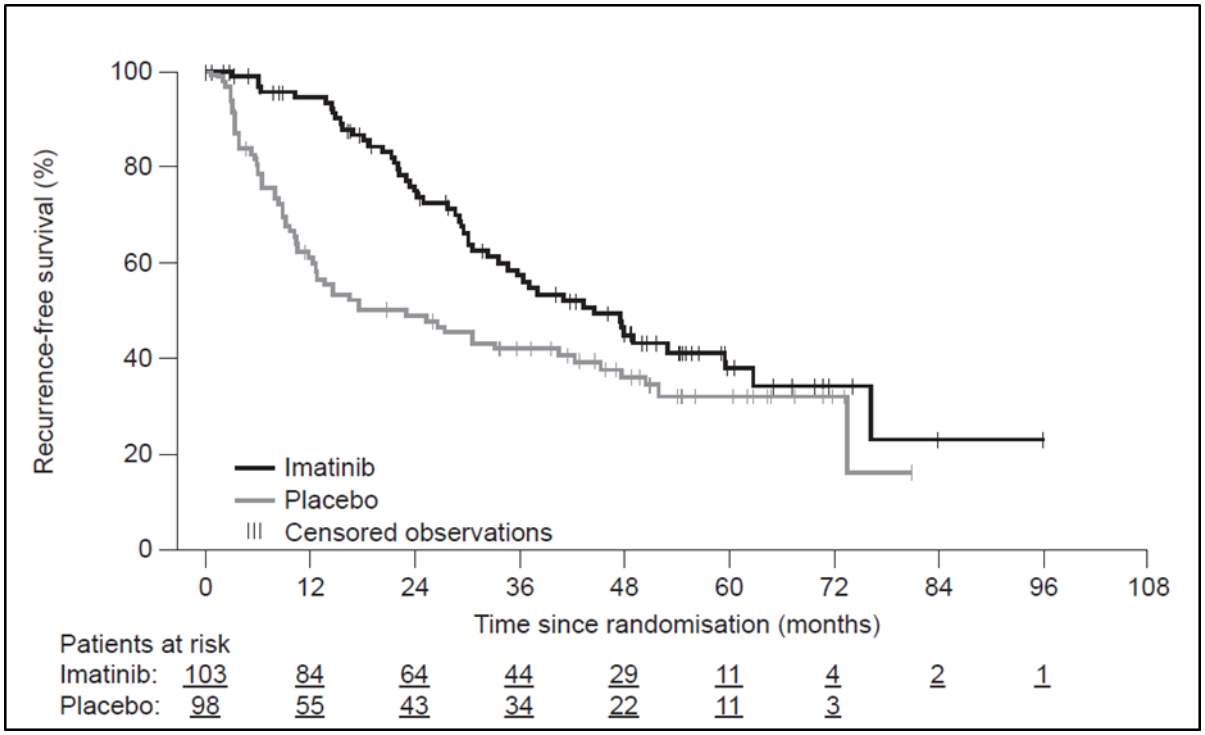
As in the primary analysis, the benefits of 1 year of adjuvant imatinib therapy were particularly marked in high-risk patient groups compared with placebo (Table B-14 and
Figure B-6).

Table B-14. Comparison of RFS probabilities (95% CI) (Full population and Miettinen high-risk population) based on the 5-year follow-up analysis of the ACOSOG Z9001 study

	Full population		**Miettinen high-risk population**	
Time period	**Imatinib (n = 359)**	**Placebo (n = 354)**	**Imatinib (n = 103)**	**Placebo (n = 98)**
6 months	99.7 (99.1 to 100)	92.8 (90.0 to 95.6)	98.9 (96.9 to 100.0)	79.6 (71.4 to 87.8)
1 year	98.1 (96.5 to 99.6)	85.7 (82.0 to 89.5)	94.6 (90.0 to 99.2)	61.0 (51.1 to 71.0)
1.5 years	95.4 (93.0 to 97.7)	80.1 (75.8 to 84.4)	86.7 (79.6 to 93.7)	49.9 (39.7 to 60.2)
2 years	91.5 (88.3 to 94.7)	77.9 (73.4 to 82.4)	76.0 (67.0 to 85.0)	48.8 (38.6 to 59.1)
3 years	83.8 (79.5 to 88.1)	74.9 (70.2 to 79.7)	57.2 (46.6 to 67.9)	41.9 (31.7 to 52.1)
4 years	76.5 (71.4 to 81.6)	70.7 (65.6 to 75.8)	44.7 (33.6 to 55.8)	36.0 (25.7 to 46.3)
5 years	72.8 (67.1 to 78.4)	68.4 (63.0 to 73.8)	37.9 (25.9 to 49.9)	32.1 (21.6 to 42.6)
6 years	69.1 (62.4 to 75.9)	68.4 (63.0 to 73.8)	34.1 (21.2 to 47.0)	32.1 (21.6 to 42.6)
7 years	66.0 (57.2 to 74.8)	61.3 (50.9 to 71.8)	22.7 (2.6 to 42.8)	Not estimated
8 years	66.0 (57.2 to 74.8)	Not estimated		
HR	0.718 (0.531 to 0.971)		0.608 (0.417 to 0.886)	
p-value	0.0305		0.009	

Censoring time was defined as the last date that a patient was known to be alive and recurrence free.
No. of patients with events/censoring: imatinib full population, 74/285; placebo full population, 98/256; imatinib high-risk population, 50/53; placebo high-risk population, 60/38
The HR was derived from a Cox proportional hazards model with treatment only in the model (unadjusted effect) and is for imatinib versus placebo. An HR less than 1 indicated a treatment effect in favour of imatinib.
ACOSOG, American College of Surgeons Oncology Group; CI, confidence interval; HR, hazard ratio; ACOSOG Z9001 study 5-year follow-up CSR.[13]

Figure B-6. RFS rates for Miettinen high-risk population receiving imatinib or placebo in the ACOSOG Z9001 study based on the 5-year follow-up analysis



ACOSOG, American College of Surgeons Oncology Group; RFS, recurrence-free survival
ACOSOG Z9001 study 5 year follow-up CSR.[13]

Five-year follow-up: OS data

At a median follow-up of 60.2 months, there were few deaths in either treatment group; 5-year OS was 91.3% for the imatinib group and 91.1% for the placebo group. No statistically significant differences in OS were noted between treatment groups over the follow-up period (HR 0.816; 95% CI 0.488 to 1.365; p = 0.4385). As for the overall population, these data are confounded by the degree of cross-over which took place when the study was unblinded. A sensitivity analysis that censored for patients eligible for crossover to 1 year of imatinib treatment showed a slightly more pronounced effect in favour of imatinib (HR 0.746; 95% CI 0.441 to 1.262; p = 0.2725). These data also suggest that the optimum treatment duration of adjuvant imatinib should be greater than 1 year.

Results for the SSGXVIII/AIO study[10]

A total of 400 patients were recruited to the SSGXVIII/AIO study and were randomly assigned to 1 year of therapy (1-year group) or 3 years of treatment (3-year group). Three patients did not give informed consent and were excluded from the analysis. The remaining 397 patients comprised the full population for which the efficacy results are described.

Patient disposition is presented in
Figure B-4. Of the 397 patients in the full population, 392 received treatment (195 and 197 in the 1-year and 3-year groups, respectively) and 281 completed treatment: 166 (83.4%) in the 1-year group and 115 (58.1%) in the 3-year group. In the 1-year group, 4 patients (2%) withdrew from treatment owing to disease recurrence compared with 12 patients (6%) in the 3-year group. The most common reasons for treatment discontinuation were AEs or abnormal laboratory values; these accounted for 15 patient discontinuations (8%) in the 1-year group and 27 patient discontinuations (14%) in the 3-year group.[9,10,56]

Overall, the groups were well balanced and were representative of a typical high-risk GIST patient population (Table B-15). The median age was 61 years and approximately 50% of patients had primary gastric tumours. The median tumour size was 10 cm, the median mitotic count was 6 mitoses/50 HPF and tumour rupture had occurred in 20% of patients.

Overall, 70% of patients were at high risk of recurrence according to the Miettinen 2006 criteria (142 in the 1-year group and 139 in the 3-year group).

Table B-15 Patient demographics and baseline tumour characteristics in the SSGXVIII/AIO study (Full population)

Characteristic	Full population		Miettinen high-risk population	
	1 year n = 199	3 year n = 198	1 year n = 142	3 year n = 139
Median age (range), years	62 (23 to 84)	60 (22 to 81)	62 (30 to 84)	59 (22 to 79)
Male, n (%)	104 (52)	97 (49)	74 (52.1)	64 (46.0)
ECOG performance status 0, n (%)	169 (85)	170 (86)	118 (83.1)	121 (87.1)
Primary tumour site, n (%)				
Stomach	97 (49)	105 (53)	54 (38.0)	58 (41.7)
Small intestine	74 (37)	62 (31)	62 (43.7)	56 (40.3)
Colon or rectum	16 (8)	19 (10)	15 (10.6)	13 (9.4)
Other	11 (6)	11 (6)	10 (7.0)	11 (7.9)
Not available	1 (1)	1 (1)	1 (0.7)	1 (0.7)
Completeness of surgery, n (%) Complete resection (R0)	169 (85)	160 (81)	116 (81.7)	107 (77.0)
Microscopic residual tumour suspected (R1)	29 (15)	37 (19)	26 (18.3)	32 (23.0)
Not available	1 (1)	1 (1)	0 (0.0)	0 (0.0)
Tumour rupture present, n (%)	35 (17.6)	44 (22.2)	18 (12.7)	25 (18.0)
Median tumour size range, cm	9 (2 to 35)	10 (2 to40)	NA	NA
< 5.1, n (%)	29 (15)	18 (9)	17 (12.0)	7 (5.0)
> 5.1 to 10.0, n (%)	91 (46)	81 (41)	60 (42.2)	57 (41.0)
> 10.0, n (%)	78 (39)	98 (50)	64 (45.1)	74 (53.2)
Not available, n (%)	1 (1)	1 (1)	1 (0.7)	1 (0.7)
Median mitotic count (range), per 50 HPF[a]	10 (0 to 250)	8 (0 to 165)	11 (0 to 200)	8 (0 to 76)
≤ 5, n (%)	86 (43.2)	98 (49.5)	38 (26.8)	48 (34.5)
> 5 to 10, n (%)	29 (14.6)	25 (12.6)	30 (21.1)	30 (21.6)
> 10, n (%)	74 (37.2)	59 (29.7)	73 (51.4)	58 (41.7)
Not available, n (%)	10 (5.0)	16 (8.1)	1 (0.7)	3 92.1)
GIST-related gene mutation site, n (%)[b]				
c-KIT exon 9	12 (6.0)	14 (7.1)	9 (6.3)	13 (9.3)
c-KIT exon 11	129 (64.8)	127 (64.1)	96 (67.6)	93 (66.9)
PDGFRA exon 12	3 (1.5)	2 (1.0)	2 (1.4)	1 (0.7)
PDGFRA exon 18	22 (11.1)	19 (9.6)	1 (0.7)	4 (2.9)
PDGFRA exon 18 D842V mutation	18 (9.0)	14 (7.1)	7 (4.9)	2 (1.4)
Other mutation	3 (1.5)	2 (1.0)	3 (2.1)	2 (1.4)
Wild type for c-*KIT* and *PDGFRA*	19 (9.5)	14 (7.1)	14 (9.9)	10 (7.2)
Not available	11 (5.5)	20 (10.1)	10 (7.0)	14 (10.1)

[a]Counts per 50 HPF of the microscope at local pathology assessment; [b]Analysed centrally after patient entry into the study
EGOG, Eastern Cooperative Oncology Group; GIST, gastrointestinal stromal tumour; HPF, high power fields; NA, not available; R0, complete resection; R1, microscopic residual tumour suspected; PDGFR, platelet-derived growth factor receptor
Joensuu et al. 2012;[10] SSGXVIII/AIO CSR.[9]

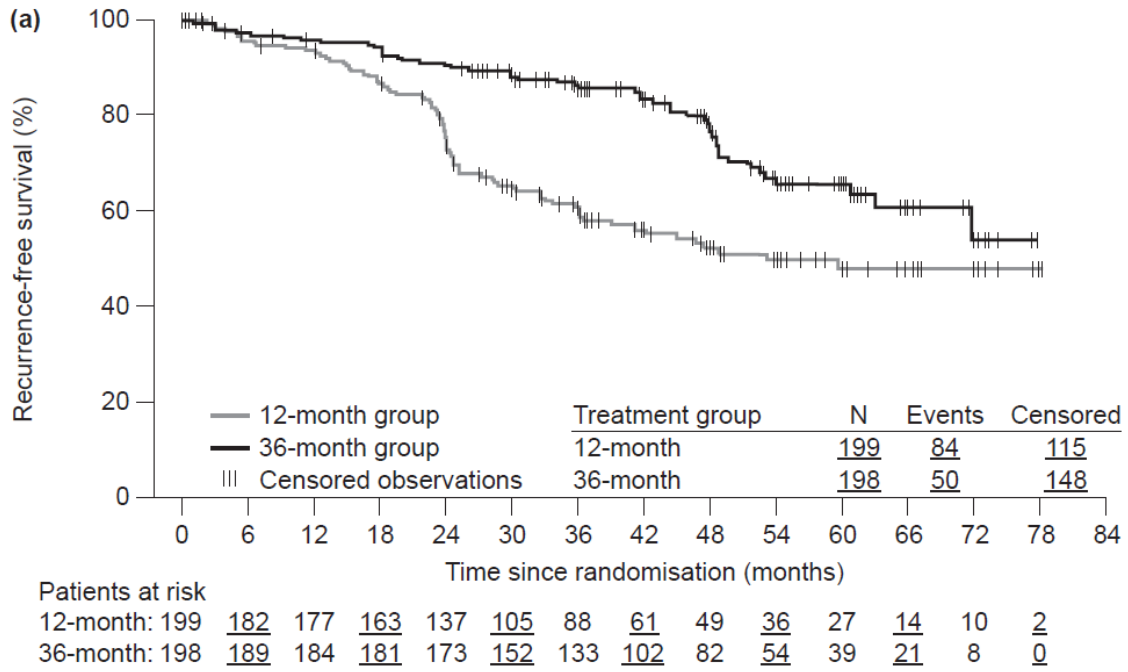
Results are reported for a median duration of follow-up of 54 months for the full population. During this time, 134 patients died or experienced GIST recurrence. Of these, 84 events (43.3%) occurred in the 1-year group compared with 50 (25.3%) in the 3-year group.[9,15,56]

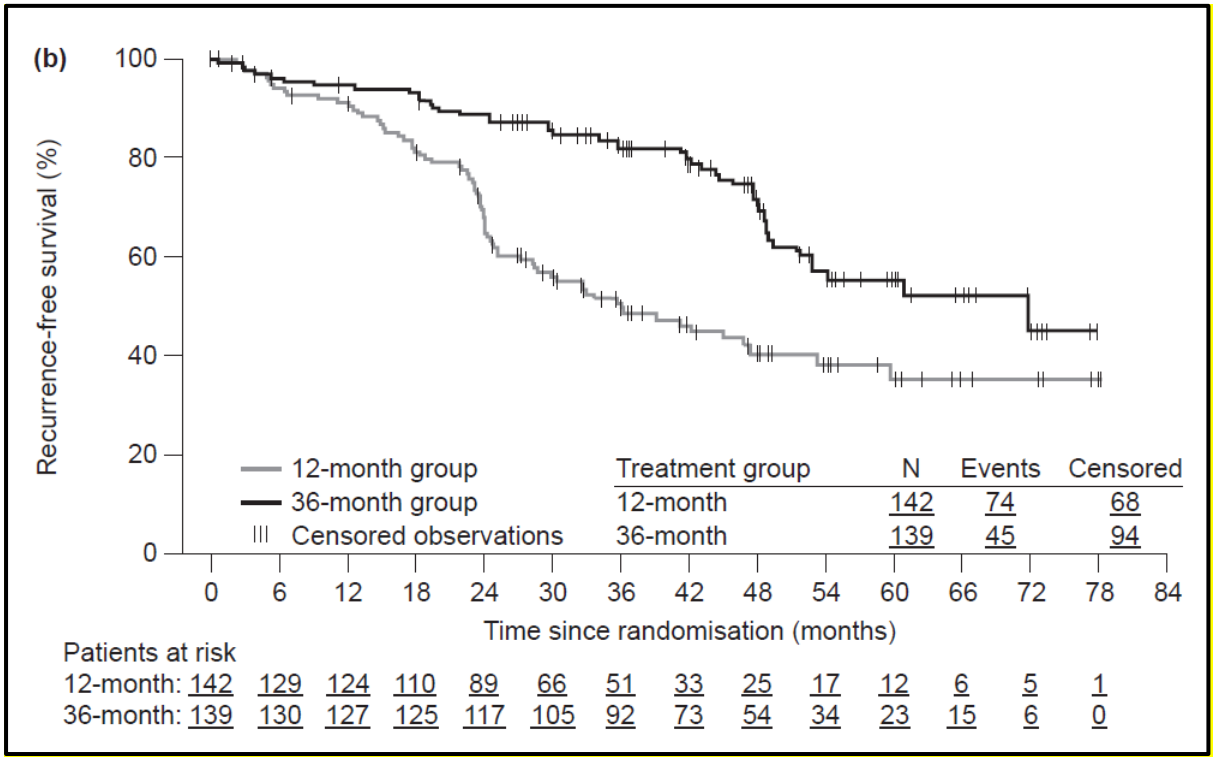
Continuing adjuvant imatinib therapy for 3 years significantly improved RFS compared with adjuvant imatinib therapy for 1 year

Kaplan–Meier plots for RFS are shown in Figure B-7. For the full population, RFS was statistically significantly longer in 3-year group than the 1-year group (HR 0.46; 95% CI 0.32 to 0.65; $p < 0.0001$; (Figure B-7a). A difference in RFS between treatment groups was evident from 18 months (1-year group, 86.8% versus 3-year group, 94.3%) and the 5-year RFS rates were 47.9% (1-year group) and 65.6% (3-year group). The median time to recurrence was 53.2 months for the 1-year group, but it was not reached for the 3-year group. Further analysis revealed there was no significant difference in the risk of recurrence or death between treatment groups during the first 1 year of treatment or after 3 years. However, a substantial difference was evident from 1 to 2 years (HR 0.26; 95% CI 0.13 to 0.53) and from 2 to 3 years (HR 0.17; 95% CI 0.07 to 0.39) after randomisation, thus providing further evidence that continuing imatinib therapy during the second and third year reduces the risk of recurrence during this period.

Similar results were reported for the Miettinen high-risk population (Figure B-7b). RFS was statistically significantly longer in the 3-year group compared with the 1-year group (HR 0.43; 95% CI 0.30 to 0.62; $p < 0.001$). Differences between treatment groups were evident at 18 months (1-year group, 81.6% versus 3-year group, 93.4%) and RFS rates at 4 years were 40.2% (1-year group) and 72.0% (3-year group). The median time to recurrence was 35.9 months in the 1-year group and 71.8 months in the 3-year group.

Figure B-7 Kaplan–Meier estimate of recurrence-free survival in (a) the full population and (b) the Miettinen high-risk population in the SSGXVIII/AIO study





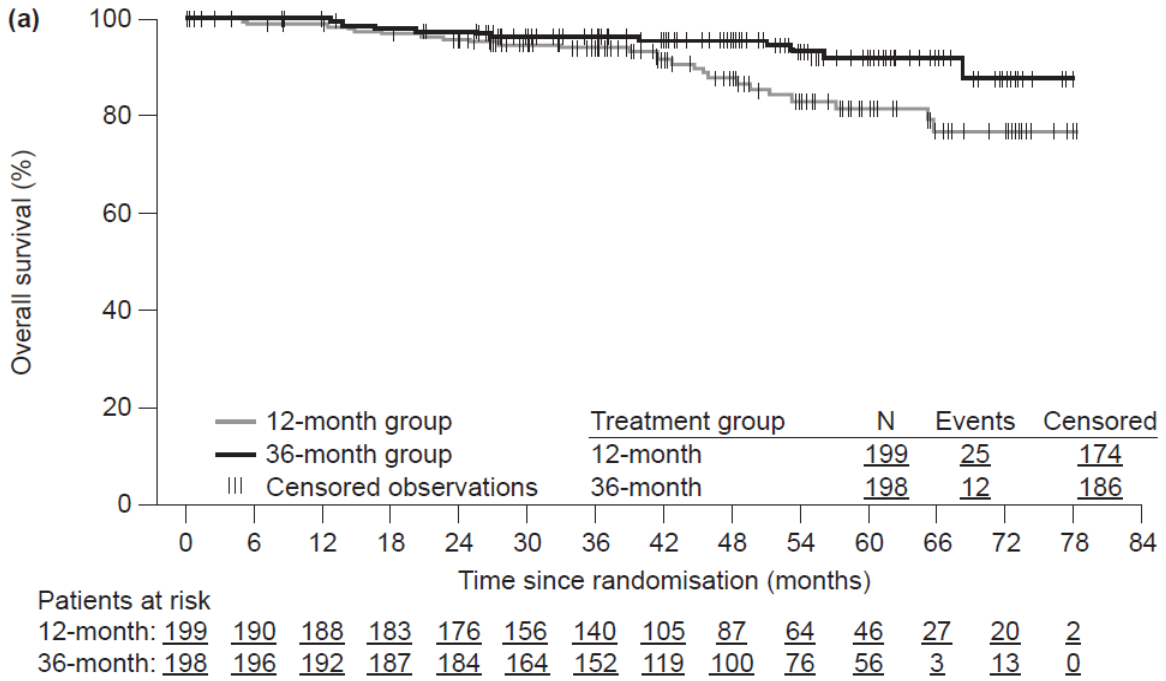
SSGXVIII/AIO, Scandinavian Sarcoma Group and the Sarcoma Group of the Arbeitsgemeinschaft Internistische Onkologie
Joensuu 2012;[10] SSGXVIII/AIO CSR.[9]

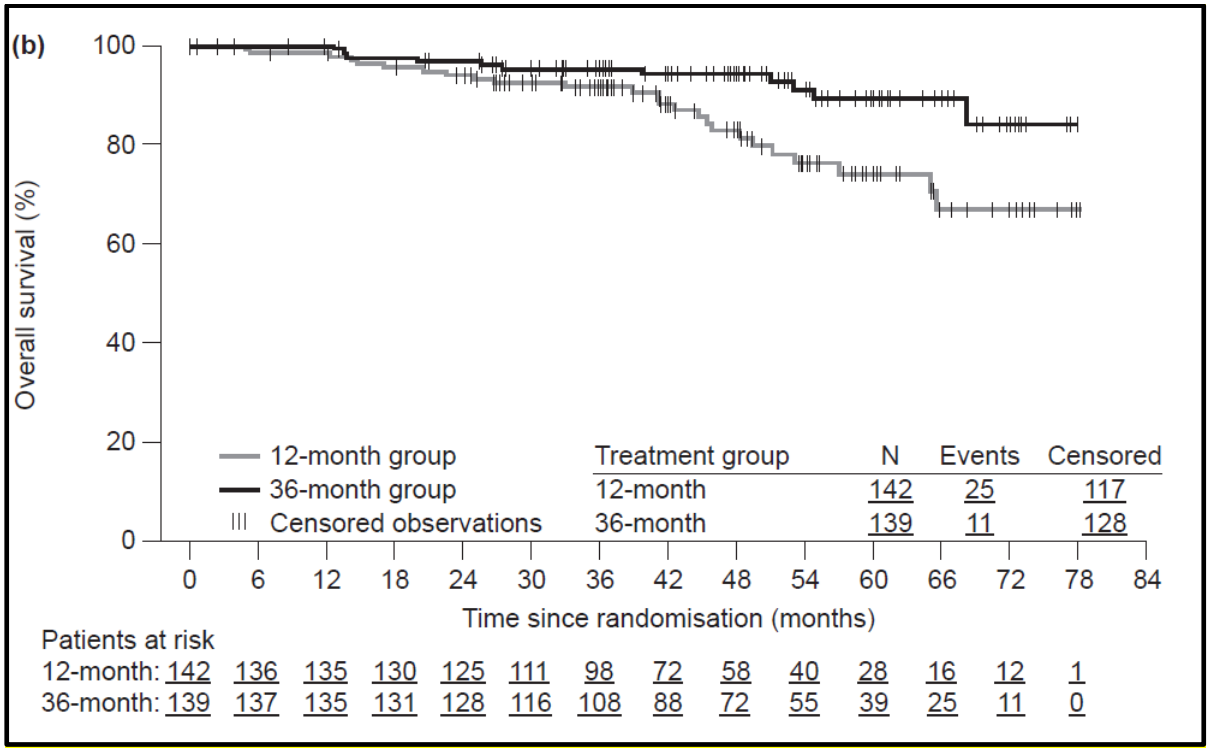
Five-year OS was statistically significantly longer in patients who received adjuvant imatinib therapy for 3 years rather than 1 year

During the study there were fewer deaths in the 3-year group than in the 1-year group (12 versus 25). Kaplan–Meier plots for OS for the full population and the Miettinen high-risk population are shown in Figure B-8. For the full population, OS was statistically significantly longer in the 3-year group than the 1-year group (HR 0.45; 95% CI 0.22 to 0.89; $p = 0.019$, Figure B-8a). The difference between treatment groups in OS was evident at 4 years (1-year group, 87.9%; 3-year group, 95.6%), and at 5 years (1-year group, 81.7%; 3-year group, 92.0%) . Median time to death was not reached for either group.

For the Miettinen high-risk population, OS was statistically significantly longer in the 3-year group compared with the 1-year group (HR 0.39; 95% CI 0.19 to 0.79; $p = 0.007$, Figure B-8b). The OS rate at 4 years was 83.0% (95% CI 73.8 to 89.1) for the 1-year group and 94.5% (95% CI 88.6 to 97.3) for the 3-year group, and at 5-year OS rates were 74.2% (1-year group) and 89.5% (3-year group). Median time to death was not reached for either group.

Figure B-8 Kaplan–Meier plot for overall survival in (a) the Full population and (b) the Miettinen high-risk population in the SSGXVIII/AIO study





SSGXVIII/AIO, Scandinavian Sarcoma Group and the Sarcoma Group of the Arbeitsgemeinschaft Internistische Onkologie

Joensuu et al. 2011;[56] SSGXVIII/AIO CSR.[9]

The EORTC 62024 trial

The objective of the randomised, phase 3, controlled, open-label EORTC 62024 trial was to assess the efficacy and safety of 2 years of imatinib as adjuvant therapy in patients having undergone resection for GIST and considered at intermediate or high risk of recurrence based on the NIH consensus criteria.[11]

The initial, planned primary endpoint was OS, with RFS as a secondary endpoint. However, owing to the prognostic improvement in patients observed in 2009, the study's independent data monitoring committee authorised that the primary endpoint be changed to 'imatinib failure-free survival' (IFS) – where 'failure' was defined as the time at which patients had to be changed to treatment with a different tyrosine kinase inhibitor (TKI) owing to disease relapse or recurrence. This is not a generally recognised endpoint and has not been used in other studies of adjuvant GIST.

The results of a planned interim analysis have been reported as a congress presentation but are only so far published as an abstract.[11] The congress-reported interim analysis was for a median follow-up is 4.5 years. A total of 908 patients were randomised to receive imatinib or no further treatment; 835 were eligible for assessment.

According to the interim analysis, adjuvant imatinib therapy significantly improved RFS in the total study population; 3-year RFS was 84% in the imatinib group compared with 66% in the observation group ($p < 0.001$). In the interim analysis, no significant differences between treatment groups were evident for IFS, either in the total study population (5-year IFS: imatinib 87%, observation 84%; HR 0.80; 98.5% CI 0.51 to 1.26; $p = 0.23$) or the subgroup of patients with high-risk disease (imatinib 77% versus observation 73%; $p = 0.44$). Conclusions regarding the effect of adjuvant therapy for 2 years on patient survival in the total population or in high-risk patients cannot be drawn as yet.

6.6 Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

6.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

6.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

Of the three RCTS, two have full data are available (ACOSOG and SSG) and have been used in the indirect comparison within the health-economic analysis. Insufficient data are available to allow the inclusion of the EORTC study.

6.6.3 If any of the relevant RCTs listed in response to section 6.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

6.7 Indirect and mixed treatment comparisons

Data from head–to–head RCTs should be presented in the reference-case analysis, if available. If data from head–to–head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

6.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.4, appendix 4.

An indirect comparison for 3 years of imatinib treatment versus no treatment was performed for the purpose of the economic model, using the two RCTs relevant to the decision problem - the ACOSOG Z9001 trial and the SSGXVIII/AIO study. However, the indirect comparison does not follow standard statistical method and was done for the purpose of populating the economic model only. Details of the indirect comparison are available in Section 7.3.1.

6.7.2 Please follow the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 10.5, appendix 5, a complete quality assessment for each comparator RCT identified.

Not applicable

6.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

Not applicable

6.7.4 For the selected trials, provide a summary of the data used in the analysis.

Not applicable

6.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

Not applicable

6.7.6 Please present the results of the analysis.

Not applicable

6.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

Not applicable

6.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

Not applicable

6.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

Not applicable

6.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

6.8.1 If non-RCT evidence is considered (see section 6.2.7), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.6 and 10.7, appendices 6 and 7.

The systematic literature review identified 12 non-RCTs that provide further evidence for the efficacy of adjuvant imatinib therapy in patients with GIST having undergone complete resection. Table B-16 provides a summary of the 12 non-RCTs and their findings. The reported data collectively support those of the RCTs and suggest that extended adjuvant therapy with imatinib confers improved RFS during long-term follow-up when compared with no treatment or historical controls.

Table B-16. Summary of results for relevant non-RCTs

Study	Study type: multicentre or single centre; country	Population	Interventions N recruited N analysed	Control N recruited N analysed	Duration of treatment and follow-up	Outcome(s)	Adverse effects/ HRQoL
Comparative studies							
Conley et al. 2012[19]	Retrospective/ observational Multicentre USA	Patients with primary resectable c-KIT (CD117)-positive GIST Risk category: high risk (system NR)	Short-term imatinib (6 months to 2 years) 246 patients	Long-term imatinib (2 years or longer) 395 patients	Short-term imatinib treated **Treatment:** Planned: 6 months to 1 year Actual: NR **Follow-up:** 884 days Long-term imatinib treated **Treatment:** Planned: 2 years or longer Actual: NR **Follow-up:** 963 days	Disease recurrence rates Short-term imatinib: 7.3% Long-term imatinib: 1.8% $p < 0.01$ Adjusted risk of recurrence (short- versus long-term) 4.77; 95% CI 1.98 to 11.48; $p < 0.01$ Mortality Short-term imatinib:	NR

Study	Study type: multicentre or single centre; country	Population	Interventions N recruited N analysed	Control N recruited N analysed	Duration of treatment and follow-up	Outcome(s)	Adverse effects/ HRQoL
						6.9% Long-term imatinib: 2.3% $p < 0.01$ Adjusted risk of mortality (short- versus long-term) 3.44; 95% CI 1.53 to 7.75; $p < 0.01$	
Hatoum et al. 2012[20]	Retrospective, population-based, matched cohort study USA	Patients with GIST who underwent surgery with or without adjuvant imatinib therapy identified from a claims database Risk category: NR	Imatinib 118 patients analysed 93 patients matched controls	No imatinib 4088 patients analysed 591 patients matched with imatinib	Imatinib treated **Treatment:** 270 days (median) **Follow-up**: 499 days (median) Non-imatinib treated **Follow-up**: 318 days	Treatment failure[a] (second surgery) Imatinib: 2% Control: 5% Time to treatment failure[a] Imatinib: 488 days	NR

Study	Study type: multicentre or single centre; country	Population	Interventions N recruited N analysed	Control N recruited N analysed	Duration of treatment and follow-up	Outcome(s)	Adverse effects/ HRQoL
					(median) *p* = 0.002	(median) Control: 290 days (median) *p* = 0.0005 <u>Time to treatment failure</u>[b] Imatinib: 433 days (median) Control: 320 days (median) *p* = 0.002 <u>Risk of treatment failure</u>[b] Imatinib: 40% Control: 52% *p* = 0.029 HR 0.501; 95% CI 0.34 to 0.74;	

Study	Study type: multicentre or single centre; country	Population	Interventions N recruited N analysed	Control N recruited N analysed	Duration of treatment and follow-up	Outcome(s)	Adverse effects/ HRQoL
						p < 0.001 Number needed to treat to prevent an additional negative outcome 4 (95% CI 3 to 7)	
Li et al. 2011[16]	Prospective (non-randomised) Single centre China	Patients with histopathologically diagnosed GIST who had undergone complete tumour resection for primary localised lesions Risk category: intermediate or high risk System: NIH	Imatinib 56 patients recruited 56 patients analysed 35 patients had high risk 21 patients had intermediate risk	No treatment 49 patients recruited 49 patients analysed 28 patients had high risk 21 patients had intermediate risk	Imatinib treated **Treatment:** Planned: 3 years Both groups **Follow-up:** 45 months (median)	Recurrence-free survival (imatinib versus control) 1 year: 100% versus 90%, *p* < 0.001 2 years: 96% versus 57%, *p* < 0.001 3 years: 89% versus 48%, *p* < 0.001 Recurrence-free survival	Patients with grade 3/4 AEs NR Common grade 3/4 AEs n (%) Granulocytopenia 3 (5), rash 2 (4) (Not reported for control group)

Study	Study type: multicentre or single centre; country	Population	Interventions N recruited N analysed	Control N recruited N analysed	Duration of treatment and follow-up	Outcome(s)	Adverse effects/ HRQoL
		consensus criteria				(intermediate risk versus control) 1 year: 100% versus 100% 2 years: 100% versus 78% 3 years: 95% versus 73% HR 0.138; 95% CI 0.017 to 1.147; *p* = 0.031 Recurrence-free survival (high risk versus control) 1 year: 100% versus 82% 2 years: 97% versus 43% 3 years: 85% versus 31% HR 0.159;	

Study	Study type: multicentre or single centre; country	Population	Interventions N recruited N analysed	Control N recruited N analysed	Duration of treatment and follow-up	Outcome(s)	Adverse effects/ HRQoL
						95% CI 0.066 to 0.381; *p* = 0.000 <u>Risk of recurrence (patients with intermediate or high risk)</u> HR 0.188; 95% CI 0.085 to 0.417; *p* < 0.001	
McCarter et al. 2012[22]	Review of data from ACOSOG studies Z9000 and Z9001 Multicentre USA	Patients who underwent resection of primary GIST in ACOSOG Z9000 and Z9001 Risk category: NR	Imatinib (1 year) 464 patients R0, n = 415 R1, n = 49	Placebo 353 patients R0, n = 330 R1, n = 23	<u>Imatinib treated</u> **Treatment:** 1 year <u>Both groups</u> **Follow-up:** 49 months (median)	<u>3-year recurrence-free survival (R1 versus R0)</u> Imatinib: 82% versus 79% HR 1.095; 95% CI 0.66 to 1.82; *p* = 0.73 Placebo: 60% versus	NR

Study	Study type: multicentre or single centre; country	Population	Interventions N recruited N analysed	Control N recruited N analysed	Duration of treatment and follow-up	Outcome(s)	Adverse effects/ HRQoL
						76% HR 1.51; 95% CI 0.76 to 2.99; *p* = 0.24 <u>Risk of recurrence (R1 versus R0)</u> Imatinib: 35% versus 27% Placebo: 39% versus 27%	
Nilsson et al. 2010[17]	Open-label Number of centres not stated Sweden	Patients with GIST Risk category: low/intermediate risk (n = 23) and high risk (n = NR, but presumably 84)	Imatinib 107 patients included 45 patients with R0 resection analysed (adjuvant) 10 patients' organ preservation	Historical control 259 patients	<u>Imatinib treated</u> **Treatment:** NR	<u>5-year recurrence-free survival (imatinib versus historic controls)</u> Adjuvant: 85% versus 35% *p* < 0.001	NR

Study	Study type: multicentre or single centre; country	Population	Interventions N recruited N analysed	Control N recruited N analysed	Duration of treatment and follow-up	Outcome(s)	Adverse effects/ HRQoL
			analysed (neoadjuvant) 28 patients with R2 resection analysed (palliative) 23 patients with low/ intermediate risk underwent surgery only			5-year PFS (imatinib versus historic controls Neoadjuvant: 100% versus 30% $p < 0.001$ 5-year Overall survival (imatinib versus historic controls) Palliative: 55% versus 5% $p < 0.001$	
Gong et al. 2009[14]	Prospective non-randomised Single-centre China	Patients with GIST who had undergone complete tumour resection and with an	Imatinib 56 patients	No treatment 49 patients	Imatinib treated **Treatment:** Planned: 3 years Actual: 20 months median	Recurrence-free survival (imatinib versus surgery controls) 1 year: 100% versus	NR

Study	Study type: multicentre or single centre; country	Population	Interventions N recruited N analysed	Control N recruited N analysed	Duration of treatment and follow-up	Outcome(s)	Adverse effects/ HRQoL
		intermediate or high risk of recurrence			(1 to 3 years) **Follow-up**: 30 months median (12 to 62 months)	89.8% p < 0.001 2 years: 94.4% versus 60.0% *p* < 0.001 HR 0.13; 95% CI 0.039 to 0.438; *p* = 0.001 <u>2-year recurrence-free survival in high-risk patients (imatinib versus controls)</u> 91.5% versus 46.2% *p* < 0.001 HR 0.107; 95% CI 0.031 to	

Study	Study type: multicentre or single centre; country	Population	Interventions N recruited N analysed	Control N recruited N analysed	Duration of treatment and follow-up	Outcome(s)	Adverse effects/ HRQoL
						0.370; $p < 0.001$	
Wu et al. 2012[24]	Retrospective analysis Single-centre China	Patients who underwent surgical treatment for GISTs (complete or palliative resection, or exploratory surgery with biopsy)	Imatinib 75 patients received adjuvant imatinib therapy	No imatinib 178 patients	Imatinib treated **Follow-up:** 7 years	5-year survival rate according to use of imatinib chemotherapy Adjuvant: 75.1% None: 13.8%* *$p < 0.001$ versus adjuvant group	NR
Jiang et al. 2011[15]	Prospective (non-randomised case–control) Single-centre China	Consecutive patients with c-KIT (CD117)-positive high-risk GIST with R0 resection Risk category: High risk (n = 90)	Imatinib 35 patients	No imatinib 55 patients	Imatinib treated **Treatment**: 33.8 months (median) Continuous treatment (n = 24) 36.7 months Interrupted treatment: (n = 11) 17.1 months $p = 0.000$	Recurrence-free survival (imatinib versus surgery only) Year 1: 100% versus 70.9% Year 2: 88.0% versus 37.8%	Common grade 3/4 AEs n (%) Leukopenia 3 (8.6), anaemia 2 (5.7), thrombocytopenia 1 (2.9), oedema 3 (8.6), fatigue 3 (8.6), nausea 1 (2.9), diarrhoea 1 (2.9), vomiting 1 (2.9),

Study	Study type: multicentre or single centre; country	Population	Interventions N recruited N analysed	Control N recruited N analysed	Duration of treatment and follow-up	Outcome(s)	Adverse effects/ HRQoL
		System: NIH modified classification (Joensuu 2008)[57]			Both groups **Follow-up**: 44 months (median)	Year 3: 88.0% versus 27.5% HR, 0.122; 95% CI 0.041 to 0.363; *p* = 0.000 Recurrence-free survival (subgroup of continuous versus intermittent imatinib use) Year 1: 100% versus 100% Year 2: 95.8% versus 63.6% Year 3: 95.8% versus 63.6% Years 2 and	rash 1 (2.9) (Not reported for controls)

Study	Study type: multicentre or single centre; country	Population	Interventions N recruited N analysed	Control N recruited N analysed	Duration of treatment and follow-up	Outcome(s)	Adverse effects/ HRQoL
						3: HR 0.103; 95% CI 0.012 to 0.883; *p* = 0.011	
Non-comparative studies							
Kanda et al. 2013[21]	Prospective open-label Multicentre Japan	Primary high-risk GIST expressing the c-KIT protein (CD117) having undergone complete resection Risk category: high risk (64) System: NIH consensus criteria	Imatinib 64 patients	None	Imatinib treated **Treatment:** 48 weeks or confirmation of tumour recurrence **Follow-up:** 3 years	1-year recurrence-free survival % (95% CI) 94.7 (88.9 to 100) 2-year recurrence-free survival % (95% CI) 71.1 (58.5 to 83.7) 3-year recurrence-free survival % (95% CI) 57.3 (43.7 to 70.8)	Patients with grade 3/4 AEs n (%) 22 (34.4) Common grade 3/4 AEs n (%) Neutropenia 9 (14.1), leukopenia 3 (4.7), lymphopenia 2 (3.1), rash 2 (3.1)
Kang et	Prospective	Patients with	Imatinib	None	Imatinib treated	Recurrence-	Patients with

Study	Study type: multicentre or single centre; country	Population	Interventions N recruited N analysed	Control N recruited N analysed	Duration of treatment and follow-up	Outcome(s)	Adverse effects/ HRQoL
al. 2013[18]	open-label Multicentre South Korea	complete resection of primary GIST with 1) c-KIT exon 11 mutation and 2) at least 10 mitoses/50 HPF or tumour size at least 10 cm, or 5 to 10 mitoses/50 HPF and tumour size 5 cm to 10 cm Risk category: high risk (100%) System: NIH consensus criteria plus c-*KIT* exon 11 mutations	47 patients		**Treatment:** 2 years unless evidence of disease recurrence or unacceptable toxicity **Follow-up:** Until disease recurrence 56.7 months median	free survival 58.9 months (median) Recurrence-free survival 1 year: 97.9% 2 years: 93.6% 3 years: 78.7% 4 years: 62.1% 5 years: 46.0% Median overall survival Not reached	grade 3/4 AEs NR Common grade 3/4 AEs n (%) Neutropenia 13 (27.7), dermatitis 4 (8.5), leukopenia 4 (8.5), anaemia 2 (4.3), anorexia 2 (4.3), ALT increased 2 (4.3)
Nishida et al. 2009[23]	Prospective open-label	Patients with a diagnosis of	Imatinib 64 patients	None	Imatinib treated **Treatment:**	3-year relapse-free	Patients with grade 3/4 AEs, n

Study	Study type: multicentre or single centre; country	Population	Interventions N recruited N analysed	Control N recruited N analysed	Duration of treatment and follow-up	Outcome(s)	Adverse effects/ HRQoL
	Multicentre Japan	histologically proven primary high-risk GIST who underwent macroscopically complete resection Risk category: high risk System: NIH consensus criteria			1 year (n = 49; 77%) **Follow-up:** Median 109 weeks (range, 0 to 150 weeks)	survival 59% 3-year OS 87%	(%) 19 (30%) Common grade 3/4 AEs, % Neutropenia 13%, hypophosphataemia 6%, rash 3%
Yalcin et al. 2012[25]	Prospective open-label Multicentre Asia Pacific, Africa, Russia, Middle East, Europe	Patients who had complete gross resection of primary GIST and were CD117 positive Risk category: intermediate/ high risk	Imatinib 127 patients	None	Imatinib treated **Treatment** Planned: 2 years Analysis at follow-up of 1 year	1-year recurrence-free survival rate 0.95 (mean); 95% CI 0.907 to 0.993	NR

[a]Second GIST-related surgery
[b]Treatment failure composite outcome of incidence of a second GIST-related surgery and loss to follow-up between the matched

Study	Study type: multicentre or single centre; country	Population	Interventions N recruited N analysed	Control N recruited N analysed	Duration of treatment and follow-up	Outcome(s)	Adverse effects/ HRQoL
cohorts ACOSOG, American College of Surgeons Oncology Group; AE, adverse event; ALT, alanine aminotransferase; CI, confidence interval; GIST, gastrointestinal stromal tumour; HPF, high power field; HR, hazard ratio; HRQoL, health-related quality of life; NIH, National Institutes of Health; NR, not reported; OS, overall survival; PFS, progression-free survival; R0, complete resection; R1, microscopic residual tumour suspected Hatoum et al. 2012;[20] Li et al. 2011;[16] Conley et al. 2012;[19] McCarter et al. 2012;[22] Nilsson et al. 2010;[17] Gong et al. 2009;[14] Jiang et al. 2011;[15] Wu et al. 2012;[24] Kanda et al. 2013;[21] Kang et al. 2013;[18] Nishida et al. 2009;[23] Yalcin et al. 2012;[25] Joensuu et al. 2008.[57]							

Non-RCT evidence supports that in high-risk groups, adjuvant imatinib therapy for 3 years improves RFS compared with no treatment

Three prospective, non-RCTs reported RFS rates for adjuvant imatinib therapy planned for periods of 3 years or around 3 years – two studies assessed 3 years of therapy[14,16] and one assessed adjuvant therapy given for a median of 44 months.[15] All studies compared outcomes with those for patients who received no adjuvant therapy. All three of these studies reported statistically significant improvements in 2-year or 3-year RFS with adjuvant imatinib therapy compared with no further treatment post-surgery. For example, in a study involving 105 Chinese patients with intermediate or high risk of GIST recurrence (by Fletcher 2002 criteria), 3 years of adjuvant therapy was superior to no treatment in terms of 3-year RFS (89% versus 48%; $p < 0.001$).[16] The OS was significantly higher ($p = 0.025$) in the imatinib group than in the no treatment group. The risk of death was significantly reduced in patients of intermediate or high risk who received adjuvant imatinib compared with no treatment (HR 0.254; 95% CI 0.070 to 0.931; $p = 0.025$). A subgroup analysis of patients at high risk of recurrence also showed higher RFS rates in imatinib-treated patients compared with no treatment controls at 1 year (100% versus 82%), 2 years (97% versus 43%) and 3 years (85% versus 31%). Adjuvant imatinib therapy led to a statistically significant reduction in the risk of GIST recurrence in these patients (HR 0.159; 95% CI 0.066 to 0.381; $p = 0.000$).

Imatinib improves RFS compared with control outcome data

Two studies compared outcomes for adjuvant imatinib therapy with historical control data. One study found significant improvements in 5-year RFS patients at high risk of recurrence (criteria not stated), in patients given adjuvant imatinib therapy (85%) compared with historical controls (35%; $p < 0.001$).[17]

Another study compared outcomes in 47 patients receiving adjuvant imatinib therapy for 2 years after resection, with historical control data. This was an open-label, non-randomised, phase 2 study involving patients at high risk of recurrence.[18] Patients were followed up for a median of 56.7 months (range: 46.7 to 74.7 months). The median RFS was 58.9 months, whereas median OS had not been reached. The RFS rates were 97.9% (1 year), 93.6% (2 years), 78.7% (3 years), 62.1% (4 years) and 46.0% (5 years). The authors noted that the reported RFS rates were markedly higher than historical controls from their previous study of patients with matched risk of recurrence but who did not receive adjuvant imatinib therapy. In the latter case, the median RFS was 22.7 months ($p < 0.0001$).

In a retrospective analysis of a claims database which compared the outcomes for patients receiving imatinib to those for matched controls that did not receive imatinib, it was shown that 2% of imatinib patients required surgery for treatment failure, compared with 5% of

patients in the control group and further, that adjuvant imatinib significantly extended the time to treatment failure.[20]

Seven-year follow-up data highlight that 5-year RFS is significantly improved with adjuvant imatinib therapy compared with no treatment

A retrospective study reported a statistically significant increase in 5-year RFS for adjuvant imatinib (75%) compared with no adjuvant therapy (14%; $p < 0.001$).[24] Although the duration of treatment and patient risk of recurrence category were not specified, this study found that prognostic factors for improved survival included complete resection ($p = 0.042$), primary tumour location (gastric tumour was associated with improved survival; $p = 0.037$), epithelial/spindle cell type ($p = 0.005$), absence of surrounding tissue invasion ($p = 0.027$), absence of cystic change ($p < 0.001$), low mitotic count (under 5 mitoses/50 HPF; $p < 0.001$), small tumour diameter ($p < 0.001$), early stage ($p < 0.001$), low potential malignant risk ($p = 0.001$) and extended resection ($p = 0.001$).

Adjuvant imatinib therapy for 1 year appears efficacious in high-risk patients in non-RCTs

A single-arm, open-label study of patients at histologically-proven, high risk of recurrence assessed RFS in patients given adjuvant imatinib therapy for 1 year.[21] The RFS at 1 year was 94.7% (95% CI 88.9% to 100%), at 2 years was 71.1% (95% CI 58.5% to 83.7%) and at 3 years was 57.3% (95% CI 43.7% to 70.8%).

Adjuvant imatinib therapy for at least 2 years in high-risk patients significantly reduced mortality and the risk of recurrence compared with adjuvant imatinib therapy given for shorter periods of 6 months to 2 years

Data from a US retrospective analysis of 246 patients receiving adjuvant imatinib therapy for 6 months to 2 years and 395 patients who received adjuvant imatinib therapy for more than 2 years confirm the benefits of prolonged adjuvant therapy with this TKI. The study reported a significant difference in disease recurrence between the two groups, with 1.8% recurrence in patients receiving adjuvant imatinib therapy for at least 2 years compared with a 7.3% recurrence rate in patients receiving adjuvant imatinib therapy for less than 2 years ($p < 0.01$).[19]

In this same retrospective analysis, a statistically significant decrease in mortality was reported (2.3% versus 6.9%, respectively for less than 2 years versus more than 2 years; $p < 0.01$). The adjusted risk of recurrence was 4.77 times higher (95% CI 1.98 to 11.48; $p < 0.01$) and the risk of mortality was 3.44 times higher (95% CI 1.53 to 7.75; $p < 0.01$) in

patients who received imatinib for less than 2 years compared with those who received imatinib for at least 2 years.

In high-risk patients, continuous adjuvant imatinib therapy for 3 years resulted in significantly improved RFS compared with intermittent therapy

Data from a single-centre experience in 90 patients provide some further insights into outcomes in high-risk patients (defined according to modified NIH criteria[57]).[15] A total of 24 patients received continuous adjuvant imatinib therapy for a median duration of 36.7 months (range 1 to 5 years) while 11 patients had interrupted treatment for a median duration of 17.1 months (range 3 months to 3 years). A statistically significant improvement in 3-year RFS was reported for patients at high risk of recurrence who received continuous adjuvant imatinib therapy (96%) compared with patients who received intermittent adjuvant imatinib therapy (64%). For patients with continuous versus intermittent adjuvant imatinib, the HR was 0.103 (95% CI 0.012 to 0.883; $p = 0.011$). The incidence of tumour recurrence was lower in patients who had received continuous adjuvant imatinib therapy (1/24 patients, 4.2%) compared with patients with interrupted adjuvant imatinib therapy (5/11 patients, 45.5%; $p = 0.002$).

6.9 Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

6.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.8 and 10.9, appendices 8 and 9.

No trials were identified which specifically assessed safety.

6.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

Table B-17. Adverse events across randomised groups

System organ/ class/adverse events	Time period 1			Time period 2 etc.		
	Intervention % of patients (n = x)	Comparator % of patients (n = x)	Relative risk (95% CI)	Intervention % of patients (n = x)	Comparator % of patients (n = x)	Relative risk (95% CI)
Class 1 (for example, nervous system disorders)						
Adverse event 1						
Adverse event 2						
Class 2 (for example, vascular disorders)						
Adverse event 3						
Adverse event 4						
CI, confidence interval Adapted from European Public Assessment Reports published by the European Medicines Agency						

6.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

There are no studies comparing imatinib with other therapies as adjuvant treatment after primary resection of GIST.

The safety profile of imatinib is well known given its indications and use in oncology. Safety data from the RCTs and non-RCTs that compare adjuvant imatinib therapy with placebo, or no treatment, provided reassurance that adjuvant imatinib therapy for up to 3 years was well tolerated in patients with GIST, including those patients defined as at high risk of recurrence. Safety data from the RCTs and non-RCTs are summarised in
Table B-18, Table B-19, and Table B-20 respectively.

RCT safety data

Data from the ACOSOG Z9001 RCT showed that adjuvant imatinib therapy for 1 year was well tolerated.[8] The incidence of AEs by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE; version 3.0) is shown in
Table B-18. Grade 3 or 4 AEs occurred in 63 patients (18%) in the placebo group and 104 patients (31%) in the imatinib group.

Table B-18. Incidence of adverse events by NCI-CTCAE grade in the ACOSOG Z9001 study[8]

NCI-CTCAE grade	Placebo (n = 345)	Imatinib (n = 337)
Grade 1	101 (29%)	81 (24%)
Grade 2	150 (43%)	148 (44%)
Grade 3	56 (16%)	86 (26%)
Grade 4	7 (2%)	15 (4%)
Grade 5	0	3 (1%)
ACOSOG, American College of Surgeons Oncology Group; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events DeMatteo et al. 2009.[8]		

The most common grade 3/4 events (imatinib versus placebo) were neutropenia (3% versus 1%), abdominal pain (3.6% versus 1.7%), dermatitis (3 % versus 0), nausea (2.4% versus 1.2%) and elevated alanine aminotransferase levels (2.7% versus 0). [8] The AE rate was low and was consistent with imatinib use in chronic myelogenous leukaemia and metastatic GIST.[8]

Three years of adjuvant imatinib had a safety profile similar to 1 year of adjuvant imatinib therapy

In the SSGVXIII/AIO study comparing 3 years of adjuvant imatinib and 1 year of adjuvant imatinib therapy at a dose of 400 mg/day, the safety profile was similar for the extended therapy and the 1-year therapy.[8] The most frequently recorded AEs are summarised in the Table B-19

Table B-19. Most frequently recorded AEs in the SGVXIII/AIO study[10]

Events	Imatinib 1 year (n = 194)	Imatinib 3 years (n = 198)	*p*-value
Any event	192 (99.0)	198 (100)	0.24
Haematological			
Anaemia	140 (72.2)	159 (80.3)	0.08
Leukopenia	67 (34.5)	93 (47.0)	0.01
Non-haematological			
Periorbital oedema	115 (59.3)	147 (74.2)	0.002
Fatigue	94 (48.5)	96 (48.5)	> 0.99
Nausea	87 (44.8)	101 (51.0)	0.23
Diarrhoea	85 (43.8)	107 (54.0)	0.04
Muscle cramps	60 (30.9)	97 (49.0)	< 0.001
Leg oedema	64 (33.0)	81 (40.9)	0.12
Biochemical			
Elevated blood lactate dehydrogenase	84 (43.3)	119 (60.1)	0.001
Elevated serum creatinine	59 (30.4)	88 (44.4)	0.005

AE, adverse event; SGVXIII/AIO, Scandinavian Sarcoma Group and the Sarcoma Group of the Arbeitsgemeinschaft Internistische Onkologie
Joensuu et al. 2012.[10]

The incidence of AEs was similar in patients administered adjuvant imatinib for 3 years (198/198, 100%) and for 1 year (192/194, 99.0%). Although the frequency of individual AEs was higher in the 3-year group than in the 1-year group, the increase was less than twofold in all cases, and therefore not proportional to the increased duration of treatment.

The incidence of grade 3 or 4 events was 20.1% in the adjuvant imatinib 1-year group and 32.8% in the 3-year group (Table B-20). The most common grade 3 or 4 AES were leukopenia and diarrhoea.[10]

Table B-20 Incidence of most common grade 3 or 4 AEs in the SGVXIII/AIO study[10]

Events	Imatinib 1 year (n = 194)	Imatinib 3 year (n = 198)	*p*-value
Any event	39 (20.1)	65 (32.8)	0.006
Haematological			
Anaemia	1 (0.5)	1 (0.5)	> 0.99
Leukopenia	4 (2.1)	6 (3.0)	0.75
Non-haematological			
Periorbital oedema	1 (0.5)	2 (1.0)	> 0.99
Fatigue	2 (1.0)	1 (0.5)	0.62
Nausea	3 (1.5)	1 (0.5)	0.37
Diarrhoea	1 (0.5)	4 (2.0)	0.37
Muscle cramps	1 (0.5)	2 (1.0)	> 0.99
Leg oedema	1 (0.5)	2 (1.0)	> 0.99
Biochemical			
Elevated blood lactate dehydrogenase	0	0	
Elevated serum creatinine	0	0	

AE, adverse event; SGVXIII/AIO, Scandinavian Sarcoma Group and the Sarcoma Group of the Arbeitsgemeinschaft Internistische Onkologie
Joensuu et al. 2012.[10]

More patients in the 3-year group (51 patients, 25.8%) discontinued imatinib[10] than in the 1-year group (25 patients, 12.9%) owing to AEs (27 versus 15 patients), patient preference (11 versus 0 patients), tumour histology not GIST (6 versus 6 patients) and reasons unspecified (7 versus 4 patients).

Cardiac AEs were reported in 8 patients (4.1%) in the 1-year group and 4 (2.0%) in the 3-year group.[10] Secondary cancer was diagnosed in 14 patients (7.2%) in the 1-year group and 13 (6.6%) in the 3-year group.

No safety data have been reported from the EORTC study to date.

Non-RCTs

Safety findings were reported for five of the non-RCTs, as summarised in Table B-18.

Among the non-RCTs that reported on extended use of adjuvant therapy for periods of around 3 years, the safety findings also suggest that imatinib was generally well tolerated.

For example, in a single-centre, prospective study, 44-month follow-up safety data have been reported for patients at intermediate or high risk of recurrence who received adjuvant imatinib

for 3 years compared with those who received no adjuvant treatment.[15] The most common grade 3 or 4 AEs in patients who received adjuvant imatinib were leukopenia (8.6%), oedema (8.6%) and anaemia (5.7%). Other grade 3 or 4 AEs occurred in fewer than 5% of patients who received adjuvant imatinib. Most AEs were grade 1 or 2 and severe AEs were uncommon.

In another study where adjuvant imatinib was administered for 2 years,[18] treatment was reported to be well tolerated in patients at high risk of recurrence. The most commonly reported AE was oedema (89.3% all grades), which was generally mild (78.7%) to moderate (10.6%) in intensity and easily managed by dose modification or standard supportive treatment. Grade 3 or 4 haematological toxicities related to imatinib were neutropenia (27.7%), leukopenia (8.5%) and anaemia (4.3%). Grade 3 or 4 non-haematological toxicities were skin rash (8.5%), anorexia (4.3%), constipation (2.1%) and diarrhoea (2.1%). Grade 3 increases in serum alanine aminotransferase (4.3%) and aspartate aminotransferase (2.1%) levels were observed, but such increases were reversible. No episodes of febrile neutropenia occurred and there were no instances of treatment-related mortality.

The studies reviewed demonstrated that adjuvant imatinib therapy was well tolerated in patients treated following GIST resection and at high risk of recurrence. Most AEs were grade 1 or 2 and generally manageable, with a low incidence of grade 3 or 4 AEs. The safety profile of adjuvant imatinib given for 3 years was consistent with the safety profile of 1-year adjuvant imatinib. The safety data on extended imatinib therapy provide reassurance that this adjuvant treatment may be administered for periods of 3 years after GIST resection without any undue increase in toxicities.

Table B-21 Overview of safety data from relevant RCTs assessing imatinib therapy in the adjuvant setting of GIST

Ref	Study type	No. patients	Treatment regimens	Key safety data
DeMatteo et al. 2009,[8] Corless et al. 2010[54]	The ACOSOG Z9001 study: randomised, phase 3, double-blind, placebo-controlled, multicentre trial (230 institutions); duration of study 57 months (median duration of follow-up 19.7 months)	713	Imatinib 400 mg/day for 1 year (n = 359) or placebo for 1 year (n = 354)	Patients with a grade 3/4 AEs Imatinib: 104 (31%) Placebo: 63 (18%) Common grade 3/4 AEs (imatinib versus placebo) Neutropenia (3.6%/1.2%), abdominal pain (3.6%/1.7%), nausea (2.4%/1.2%), diarrhoea (3.0%/1.4%), elevated ALT (2.7%/0%)

Joensuu et al. 2012[10]	The SSGXVIII/AIO study: randomised, phase 3, prospective, open-label, multicentre (24 institutions); duration of study 82 months (median duration of follow-up 54 months)	397	Imatinib 400 mg/day for 1 year (n = 199) or imatinib 400 mg/day for 3 years (n = 198)	Patients with a grade 3/4 AE 3-year imatinib: 32.8% 1-year imatinib: 20.1% Common grade 3/4 AEs: leukopenia (3.0%/2.1%), diarrhoea (2.0%/0.5%)
Casali et al. 2013[11]	The EORTC 62024 study: randomised, phase 3, controlled (no other post-surgical treatment) observational open-label; duration of study 2 years (median duration of follow-up 4.7 years)	908	Imatinib 400 mg/day for 2 years (n = 454) versus no other therapy after surgery/observation (n = 454)	NR

ACOSOG, American College of Surgeons Oncology Group; AE, adverse event; ALT, alanine aminotransferase; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; NR, not reported; SSGXVIII/AIO, Scandinavian Sarcoma Group and the Sarcoma Group of the Arbeitsgemeinschaft Internistische Onkologie
DeMatteo et al. 2009;[8] Joensuu et al. 2012;[10] Corless et al. 2010;[54] Casali et al. 2013.[11]

6.10 Interpretation of clinical evidence

6.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

The results of the two RCTs with complete outcomes consistently demonstrate an improvement in RFS for adjuvant imatinib therapy in patients at high risk of recurrence and these data are supported by preliminary results from another RCT and the results reported for the non-RCTs.[8-25] Furthermore, the RCT comparing 3 years of adjuvant imatinib therapy to 1 year of adjuvant imatinib therapy observed an OS advantage for high-risk patients given the longer-term therapy.[10]

At a median follow-up of 19.7 months, the ACOSOG Z9001 study demonstrated a statistically significant improvement in RFS for patients receiving adjuvant imatinib therapy for 1 year versus no treatment. The benefit was evident as early as 6 months from randomisation and peaked at 18 months (1-year RFS: imatinib, 98%; placebo, 83%). [8] Thereafter, the difference between treatment groups decreased but a difference in favour of adjuvant therapy over placebo remained for up to 7 years in an analysis performed at a median follow-up of 46.3 months (HR 0.718, 95% CI 0.531 to 0.971; $p = 0.0305$).[13]

A *post hoc* analysis of RFS for patients with high-risk disease according to the Miettinen 2006 criteria also revealed a statistically significant benefit for adjuvant therapy and the difference between treatment groups was more marked than for the total population (primary analysis 1-year RFS: imatinib, 98.7%, placebo, 56.1%; HR:0.265, 95% CI 0.148 to 0.477, $p < 0.0001$. 5-year follow-up analysis: HR 0.608, 95% CI 0.417 to 0.886; $p = 0.009$).[13]

In the SSGXVIII/AIO study, continuing therapy for 3 years significantly improved RFS compared with 1 year of therapy: 5-year RFS was 47.9% for the 1-year group compared with 65.6% for the 3-year group (HR 0.46, 95% CI 0.32 to 0.65; $p < 0.0001$). The difference in risk of recurrence between groups was particularly marked during the second and third years, reflecting the benefits of more prolonged therapy.

Similar results were evident for the subgroup of patientsin the SSG trial with high-risk disease according to the Miettinen 2006 criteria where the RFS was longer in the 3-year group than in the 1-year group (HR 0.43, 95% CI 0.30 to 0.62; $p < 0.0001$). RFS rates at 4 years were 40.2% (1-year group) and 72.0% (3-year group).[9]

Improvements in RFS following adjuvant imatinib therapy were also evident from an interim analysis of the EORTC 62024 study performed at a median follow-up of 4.7 years. There was a statistically significant improvement in 3-year RFS, in both the total study population (imatinib, 69%; observation, 63%; $p < 0.001$) and in a subgroup with high-risk disease according to the NIH consensus criteria.[11] Furthermore, non-RCTs have reported that treatment with adjuvant imatinib for periods of 2 to 3 years is associated with 3- and 5-year RFS rates of between 80% and 89% in patients deemed to be at high risk of disease recurrence.[16-18]

The improvement in RFS associated with adjuvant imatinib therapy would be expected to translate into improvements in patients' HRQoL, since periods that are recurrence-free are likely to be associated with better HRQoL than recurrence of GIST or its advance to metastatic disease.

The available clinical evidence also includes reports that longer-term adjuvant imatinib therapy can confer OS benefits. In the SSGVIII/AIO study, a statistically significant improvement in OS was observed for 3 years of adjuvant imatinib compared with 1 year of therapy, both in the total study population (HR 0.45, 95% CI 0.22 to 0.89; $p = 0.019$; 5 years OS 81.7% in the 1-year group and 92.0% in the 3-year group) and in the Miettinen high-risk subgroup (HR 0.39, 95% CI 0.19 to 0.79; $p = 0.007$; 5 years OS 74.2% in the 1-year group and 89.5% in the 3-year group).[9,10] In the ACOSOG Z9001 study, the difference in OS was not statistically significant for either the primary analysis or 5-year follow-up. For the primary analysis, this reflects the low number of events and the fact that follow-up was too short. For the 5-year follow-up, the data are confounded by the high degree of crossover to active treatment by recurrence-free placebo patients when the study was unblinded.[8,13]Non-RCT evidence also suggests that the RFS benefits of long-term adjuvant therapy in high-risk groups can be associated with survival benefits, with 2 to 3 years of adjuvant therapy for example, reported to significantly extend survival compared with no therapy.[16,19] The preliminary results reported from the EORTC 62024 study of 2 years of adjuvant therapy versus no adjuvant therapy do not allow any clear conclusions on the impact of treatment on OS in high-risk patient groups.[11]

The observation of OS benefits from adjuvant imatinib therapy is of particular note, and appears to indicate that extending the time patients remain recurrence-free confers survival benefits extending for periods of 5 years and longer from the time of their primary GIST resection. The OS benefits may reflect not only the efficacy of adjuvant imatinib therapy in reducing the risks of local disease recurrence but also the potential benefits to patients of receiving a therapy, long-term, which serves to slow or suppress disease progression. The notion that continued therapeutic suppression of tyrosine kinase in GIST can slow, although not halt, disease progression has emerged from the observation that even in patients with

disease that appears refractory to all standard TKIs (patients with metastatic disease in whom earlier lines of treatment, including imatinib, have failed), the re-challenge of patients with TKI-based therapy can confer progression-free survival benefits, possibly because there remain malignant clones that are still sensitive to these agents.[58] The continued responsiveness to agents such as imatinib is also important for patients with GIST who have received this treatment in adjuvant settings. This is because, in the event of disease progression either during adjuvant therapy or following cessation of adjuvant therapy, the recommended next therapeutic manoeuvre is to consider use of an imatinib regimen for management of unresectable or metastatic disease.[1,6] In fact, follow-up data from both the ACOSOG Z9001 study and SSGVIII/AIO study have demonstrated that patients who are re-challenged with imatinib following recurrence post-adjuvant treatment do respond, and in similar fashion to those who have not received adjuvant treatment.[59,60]

Across the RCTs and non-RCTs assessing adjuvant imatinib therapy, it has been observed that long-term daily treatment with 400 mg/day is well tolerated, with no notable increase in AEs during 3 years of treatment when compared with 1 year of treatment. This suggests that the risk–benefit profile of adjuvant therapy is favourable and that patient HRQoL is unlikely to be negatively impacted by the tolerability profile of treatment.

6.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

The available RCT data have a number of strengths. The two key RCTs have assessed robust study endpoints and provide long-term outcome and follow-up data on the efficacy and safety of adjuvant imatinib therapy following primary resection of localised GIST. Both studies were multicentre trials that included a large number of patients in each treatment arm, and each of the RCTs evaluated the adjuvant imatinib regimen corresponding to the product label and licence. The availability of patient-level data has enabled an analysis of outcomes according to currently accepted definitions and categories of risk (Miettinen). This has ensured that the clinical and health economic outcomes presented reflect the use of adjuvant imatinib in patient populations where this treatment is recommended according to current clinical and expert guidance for management of patients with GIST in the UK. The SSGXVIII/AIO study provides the first RCT evidence relating to long-term (3-year) adjuvant imatinib therapy and highlights that continued therapy confers RFS and OS benefits for patients at high risk of recurrence. The demonstration of both RFS and OS benefits is a particular strength, highlighting that adjuvant therapy in high-risk patients can prevent disease progression to a point where, otherwise, patient HRQoL might be expected to suffer, as well as extending patient survival, as shown during long-term follow-up extending beyond 5 years from the time of primary resection.

Limitations of the RCT data include the differences in study methodologies and, in particular, the fact that the studies applied different criteria for defining patient risk for recurrence. Neither the ACOSOG Z9001 study nor the SSGXVIII/AIO study applied the currently accepted Miettinen 2006 criteria for defining high-risk patient groups because the criteria did not exist at the time of study design. Post-hoc analyses have been used to apply these criteria, retrospectively, to patient-level data. By applying the Miettinen criteria to both studies in order to extract a sub-group, the differences between the studies have been kept to a minimum but unkown differences which exist cannot be accounted for.

The ACOSOG Z9001 study assessed adjuvant therapy given for only 1 year and the early stopping of this study and cross-over of recurrence-free placebo patients to active treatment, albeit because of the clear efficacy of imatinib therapy, confounds interpretation of the long-term recurrence and survival data. On stopping of accrual and unblinding of the study, patients in the placebo group who were still recurrence-free were permitted to crossover to active treatment: 72/79 (91%) eligible patients (of whom 18/20 were Miettinen high-risk) chose to receive “adjuvant” imatinib therapy initiated at time points later than would be usual for post-surgical commencement of adjuvant treatment. The 1-year treatment duration and the crossover of patients from the placebo group to imatinib treatment confounds assessment of the effects of 1 year of therapy and the clear interpretation of long-term outcomes following 1 year of adjuvant therapy.

Another limitation of the available datasets is that no HRQoL data on adjuvant imatinib therapy in GIST were collected from the RCTs. This may, in part, reflect the fact that both trials (ACOSOG and SSG) were designed over a decade ago, when the collection of such data was not routine.

6.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The evidence base presented from the RCTs and non-RCTs is highly relevant to the decision problem. Data are available for both RFS and OS, both of which are clinically and patient-relevant endpoints rather than surrogates.

All studies assessed imatinib at a dose and regimen that corresponds to the licensed indication.

Patients with a high risk of disease recurrence is a subgroup of the licensed indication for imatinib , which is termed significant risk of disease relapse or recurrence.[1] This fulfils the currently accepted criteria and guideline-recommended definition of high risk and recognises

that these patients are those for whom there is the greatest capacity to benefit from treatment.[6] It also allows for the greatest use of the available evidence: in order to represent the full licensed population of “significant risk” it would have been unclear how to incorporate the SSG data since this is restricted to only high-risk patients.

Current guidelines on the management of patients after primary resection of GIST note that the optimal treatment duration for adjunctive therapy with imatinib has not been established. The evidence reviewed here includes the ACOSOG Z9001 study that compared 1 year of therapy with no adjuvant therapy; at the time that study was designed there was no evidence-base on adjuvant treatment following primary GIST resection or, indeed, much evidence for imatinib in the metastatic setting. It also includes the SSGVIII/AIO study that has looked at 3 years versus 1 year of adjuvant therapy. This latter study provides the best currently available RCT data on long-term adjuvant imatinib therapy in this setting. There continue to be no other comparator therapies in this indication.

The AE profile of long-term adjuvant imatinib therapy was an important and detailed outcome in each of the two key RCTs described. The SSGVIII/AIO study provides data on 3 years of continuous adjuvant therapy together with long-term patient follow-up extending beyond 5 years from start of treatment. This offers valid and reliable insights into the tolerability and safety profile of imatinib in the patient population of interest.

6.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

There are no factors that influence the external validity of study results to patients in routine clinical practice. The dose and regimen for adjuvant imatinib investigated in the ACOSOG Z9001 and SSGXVIII/AIO trials correspond to that used in routine clinical practice and both are in accord with the imatinib licence. Treatment monitoring, and patient follow-up and management in these trials was also in keeping with current practices and care of patients with GIST.

The ACOSOG Z9001 study included all patients, regardless of risk, whilst the SSG trial included high-risk patients but using a different definition than currently recommended. UK

guidelines do not recommend adjuvant treatment unless patients are at high risk of recurrence and endorse the use of the Miettinen criteria to make this assessment. Accordingly, the submission focusses on the Miettinen-defined high-risk sub-group.

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

Identification of studies

7.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 10.10, appendix 10.

A previous systematic review was available with searches conducted up to 2009.[61] This systematic review was updated to identify new economic evaluation studies from 2009 onward. Systematic searches were carried out between the 13th and 18th of December 2013 to retrieve relevant economic studies from the following databases:

- MEDLINE and MEDLINE in Process: Ovid. 1946 to Present
- EMBASE: Ovid. 1974 to 2013 December 05
- Cochrane Library
    - Cochrane Database of Systematic Reviews (CDR): Wiley Interscience. 1996-present
    - Health Technology Assessment Database (HTA): Wiley Interscience. 1995-present
    - Database of Abstracts of Reviews of Effects (DARE): Wiley Interscience. 1995-present
    - NHS Economic Evaluation Database (NHS EED): Wiley Interscience. 1995-present
- Science Citation Index: Web of Science. 1899-present
- Conference Proceedings Index: Web of Science. 1990-present
- *EconLit: Ovid. 1961 to November 2013*

The population terms for GIST (e.g. statements 1-33 in the Medline strategy) were combined with a methodological filter (where applicable) for retrieving economic evaluation studies (e.g. statements 34-64 in the Medline strategy). No intervention terms were included in the search

strategy as all treatments for GIST were considered in the economic evaluation. Searches were limited from 2009 onwards. Details of the search terms used are available in section 10.10, Appendix 10.

Studies were also identified from reference tracking and citation searching of included studies.

All search strategies are provided in Section 10.10, Appendix 10.

The inclusion criteria used for the population, intervention and comparators were used as they include all scenarios that are potentially relevant to the submission. The outcome and study type criteria were used to limit the studies to the relevant analyses. The language criteria were included as studies published in a language other than English are unlikely to be relevant to a NHS setting.

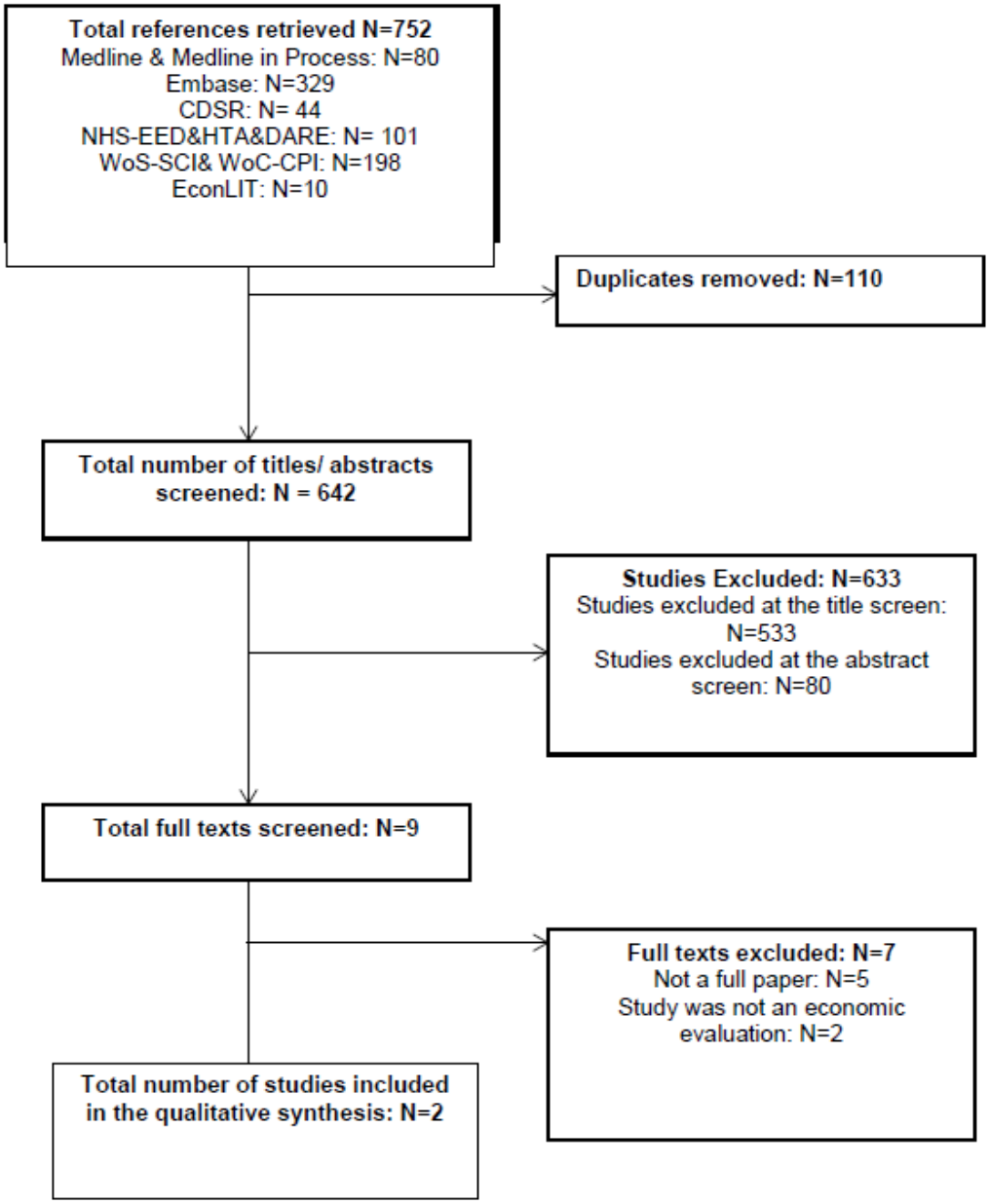
Table B-22. Eligibility criteria used for abstract screening and study selection

Selection Criteria	Inclusion	Exclusion
Population	Adult patients (> 18 years) with a GIST	–
Intervention	Adjuvant imatinib (Gilvec) with surgical resection	–
Comparators	Surgical resection alone, adjuvant imatinib (Gilvec) with surgical resection given for a different time period than the intervention	–
Outcomes	Cost effectiveness, cost utility analysis, cost benefit analysis	–
Study Type	Economic evaluation Full papers	Conference abstracts
Language	English only	–

Titles and abstracts were screened by one reviewer in accordance with pre-defined inclusion/exclusion criteria (Table B-22).

The flow diagram of included and excluded economic evaluation is presented in Figure B-9.

Figure B-9. Flow diagram of included and excluded cost effectiveness studies from the updated review



Adapted from the PRISMA (formerly QUOROM) statement, http://www.prisma-statement.org/

Overall, two studies met the inclusion criteria; Majer et al (2013) and Sanon et al (2013).[62,63] Seven studies were rejected at the screening stage. Five studies were only available in abstract form (El Quagari et al, 2010; Nagy et al, 2012; Parthan et al, 2012; Pawar et al, 2010; and Raikou et al, 2012).[64-68] Two studies (Rutkowski et al, 2013 and Vetto et al, 2009) were not economic evaluations, so were not considered further.[69,70]

Description of identified studies

7.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

A tabulated summary of the two included studies included in the review is presented in Table B-23. A description of these studies along with a quality assessment checklist is provided below.

Table B-23. Summary of the two included studies

	Majer et al, 2013[62]	**Sanon et al, 2013[63]**
Country of origin	Netherlands	USA
Trial population	Patients in the SSGXVII/AIO trial	Patients in the SSGXVII/AIO trial
Population Age	61	61
Model type	Markov/ State transition	Markov/ State transition
Time horizon	Lifetime	Lifetime
Cycle length	Monthly	Monthly
Perspective	Dutch Health Care Provider	US third payer
Discounting	Costs: 4.5% QALYs: 1.5%	Costs: 3% QALYs: 3%
Transition probabilities		
Probability of first recurrence		
Data	High risk patients in the SSGXVII/AIO trial.	Patients in the SSGXVII/AIO trial, data from Joensuu et al 2011.
Extrapolation technique	Log-logistic model	Uses a constant recurrence rate
Probability of second recurrence		
Data	Published sources[71-73]	Published sources[71,73,74]
Extrapolation technique	None, use time independent transition probabilities	None, use time independent transition probabilities
Mortality rates from GIST recurrence		
Data	Published sources[59,71-73]	Patients in the SSGXVII/AIO trial and published sources
Extrapolation technique	None, use time independent transition probabilities	Use observed data pre-year 5, use literature afterwards
Discontinuation Probabilities during adjuvant treatment		

Data	High risk patients in the SSGXVII/AIO trial.	SSGXVII/AIO
Assumptions	Those patients who discontinued had the same recurrence rate as those who did not	Discontinuation rates were time independent after the first year
HRQL		
Values and Health states	Recurrence – free health state: 0.785 ± 20% of the mean[75] Reduction during imatinib treatment 0.081 ± 20% of the mean[76] First GIST recurrence: 0.748 (assumption) Second GIST recurrence: 0.712 ± 0.014[76] Best Supportive Care: 0.577 ± 0.029[76]	Recurrence - free GIST: 1.00 (assumption) Recurrent GIST: 0.87 (and expert opinion)[77] Second recurrence: 0.71 (expert opinion) Best supportive care: 0.58[76] Death: 0.00 Utility decrement when adjuvant imatinib is discontinued: -0.02 No uncertainty was presented in the paper.
Data	Published sources [75,76]and an assumption	Published sources, expert opinion and assumptions[76,77]
Assumptions used	The utility at first recurrence is the average of the utility at the second recurrence and the utility for recurrence free survival	The utility for patients who were surgically resected and without recurrence were in perfect health
Age adjustment	No	Yes[Hanmer et al; 2006][78]
Utility decrement whilst on imatinib	Yes, assumed the Chabot et al 2008[76] utility decrement for sunitinib could be applied to patients on imatiinb	Yes, obtained using expert opinion
Costs		
Currency	2011 €	2010 US$
Technology costs (monthly)	400 mg imatinib €2,578 800 mg imatinib €5,156 Sunitinib €3,700	400 mg imatinib $5,004 800 mg imatinib $10,008 Sunitinib $6,101
Other resource counts	Costs of monitoring therapy, test procedures and surgery for recurrent GIST. General practioner vists, oncologist visits and required tests. Best standard care	Monitoring therapy, adverse events, GIST recurrence, Best supportive care.

Sources	European Guidelines,Casali et al 2010 Polder et al 2006 or expert opinion[79,80]	ACOSOG Z9001 trial, Yabroff et al 2008,[81] US Physician fee and coding guide,USA DRG codes.
Base Case Results		
Discounted lifetime cost of 1 year adjuvant imatinib	€79,361	$217,800
Discounted lifetime cost of 3 years adjuvant imatinib	€120,196	$302,100
Discounted lifetime QALYs of 1 year adjuvant imatinib	5.18	7.18
Discounted lifetime QALYs of 3 years adjuvant imatinib	6.55	8.53
ICER of 3 years of adjuvant imatinib compared to 1 year of adjuvant imatinib	€29,872 per QALY	$62,600 per QALY
Sensitivity analyses		
Deterministic analyses	Yes: 1) model time horizon 2) the method of estimation of recurrence rates 3) the cost of imatinib	Yes: Key parameters were varied by ± 25%
Probabilistic Analysis conducted	Yes	Yes

The two identified studies were similar and used a Markov/state transition approach to evaluate the cost effectiveness of 3 years of adjuvant imatinib compared with 1 year of adjuvant imatinib, using data from the SSGXVII/AIO trial (population at high risk of recurrence).

Both studies took the perspective of the funder of health care within their respective country. In Majer et al (2013),[62] costs were discounted at 4.5% and QALYs were discounted at 1.5% as recommended by the Dutch Health Care Insurance Board (CvZ). In Sanon et al (2013)[63] a discount rate of 3% was used for both the costs and benefits.

The model structure is broadly similar. In both models, patients enter the model as being free of recurrent GIST and can remain free-recurrence, have a recurrent GIST or die (from GIST or other causes). In both models, treatment for recurrence was 400 mg/day imatinib, 800 mg/day imatinib or sunitinib. The only difference between the two models is that in the Majer model[62] a patient who was receiving, or had completed, adjuvant imatinib at 400 mg per day treatment could receive sunitinib or imatinib upon their first recurrence. In the Sanon et al (2013)[63] model upon first recurrence patients could only receive imatinib.

Both studies used the recurrence free survival (RFS) rate from the SSGXVII/AIO trial to inform the transition probabilities for the first GIST recurrence in the first 6 years of the model. Majer et al (2013)[62] used data from the SSGXVII/AIO trial for only those patients who were

considered to be at a Miettinen high risk of recurrence (n = 281, 70% of the total patient population) whereas Sanon et al (2013)[63] used data from the whole trial population.

The method used to extrapolate RFS beyond the observed period was different in the two studies. Sanon et al (2013)[63] applied the observed monthly recurrence rate at Year 5 in the 1-year imatinib arm to both treatment arms as a proxy for expected efficacy once the treatment is completed at the end of the 5 years of follow-up for those patients who received adjuvant imatinib for 1 year for both treatment groups, whilst Majer et al (2013)[62] used a log-logistic model to extrapolate from the RFS curve.

In Majer et al (2013)[62] published sources were used to inform monthly probabilities of recurrence associated with a second GIST recurrence and monthly mortality probabilities following GIST recurrence following treatment with imatinib, sunitinib and BSC.[71,73,82] Probabilities were assumed to follow an exponential distribution (constant).

The approach to modelling post-recurrence mortality was also different between the two studies. Sanon et al (2013)[63] used overall survival data from the SSGXVIII/AOI trial up until the fifth year of the model. After the fifth year treatment specific published sources were used[71,74,83,84] Majer et al (2013)[62] did not use the trial data and just used treatment specific mortality rates from the published literature.[71-73]

Whilst the two models had similar health states, the sources used for utility weights were different. Majer et al (2013)[62] used EQ-5D data from the published literature[75,76] whilst Sanon et al (2013)[63] used data used in Wilson et al 2005[77] supplemented by expert opinion and/or assumptions.

Similarly, the two studies used different methods to value the costs associated with each health state. Both studies took the appropriate technology costs from national sources; Majer et al (2013)[62] use the online database of the Dutch Health Care Insurance Board (College voor zorgverzekeringen - CvZ)[85] to provide information on the consumer price of drugs . The prices are then adjusted so that they reflect the price paid by pharmacies to acquire the drugs. Sanon et al (2013)[63] used the 2010 Drug Topics Red Book[86] to obtain the monthly pharmacy costs of acquiring imatinib or sunitinib. Majer et al (2013)[62] used European guidelines and expert opinions to inform the monthly cost in each recurrent health state, taking into account the frequency of oncologist visits, general practitioner visits and the required tests. To provide a monthly cost for the recurrent health states, there was a one-time cost upon recurrence, ongoing costs and a cost for treating adverse events. Best standard care was calculated using the weighted average of resource use in the last year of life and the period before the last year of life. To estimate the continuing costs, Dutch oncologists were consulted.

Sanon et al (2013)[63] estimated physician and other resource use costs from the physician fee and coding guide. Procedure costs were estimated from the DRG codes. The monthly monitoring costs were derived from the ACOSOG Z9001 trial. The cost of best supportive care was taken from Yabroff et al (2008).[81]

The incremental cost effectiveness ratio for 3 years of adjuvant imatinib compared with 1 year of adjuvant imatinib was € 29,872 per QALY in Majer et al (2013)[62] and $62,600 per QALY in Sanon et al (2013).[63]

Both studies conducted deterministic sensitivity analyses. In Majer et al (2013)[62] a series of sensitivity analyses were conducted on key modelling assumptions. The authors found that the model was highly sensitive to the time horizon used. Assuming a 5 year time horizon increased the ICER to €84,332 per QALY gained (mostly due to a decrease in the incremental QALYs). Sensitivity analyses were also conducted examining different parametric functions (Weibull and Gompertz) when estimating the transition probabilities. The assumptions that there was an equal rate of RFS in the two trial arms after the observation period and a gradual convergence of RFS after the observation period were also examined.

In Sanon et al (2013)[63] the deterministic sensitivity analysis involved varying key parameters by ± 25% from the base case value. The model was most sensitive to changes in the rate of GIST recurrence beyond 6 years in both arms and the monthly cost of imatinib.

Both studies conducted a probabilistic sensitivity analysis. Majer et al (2013)[62] reported that the probability of 3 years of adjuvant imatinib being cost-effective compared with 1 year of adjuvant imatinib in the Dutch health care setting was 12.2%, 51.0%, 68.1% and 80.4% at willingness to pay thresholds of €20,000, €30,000, €40,000, €50,000 per QALY gained, respectively. Sanon et al (2013)[63] reported that 3 years of adjuvant imatinib has a 100% probability of being cost effective compared with 1 year of adjuvant imatinib at a willingness to pay threshold of $100,000 per QALY gained.

7.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[1] or Philips et al. (2004)[2]. For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.

A quality assessment of each study is provided below in Table B-24 and Table B-25.

Table B-24. Quality assessment of Sanon et al. (2013)[63]

	(Sanon et al)[63]	
Study question	**Grade(yes/no/ not clear/ N/A)**	**Comments**
Study Design		
1. Was the research question stated?	Yes	To compare the treatment outcomes and costs for those patients who receive 3 years of adjuvant imatinib and 1 year of adjuvant imatinib.
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoints of the analysis clearly stated and justified?	Yes	USA third party payer
4. Was a rationale reported for the choice of alternative programmes or interventions compared?	Yes	1 year adjuvant imatinib had already been approved in the USA and a new study was available with data on the effects of providing imatinib for 3 years
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation clearly stated?	No	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Not clear	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	First recurrence rates, mortality rates and discontinuation rates were collected from the SSGXVIII/AIO trial. HRQL data

[1] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.
[2] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

		was taken from other studies, expert opinion or assumed
9. Were the details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcomes measure(s) for the economic evaluation clearly stated?	Not clear	
12. Were the methods used to value health states and other benefits stated?	Yes	HRQL data was taken from Wilson et al,[77] Chabot et al,[76] or based on expert opinion and assumptions.
13. Were the details of the subjects from whom valuations were obtained given?	No	Not mentioned in this paper, however there are references to other papers which may contain this information.
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	No	As this is from the third party payer perspective, productivity changes may not be relevant
16. Were quantities of resources reported separately from their unit cost?	No	Only monthly costs were reported
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Each cost was sourced and resource use data was taken from the ACOSOG Z9001 trial
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	All prices were in or converted to 2010 US$
20. Were details of any model used given?	Yes	Markov Model
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	The model made use of the new data regarding the effectiveness of adjuvant imatinib reported for the SSGXVIII/AIO trial
Analysis and interpretation of results		
22. Was time horizon of cost and benefits stated?	Yes	Lifetime
23. Was the discount rate stated?	Yes	3%
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals	No	

given for stochastic data?		
27. Was the approach to sensitivity analysis described?	Not clear	Probabilistic and deterministic sensitivity analyses were conducted. In the deterministic sensitivity analysis it is unclear which variables were altered. In the probabilistic sensitivity analysis the distribution used for each variable is given but not the standard error used.
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	Yes No	In the deterministic analysis the key variables were altered to 25% above and below the base case values In the probabilistic sensitivity analysis no information is provided regarding the standard error of each variable
30. Were relevant alternatives compared? (i.e. Were appropriate comparisons made when conducting the incremental analysis?)	Not clear	It is only stated that 1 year of adjuvant imatinib has been approved in the USA. It is not made clear whether this is the relevant comparator.
31. Was an incremental analysis reported?	Yes	ICER: $62,600 per QALY
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	3 years of adjuvant imatinib therapy is cost effective from the US payer's perspective compared to 1 year of adjuvant imatinib therapy
34. Did conclusions follow from the data reported?	Yes	The paper quotes Nadler et al (2006),[87] that US physicians felt that oncology treatments could be considered cost effective at $300,000 per QALY. The quoted ICER falls below this value, as such the treatment can be considered as being a cost effective treatment.
35. Were conclusions accompanied by the appropriate caveats?	Yes	Resource use was based on trial data and the model may oversimplify the disease natural history
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275-83. Cited in Centre for reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination.		

Table B-25. Quality assessment of Majer et al. (2013)[62]

	(Majer et al)[62]	
Study question	**Grade(yes/no/ not clear/ N/A)**	**Comments**
Study Design		
1. Was the research question stated?	Yes	To assess the value of adjuvant imatinib for 3 years post-surgery for high risk patients in the Netherlands in the long term
2. Was the economic importance of the research question stated?	Not clear	
3. Was/were the viewpoints of the analysis clearly stated and justified?	Yes	Dutch health care provider perspective
4. Was a rationale reported for the choice of alternative programmes or interventions compared?	Yes	Trial demonstrated an overall survival advantage over 5 years of providing 3 years adjuvant imatinib as compared to providing 1 year adjuvant imatinib
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation clearly stated?	Yes	Cost effectiveness/ cost utility analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were the details of the design and results of the effectiveness study given (if based on a single study)?	Yes	The design and results of both effectiveness studies were given. The RFS and OS estimates from the SSGXVIII/AOI trial were used
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcomes measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	They were obtained from two other papers
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of	No	

productivity changes to the study question discussed?		
16. Were quantities of resources reported separately from their unit cost?	No	The total costs for each model cycle are reported, however the paper does refer to an appendix for the derivations of the cost
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	All costs were converted into 2011 €
20. Were details of any model used given?	Yes	Markov Model
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	The key parameters for the Markov model were described.
Analysis and interpretation of results		
22. Was time horizon of cost and benefits stated?	Yes	Lifetime
23. Was the discount rate stated?	Yes	4% for costs and 1.5% for quality adjusted life years
24. Was the choice of rate justified?	Yes	Rate recommended by the Dutch Health Care Insurance Board
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	Where appropriate, standard errors and statistical distributions were reported for the model parameters
27. Was the approach to sensitivity analysis described?	Yes	Probabilistic and Deterministic approaches were taken. There was no reported PSA for each deterministic analysis
28. Was the choice of variables for sensitivity analysis justified?	Yes	There was uncertainty as to how to model RFS so multiple different approaches were used. Costs were changed to demonstrate the effect of different pricing for imatinib
29. Were the ranges over which the parameters were varied stated?	Yes	The price reductions for the cost of imatinib were stated. Standard errors and the statistical distribution used for each variable used in the PSA was reported.
30. Were relevant alternatives compared? (i.e. Were appropriate comparisons made when conducting the incremental analysis?)	Yes	3 year adjuvant imatinib was compared to 1 year adjuvant imatinib.
31. Was an incremental analysis	Yes	An incremental analysis was

reported?		reported for all scenarios conducted
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	Concluded that high-risk patients should be treated with 3 years of adjuvant imatinib
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	There was a whole limitations section
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275-83. Cited in Centre for reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination.		

7.2 De novo analysis

Patients

7.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

The licensed indication for Imatinib relevant to this submission is the adjuvant treatment of adult patients who are at significant risk of relapse following resection of KIT (CD117)-positive GIST.[1] Patients who have a low or very low risk of recurrence should not receive adjuvant treatment.

The definition of what constitutes “significant risk” is vague, but has been interpreted to encompass both patients at high and intermediate/moderate risk of GIST relapse.

Whilst the ACOSOG Z9001 trial included a broader population (from low to moderate and high risk patients), the SSGXVII/AIO trial only included patients deemed to be at high risk of recurrence. Therefore the cost effectiveness analysis has been conducted from the perspective of patients at high risk of recurrence (based on the Miettinin criteria) treated with surgical resection followed by three years of adjuvant imatinib..

The most recent UK guidelines, published in 2009, recommend adjuvant therapy with imatinib for patients at high risk of recurrence after primary resection.[6] More specifically, the ESMO guideline recommends adjuvant therapy with imatinib for 3 years for patients with a high risk of relapse. The ESMO guideline indicates that adjuvant therapy should not be considered for patients at low risk of relapse, and that there is more uncertainty around appropriate treatment when the risk is intermediate.

Evidence for patients at moderate risk is less developed and therefore the uncertainty is greater for those patients. Whilst adjuvant imatinib may be beneficial for patients at moderate risk, a longer follow-up is required in order to demonstrate the benefit in this subpopulation. Patients at high risk of relapse have the greatest capacity to benefit from adjuvant imatinib,

and shorter follow-up is needed to demonstrate the clinical benefit of adjuvant imatinib in this population.

Consequently, the economic model considers a subset of the licensed indication, i.e. only those patients who are at high risk of relapse. Patients at moderate risk of relapse are not considered in this submission due to the limited evidence up to date and likely use of adjuvant imatinib in UK clinical practice.

In this assessment, patients are considered to be at high risk of recurrence if they meet the the Miettinen 2006 criteria for high risk.[2] The Miettinen criteria was used as per UK clinical guideline.[6]

As previously described, UK guidelines do not stipulate the duration over which adjuvant therapy with imatinib should be given; current ESMO guidelines consider a 3-year treatment duration to be standard treatment for patients with a high risk of relapse.[5]

To date, two relevant RCTs of adjuvant imatinib therapy have reported (refer to section 6.2.4). The ACOSOG Z9001 study was designed based on a conservative treatment period of 1 year, since this study was designed at a time when imatinib in the advanced setting was itself under investigation.[8,54] It was the first large study to explore the use of imatinib in the adjuvant setting. More recently the SSGXVIII/AIO study comparing 3 years of adjuvant imatinib therapy to 1 year of imatinib adjuvant therapy suggested that 3 years of adjuvant imatinib is associated with advantages for both RFS and overall survival when compared with the shorter treatment duration of 1-year.[10] The difference in risk of recurrence between groups was particularly marked during the second and third years, reflecting the benefits of more prolonged therapy. In the subgroup of patients with high-risk disease according to the Miettinen 2006 criteria the RFS was longer in the 3-year group than in the 1-year group (HR 0.43, 95% CI 0.30 to 0.62; $p < 0.0001$). Differences between treatment groups were evident at 18 months (1-year group, 81.6% versus 3-year group, 93.4%) and RFS rates at 4 years were 40.2% (1-year group) and 72.0% (3-year group).[9]

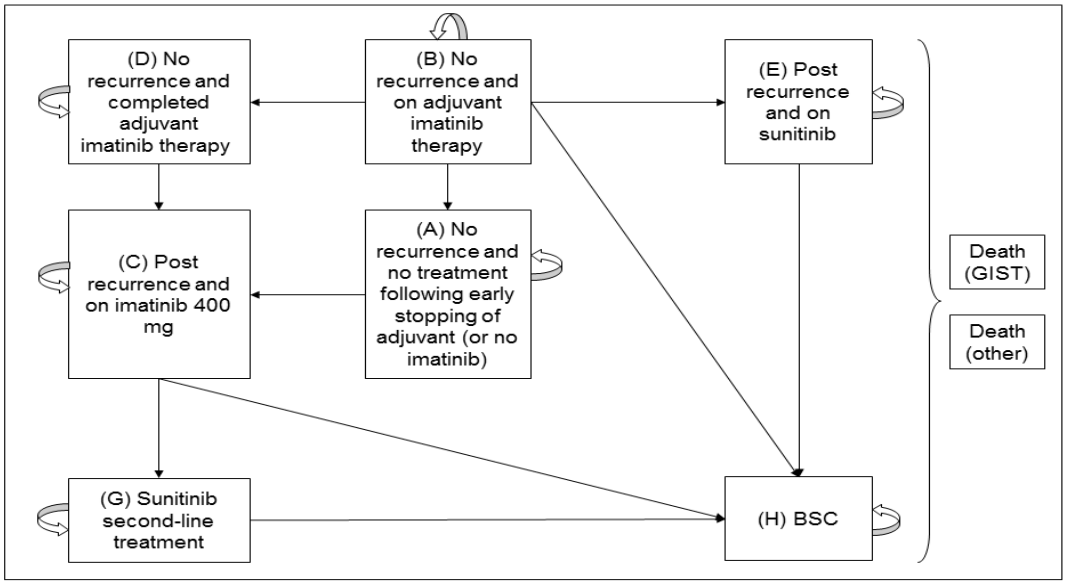
Based on the existing evidence base, the economic model considers patients treated with surgical resection followed by 1 or 3 years of adjuvant imatinib therapy, compared with no adjuvant treatment. Given that there is no direct comparison between patients treated with surgical resection followed by 3 years of adjuvant imatinib and patients treated with surgical resection only, the inclusion of adjuvant 1 year of treatment acts as a bridge between these arms.

Model structure

7.2.2 Please provide a diagrammatical representation of the model you have chosen.

The model used a Markov/state-transition approach. A simplified schematic of the model structure is presented in Figure B-10. During each cycle of the model (monthly), patients can remain recurrence-free, have a recurrent GIST (first or second recurrence), have progressive disease (and be treated with BSC) or die (from GIST or other causes). Transition probabilities between the health states are based on probabilities of recurrence/discontinuation associated with the treatment received. Further description of the probabilities used to govern the transition between the different health states in the model is provided in section 7.3.2.

Figure B-10. Model structure



Notes: BSC, best supportive care; GIST, gastrointestinal stromal tumour. Heath state F: Dose escalation to 800mg (used in scnario analysis only as option following 400mg imatinib for recurrnece) not shown.

Patients in the comparator arm who receive no adjuvant treatment (surgical resection only) start in health state A (*"No recurrence & no treatment"*). Patients receiving adjuvant imatinib therapy – either 1 year or 3 years – start in health state B (*"No recurrence and on imatinib adjuvant therapy").*

Patients who discontinue adjuvant therapy (before the end of the planned treatment duration) due to adverse events (AEs) move to the "*No recurrence and no treatment*" state (Health state A). These patients are assumed to have the same rate of recurrence as patients remaining on adjuvant imatinib as these patients were not censored when calculating the RFS

and therefore the RFS used in the economic model is for all patients randomised to the adjuvant treatment arm (therefore a mix of patients who discontinued and did not discontinue). The majority of patients (90%) who experience a first recurrence whilst on adjuvant therapy are assumed to receive sunitinib (health state E- *"Post recurrence and on sunitinib"*). A small proportion (10%) of patients who are considered too fragile to be suitable for further treatment will receive best supportive care (BSC - health state H). Patients who have remained recurrence-free after the planned adjuvant treatment period (1 or 3 years) has elapsed, move to the "*No recurrence and completed adjuvant imatinib therapy*" state (Health state D).

The majority of patients (90%) who experience a first recurrence whilst on adjuvant therapy are assumed to receive sunitinib (health state E- *"Post recurrence and on sunitinib"*). A small proportion (10%) of patients who are considered too fragile to be suitable for further treatment will receive best supportive care (BSC - health state H). Patients who have remained recurrence-free after the planned adjuvant treatment period (1 or 3 years) has elapsed, move to the "*No recurrence and completed adjuvant imatinib therapy*" state (Health state D).

Patients treated with surgical resection only (Health state A), patients who discontinue adjuvant imatinib before the planned treatment duration (Health state A) and patients who completed the planned adjuvant treatment duration who did not experience a recurrence (Health State D) remain in their respective health state until first recurrence or death. These patients move to the "*post-recurrence and on imatinib 400 mg*" (Health state C) state following a recurrence (first recurrence) and receive first-line imatinib 400 mg/day treatment. Patients who had a first recurrence and were treated with first-line imatinib 400 mg/day (Health state C) remain in this health state until death or move to health state G (*"sunitinib second-line treatment"*) or H (*"BSC"*) following a second recurrence. Patients treated with sunitinib second-line in the metastatic setting (Health state E and G) remain in these respective health states until further progression and move to "BSC" (Health state H) or die from GIST or other causes. Patients in the BSC (Health state H) state are assumed to have progressive disease and remain in this health state until death.

Further description of the health states is provided in section 7.2.4 (Table B-26)

7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

The economic model considers patients at high risk of recurrence and reflects the UK clinical pathway. Current standard treatment in England according to NICE guidance is observation after surgery i.e. no adjuvant therapy.[88] Patients who receive no adjuvant treatment (the

comparator arm) start in health state A (*"No recurrence & no treatment"*) of the economic model.

On recurrence, a small proportion of patients may be eligible for further surgery and imatinib treatment at 400 mg/day is recommended as first-line management of people with KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic GISTs[89] (Health state C). In the economic model, following a first recurrence, patients move to the health state C ("post-recurrence and on imatinib 400 mg") and receive imatinib first-line treatment. It is assumed that a small proportion (15%) of patients have further surgery. This is not explicitly modelled. Only the cost associated with further surgery was included in the economic model, eg. no effectiveness was modelled for those patients.

An increase in the dose of imatinib is not recommended for people receiving imatinib who develop progressive disease after initially responding to imatinib and so this is not included in the base case.[89] Sunitinib is recommended as a treatment option for people with unresectable and/or metastatic malignant GISTs following failure of imatinib treatment due to resistance or intolerance (Health states E and G).[90] In the economic model, patients who experience a recurrence whilst on adjuvant imatinib receive sunitinib as a second-line treatment (Health state E – 90%) or are considered to be too fragile for further treatment and move to BSC and are assumed to have progressive disease (Health state H – 10%). Similarly, patients who experience recurrence or progression following Imatinib 400 mg/day first-line treatment are either switched to sunitinib second-line treatment (Health state G – 90%) or receive BSC (Health state H – 10%). The proportion of patients moving to BSC following recurrences whilst on adjuvant imatinib or imatinib first line treatment was varied in sensitivity analysis.

The probability of patients eligible for further surgery following first-recurrence and second-line treatment received (sunitinib, BSC) following discontinuation or recurrence (whilst on adjuvant imatinib therapy or following first-line imatinib 400 mg/day treatment) was informed by a validation exercise undertaken with 5 UK clinical experts used in a previous submission to NICE (See also Section 7.3.5).[61,91]

7.2.4 Please define what the health states in the model are meant to capture.

The model used a Markov/state-transition approach. Health states are defined according to the natural history of GIST progression, with the primary health states grouping patients into the following three categories:

- free of recurrence;
- recurrent GIST (first, second and progression); and

- death (from GIST or other causes).

These primary health states were combined with a description of the treatment received: adjuvant imatinib therapy 400 mg/day, imatinib therapy 400 mg/day for treatment of recurrences, sunitinib 50 mg/day for treatment of recurrences, and best supportive care.

A description of the health states is given below

Table B-26 Description of the health states included in the economic model

A: No recurrence and no adjuvant treatment.	Recurrence-free	Patients who receive no adjuvant treatment (the comparator arm) start in this health state. In addition, patients on adjuvant treatment who discontinue due to adverse events move to this state. If these patients do not experience a recurrence, they remain in this state until death. Upon recurrence, all patients initiate imatinib 400 mg once daily therapy (Health state C), as per the licence.
B: No recurrence and on imatinib adjuvant therapy.	Recurrence-free	All patients who receive adjuvant imatinib, given for 1 or 3 years, after surgical resection begin in this state. After the fixed treatment period (1 or 3 years) has elapsed, patients who have remained recurrence free move to the "No recurrence and completed adjuvant imatinib therapy" state (Health state D). Patients who discontinue adjuvant therapy due to AEs move to the "No recurrence and no treatment" state (Health state A). Patients who experience recurrence during adjuvant imatinib treatment move to either sunitinib treatment (Health state E) or BSC (Health state H). Patients who experience recurrence are either switched to sunitinib treatment (Health state E) (90%), or receive BSC (Health state H) (10%).
C: Post-recurrence and on imatinib 400 mg once daily.	First recurrence	Patients who experience recurrence *after* completing the period of adjuvant imatinib therapy move to this health state. A small proportion of patients (15%) will be eligible for surgery. Patients who do not experience a second recurrence/progression and tolerate imatinib continue treatment on 400 mg once daily and remain in this state. Patients who discontinue therapy due to AEs either move to BSC (Health state H) (10%) or sunitinib second-line treatment (Health state G) (90%). Patients who experience recurrence or progression are either switched to sunitinib second-line treatment (Health state G) (90%), or receive BSC (Health state H) (10%).
D: No recurrence and completed adjuvant imatinib therapy.	Recurrence-free	After cessation of adjuvant therapy, patients who do not experience a recurrence remain in this state until death. If recurrence occurs, therapy with imatinib 400 mg once daily is re-initiated (Health state C).
E: Post-recurrence and on	First recurrence	Patients who experience a recurrence *during* adjuvant therapy on imatinib enter this health state and

sunitinib (For patients experiencing recurrence during adjuvant imatinib treatment)		receive second-line sunitinib (or they may go direct to BSC (Health state H). If post-recurrence sunitinib is not well tolerated, patients move to BSC (Health state H).
G: Sunitinib second-line treatment.	Second recurrence	Patients who fail imatinib treatment for recurrence (Health state C) enter this state. These patients continue sunitinib therapy until either treatment failure or discontinuation of therapy due to AEs. In both cases, patients move to BSC (Health state H).
H: Best supportive care.	Progressive disease	Patients who enter this health state are assumed to have recurred (including metastatic disease) and are no longer being actively treated with either imatinib or sunitinib. Once in this state, patients remain there until death.
Death from GIST	Death	
Death from other causes	Death	

7.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

The model structure is based on the structure used in a previous submission to NICE.[61] The model structure and treatment pathways were informed by discussion with five UK clinicians.[91] Further description is provided in section 7.3.5.

It is considered that the model structure reflects all essential features of the condition in terms of risk of GIST recurrence or death and treatment received following recurrences.

In the economic model, the underlying disease progression is based on the rate of recurrence for patients receiving surgical resection only (i.e. no adjuvant therapy) based on data from the placebo arm in the ACOSOG Z90001 trial (section 7.3.2).

The aim of adjuvant imatinib therapy is to avoid or delay recurrence.

Patients who experience a first recurrence, may experience further progression/recurrences. This is informed by evidence from the published literature (section 7.3.2).

7.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

The analyses are conducted from the perspective of the NHS in England and Wales and use a lifetime horizon in the basecase. Key features of the analysis are summarised in Table **B-27**.

Table B-27. Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	Lifetime (50 year)	NICE reference case To capture all relevant outcomes and costs over the lifetime of GIST patients, in particular to take account of the differential survival effect between the alternative treatments.	NICE Methods Guide[92]
Cycle length	Monthly	NICE reference case Appropriate to capture accurately recurrence and the discontinuation of treatment	NICE Methods Guide[92]
Half-cycle correction	No	The importance of the half cycle correction depends on cycle length Given the cycle length of 1 month, which is short relative to the mean survival of these patients, the difference between actual and simulated survival is expected to be small and the impact of half cycle correction would be minimal.	Sonnenberg and Beck[93]
Were health effects measured in QALYs; if not, what was used?	Yes	NICE reference case	NICE Methods Guide[92]
Discount of 3.5% for utilities and costs	Yes	NICE reference case	NICE Methods Guide[92]
Perspective (NHS/PSS)	Yes	NICE reference case	NICE Methods Guide[92]
NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years			

Technology

7.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

The intervention and comparator(s) implemented in the model are as per their marketing authorisations/CE marking and doses (see sections 1.3 and 1.5).

The economic model simulates three hypothetical cohorts of patients diagnosed with primary GIST:

- patients treated with surgical resection only (comparator arm)
- patients treated with surgical resection followed by 1 year of adjuvant imatinib therapy (400 mg/day)
- patients treated with surgical resection followed by 3 year of adjuvant imatinib therapy (400 mg/day)

In the basecase, dose reductions and interruptions were not considered and patients treated with adjuvant imatinib therapy were assumed to receive the full recommended dose of adjuvant imatinib (400 mg/day) as per SPC. A sensitivity analysis was conducted assuming a mean dose intensity of 386.9 mg as seen in the ACOSOG Z9001 study and 393.73 mg from the SSGXVII/AIO trial (section 7.6.2). Of note, these estimate only account for dose reductions and do not account for dose interruptions.

7.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the ‘response’ criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.

- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

No continuation rule is implemented.

7.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 6). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

7.3.1 Please demonstrate how the clinical data were implemented into the model.

The movement between the different health states are governed by probabilities of events (namely recurrences, AEs and death) taken from the pivotal trials [8,10] and published sources[73,83,84,94].

The risk of recurrence for patients treated with surgical resection only (comparator arm) and patients treated with surgical resection followed by 1 or 3 years of adjuvant imatinib therapy was derived from an analysis of the SSGXVIII/AIO (SSG) and ACOSOG Z9001 (ACOSOG) trials. The ACOSOG Z9001 trial compared 1 year of adjuvant imatinib treatment vs. no adjuvant treatment (surgical resection only) whilst the SSGXVIII/AIO trial compared 3 years of adjuvant imatinib treatment vs. 1 year of imatinib adjuvant treatment.

There is no head-to-head trial directly comparing the strategies of surgery alone versus 3 years of adjuvant imatinib. This treatment effect is required for the economic model in order to compare No adjuvant treatment (surgical resection only) vs. 3 years of adjuvant imatinib treatment.

In the economic model, the baseline risk of recurrence for patients treated with surgical resection only was taken from the ACOSOG Z9001 trial. A parametric survival model was fitted to the data from the placebo arm of the ACOSOG Z9001 trial (see section 7.3.2 for further details).

A treatment effect (estimated from the pivotal trials – further details are provided in section 7.3.2) for adjuvant imatinib was applied to the baseline risk of recurrence for patients treated with surgical resection only (underlying progression) to estimate the risk of recurrence for patients treated with surgical resection followed by 1 or 3 years of adjuvant imatinib therapy.

7.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Transition probabilities were estimated from clinical data from the pivotal phase III trials of adjuvant imatinib (ACOSOG Z9001 and SSGXVII/AIO) and scientific publications for:

- the baseline risk of recurrence for patients treated with surgical resection only (comparator arm) – underlying progression
- the risk of recurrence for patients treated with surgical resection followed by 1 or 3 years of adjuvant imatinib therapy
- the risk of discontinuation (following adjuvant imatinib, first-line imatinib therapy, second-line sunitinib)
- the risk of second recurrence following first-line imatinib 400 mg/day treatment, second-line sunitinib
- the risk of death from GIST (according to the treatment line) and other causes.

The methods and sources used to calculate the different transition probabilities used in the economic model are described in turn below.

a) Estimation of the baseline risk of recurrence for patients receiving surgical resection only (comparator arm) – transition from Health State A to C

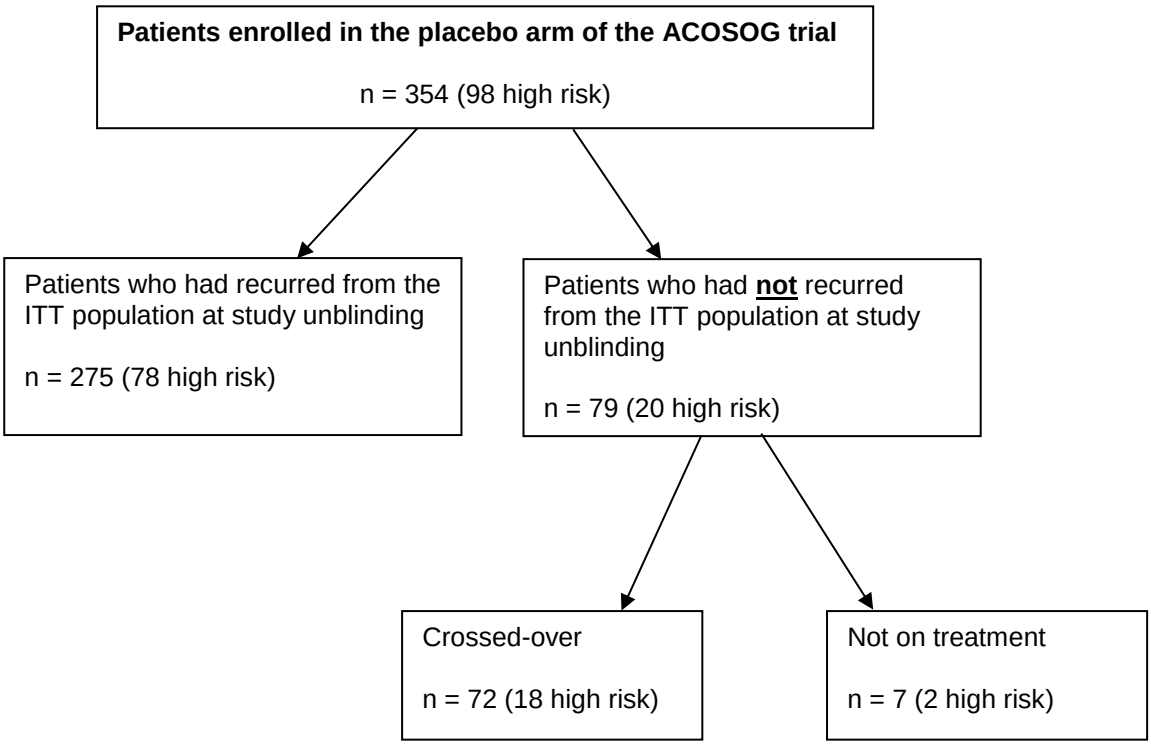
The baseline risk of disease progression for patients treated with surgical resection only is based on data from the placebo arm from the ACOSOG Z9001 trial. Supplemental analyses of the ACOSOG Z9001 trial were undertaken. Data were available for both the primary analysis[11,55] (dataset at study unblinding before patients on placebo were eligible to cross-over) in April 2007 and for the updated dataset in November 2011 (including 5-year additional follow-up data, but patients on placebo were eligible to cross-over and receive adjuvant imatinib).

As described in section 7.2.1, the economic model considers patients classified at being at high risk of GIST recurrence according to Miettinen risk classification. In the ACOSOG Z9001

trial, some data required to define the risk groups were unavailable at the time of the primary analysis (at study unblinding) but were subsequently updated for the most recent 5-year follow-up clinical study report. As a result, the Miettinen risk group for patients in this trial was derived from the most recent dataset acquired from the trialists. For the primary analysis, 165 patients were classified as having Miettinen high-risk disease and these were evenly distributed between the two treatment groups. At 5-year follow-up, retrospective data were available for a further 71 patients in total (of which 36 were classified as high risk), leading to 103 high-risk patients in the imatinib group and 98 patients in the placebo group.

Furthermore, as described in section 6.3.2, patients recruited to the placebo arm of the ACOSOG Z9001 trial who had not had a GIST recurrence were eligible to cross over to receive imatinib therapy at study unblinding, which took place on 12 April 2007. The distribution of patients who crossed over is presented in Figure B-11.

Figure B-11 : **Distribution of patients treated with Placebo in the ACOSOG Z9001 trial who did not experience a recurrence and crossed over to adjuvant Imatinib**



Of the 354 patients enrolled in the ACOSOG Z9001 trial in the placebo arm, 79 patients did not experience a recurrence at study unblinding and were eligible to cross over to receive adjuvant imatinib therapy. Of the 79 patients eligible to cross over, most of the patients (n=72; 91%) crossed over to receive adjuvant imatinib prior to recurrence. Similarly, of the 98 patients classified as being at high risk of recurrence according to the Mietinnen criteria,[32] 20 patients did not experience a recurrence at study unblinding and were eligible to cross over to

receive adjuvant imatinib therapy. Of the 20 patients eligible to cross over, the majority of patients (n=18; 90%) crossed over to receive adjuvant imatinib prior to recurrence. The mean time spent on placebo prior to crossover for these patients was 156 days (range 0 to 379).

Individual patient-level data from the ACOSOG Z9001 trial were analysed to estimate the baseline risk of recurrence in patients treated with surgical resection only (placebo arm). Analyses were conducted using data from the primary analysis (at study unblinding, ie before cross-over was allowed) and restricted to patients classified at high-risk of recurrence according to the Miettinen risk group classification (n = 98).

Parametric survival models were fitted to the recurrence-free survival (RFS) KM data for patients treated with surgical resection only (placebo arm) from the ACOSOG Z9001 trial. Five different parametric survival models (exponential, Weibull, gamma, loglogistic, Gompertz) were examined. Model fitting was carried out using maximum likelihood methods, implemented in the software package R. Goodness-of-fit was examined visually and using AIC and BIC statistics, and the extrapolation beyond the period observed in the trial was assessed for face validity with reference to published literature where appropriate.

Model selection based on minimisation of AIC and BIC alone (Table B-31) is not considered to be sufficient: AIC and BIC statistics assess the fit of the distribution to the observed data but do not provide information on the appropriateness of the extrapolation beyond the data. Consequently, the most plausible distribution was selected using an iterative process, including a visual inspection of each distribution's fit to the observed data and validity of the extrapolation beyond the evidence.

Table B-28. Goodness of fit statistics

GOF statistics	Exponential	Weibull	Loglogistic	Gamma	Gompertz
AIC	395.60	397.37	390.48	396.63	396.38
BIC	398.19	402.54	395.65	397.21	396.96

In terms of AIC and BIC statistics (Table B-31), the log-logistic distribution provided the best fit to the data to the observed period. The long-term behaviour of the extrapolated curves differs between the candidate probability distributions. The exponential, Weibull and Gamma functions predicted a 5-year RFS of 6.70%, 5.44% and 4.72% respectively. The 5-year RFS predicted using the log-logistic and Gompertz was 10.55% and 14.30% respectively.

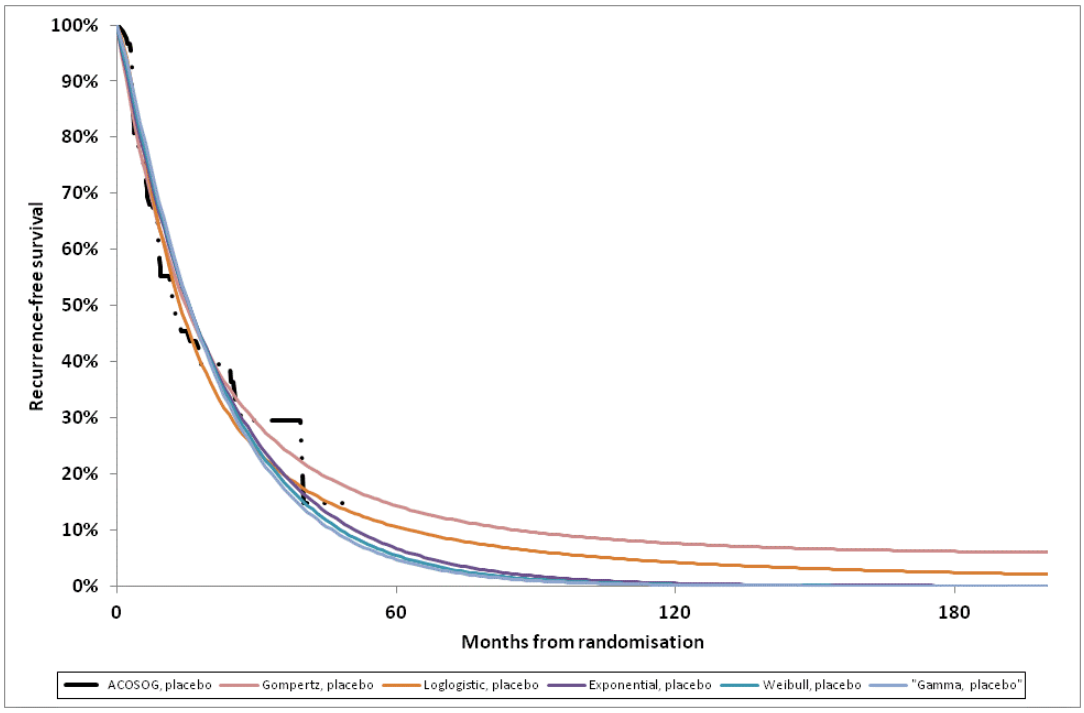
Rutkowski et al (2011) reported the risk of relapse from a series of 640 consecutive patients with primary, resectable, CD117-immunopositive GIST who did not receive adjuvant imatinib collected prospectively in the Polish Clinical GIST Registry database between September 1, 2001 and January 31, 2010. The median follow-up time after tumour resection was 39

months. According to the Joensuu classification, patients with high risk GIST had 29% (95% CI, 24–35%) 5-year RFS rate.. The authors reported that patients with high risk tumour according to the NCCN-AFIP classification had a 21% (95% CI, 16–28%) 5-year RFS rate.

Historical evidence for the pattern of long term recurrences for patients not receiving adjuvant therapy is provided by Miettinen et al. (2005) in a paper that presented data from 1765 cases with long-term follow-up.[51] This included 341 patients who qualify as 'high risk' according to the Miettinen 2006/AFIP criteria. The follow-up demonstrated that a small group of patients will achieve RFS of relatively long duration. Thus, when considering factors which confer high risk, the following was reported: in patients with gastric tumours between 5 cm and 10 cm in diameter, with a mitotic count greater than 5/50 HPF, 26% were still alive and with no evidence of disease at median follow-up of 13 years (range, 4 years to 32 years); in patients whose tumours were more than 10 cm in diameter and who had a mitotic count greater than 5/50 HPF, 10% remained alive and disease free at a median follow-up of 19 years (range, 5 years to 29.5 years).

Overall, comparing the predicted long-term extrapolation and historical data, the exponential, Weibull and gamma functions were deemed to be inappropriate to represent the long-term risk of recurrence for patients treated with surgical resection only and tended to overestimate the risk of recurrence in the long term in comparison to the external sources. The Gompertz and log-logistic distributions provided more credible long-term extrapolation. The Gompertz distribution was used in the basecase model on the basis of the historical evidence described above, which suggests that, even for high risk patients, 10% or more patients may remain recurrence free at nearly 20 years. Other parametric distributions are used in sensitivity analysis. See section 7.4.1.

Figure B-12. Parametric survival models (exponential, Weibull, gamma, loglogistic, Gompertz) for RFS for patients treated with surgical resection only



b) Estimation of the risk of recurrence for patients treated with surgical resection followed by 1 and 3 years of adjuvant imatinib – transition from Health State B to D, E and H and from D to C

This involved two steps:

- Step one: estimating the treatment effect compared with no treatment (placebo)
- Step two: applying the estimated treatment effect (Step One) to the baseline risk of recurrence for patients treated with surgical resection only (Figure B-12).

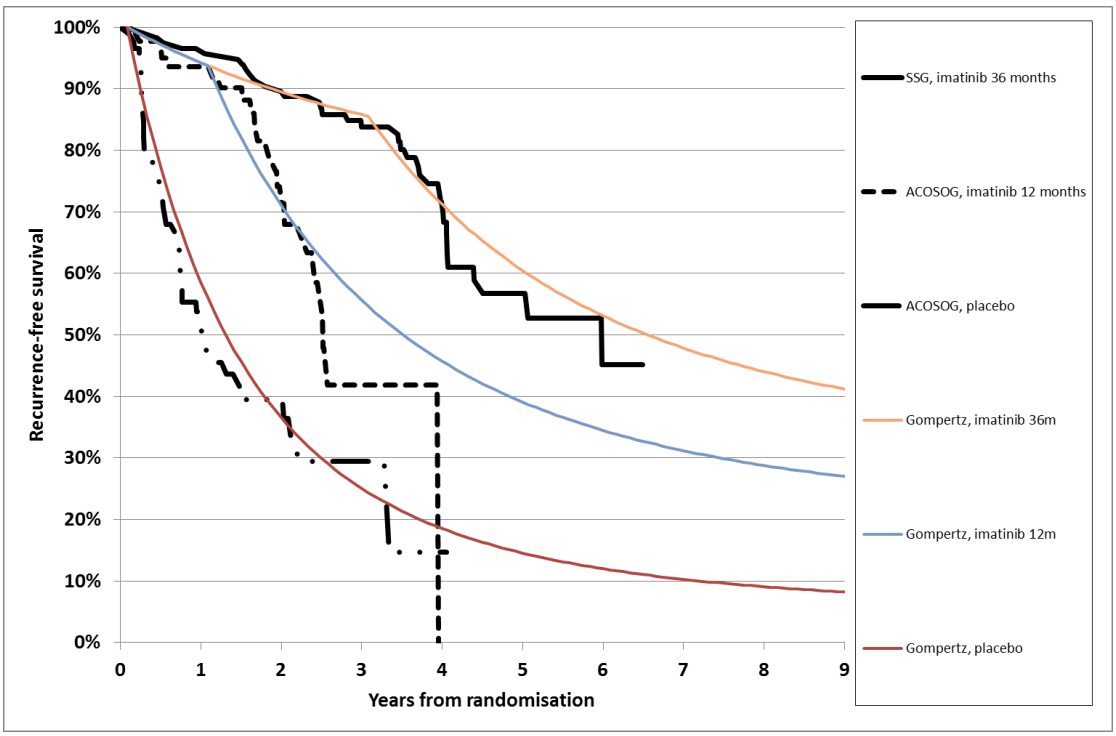
The treatment effect was estimated for two distinct periods: the period patients received adjuvant imatinib ("*on treatment*" period) and the period immediately after cessation of adjuvant imatinib ("*off-treatment*" period). Such approach was employed as the assumption of proportional hazard was deemed to be inappropriate for the whole duration of the observed data (details are provided below).

The treatment effect during the "on treatment" period was assumed to be the same irrespective of the planned treatment duration but was applied to the respective adjuvant imatinib treatment duration (1 or 3 years). The HR for risk of recurrence on adjuvant imatinib compared with placebo was estimated to be 0.111 (0.043 – 0.281) during the "*on treatment*" period. Further details are provided thereafter.

The treatment effect for patients receiving 1 or 3 years of adjuvant imatinib during the "off treatment" period (i.e. after cessation of adjuvant imatinib) compared with placebo (no treatment) was estimated from a frequentist "indirect comparison" between placebo vs. 1 year of adjuvant treatment, and 1 year of adjuvant vs. 3 years of adjuvant therapy.[95] Further details are provided thereafter. The estimated HR for the "off treatment" period for patients receiving 1 year of adjuvant imatinib vs. placebo was estimated to be 0.519 (0.297 – 0.906). The HR for the "off treatment" period for patients receiving 3 years of adjuvant imatinib vs. placebo was estimated to be 0.344 (0.160 – 0.741).

The estimated HR for the "on treatment" and "off treatment" period was applied to the baseline risk of recurrence for patients treated with surgical resection only to estimate the risk of recurrence for patients treated with surgical resection followed by 1 and 3 years of adjuvant imatinib. The estimated risk of recurrence for patients receiving adjuvant imatinib is presented in Figure B-13.

Figure B-13 Parametric survival curves used for the base case (Gompertz) for RFS



The method used to derive the risk of recurrence for patients treated with surgical resection followed by 1 or 3 years of adjuvant therapy is described below.

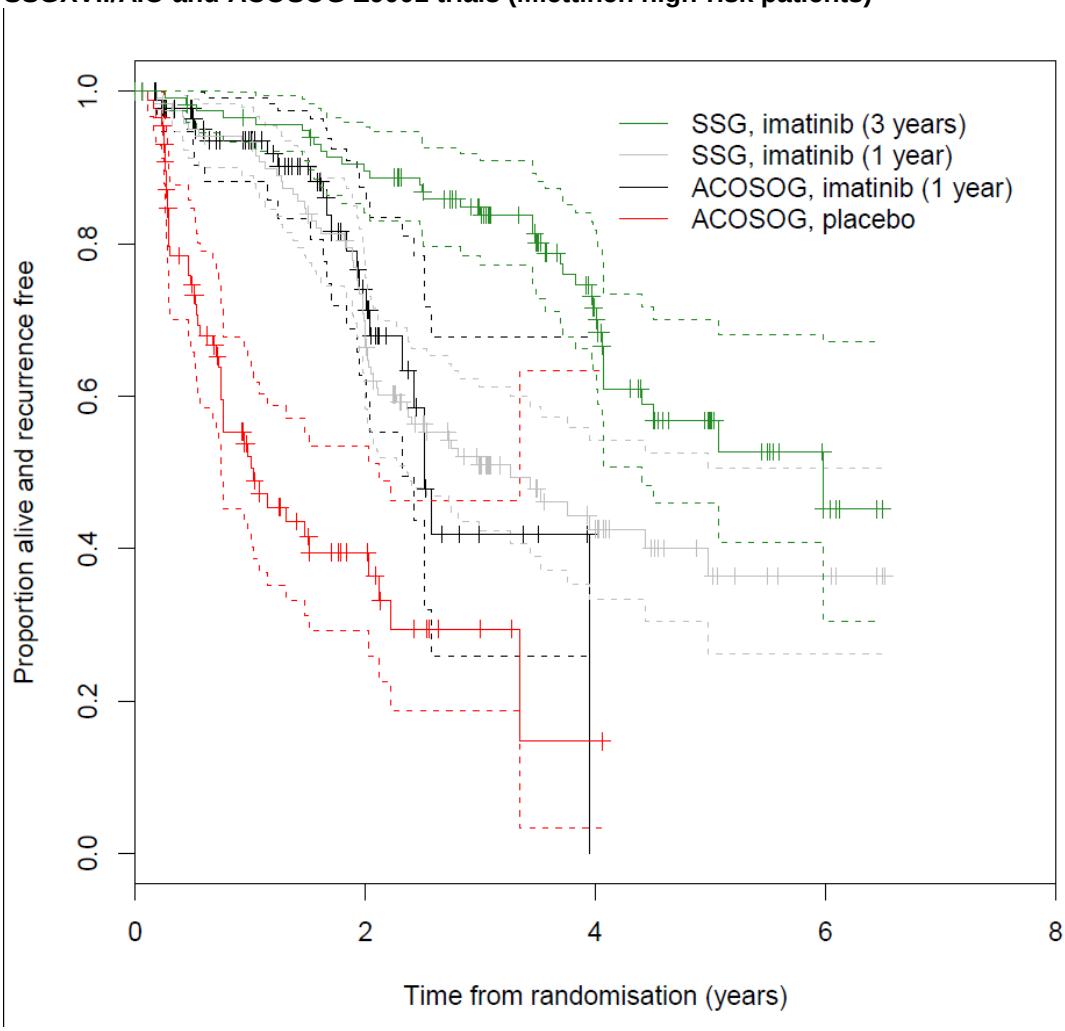
Estimating the treatment effect for patients treated with surgical resection followed by 1 or 3 years of adjuvant imatinib therapy vs. no treatment

The ACOSOG Z9001 trial compared patients treated with surgical resection only (placebo) with patients treated with surgical resection followed by 1 year of adjuvant imatinib therapy. The SSGXVII/AIO trial compared patients treated with surgical resection followed by 1 year of adjuvant imatinib therapy with patients treated with surgical resection followed by 3 years of adjuvant therapy.

There is no head-to-head trial directly comparing the strategies of surgery alone versus 3 years of adjuvant imatinib. This treatment effect is required for the economic model.

Where head-to-head comparisons between treatments are unavailable, an alternative approach is to derive treatment effects from an indirect comparison using a network of randomised controlled trials which contains the treatment strategies of interest. Indirect comparisons of data from trials with time-to-event endpoints are often conducted on the log hazard ratio with pairwise treatment comparisons calculated under the assumption of constant proportional hazards. However, inspection of the published Kaplan-Meier (KM) curves for RFS derived from the adjuvant imatinib studies clearly demonstrates that the assumption of proportional hazards does not hold in this case (Figure B-14) as the shapes of the curves are qualitatively different for each treatment arm. As a result, it is unlikely that a simple parametric proportional hazards model fitted to these curves would accurately estimate the expected value for mean survival under each treatment option.

Figure B-14. Kaplan-Meier estimates of RFS based on the observed data from the SSGXVII/AIO and ACOSOG Z9001 trials (Miettinen high-risk patients)[9,12]



As a traditional approach could not be used, an alternative approach was employed. Visual inspection of the Kaplan-Meier curves suggests that the hazard (risk) of recurrence for patients randomised to adjuvant imatinib behaves differently in two distinct periods; the period on treatment (1 or 3 years) and the period after cessation of treatment. In the treatment period (1 or 3 years) patients randomised to receive imatinib experience few recurrence or mortality events, which contrasts with the high event rate observed in the untreated patients in the corresponding period after initial surgery. Soon after the treatment period ends, the event rate in treated patients increases sharply, with the shape of the RFS curve showing qualitatively similar behaviour to that of the untreated patients immediately after surgery. This pattern suggests that a sensible modelling approach would be to estimate the hazard functions for patients treated with adjuvant Imatinib separately for two distinct periods:

- Hazard of recurrence on treatment
- Hazard of recurrence off treatment (at the end of the planned treatment duration)

Estimation of the hazard (risk) of recurrence during the period on-treatment (planned treatment duration of 1 or 3 years)

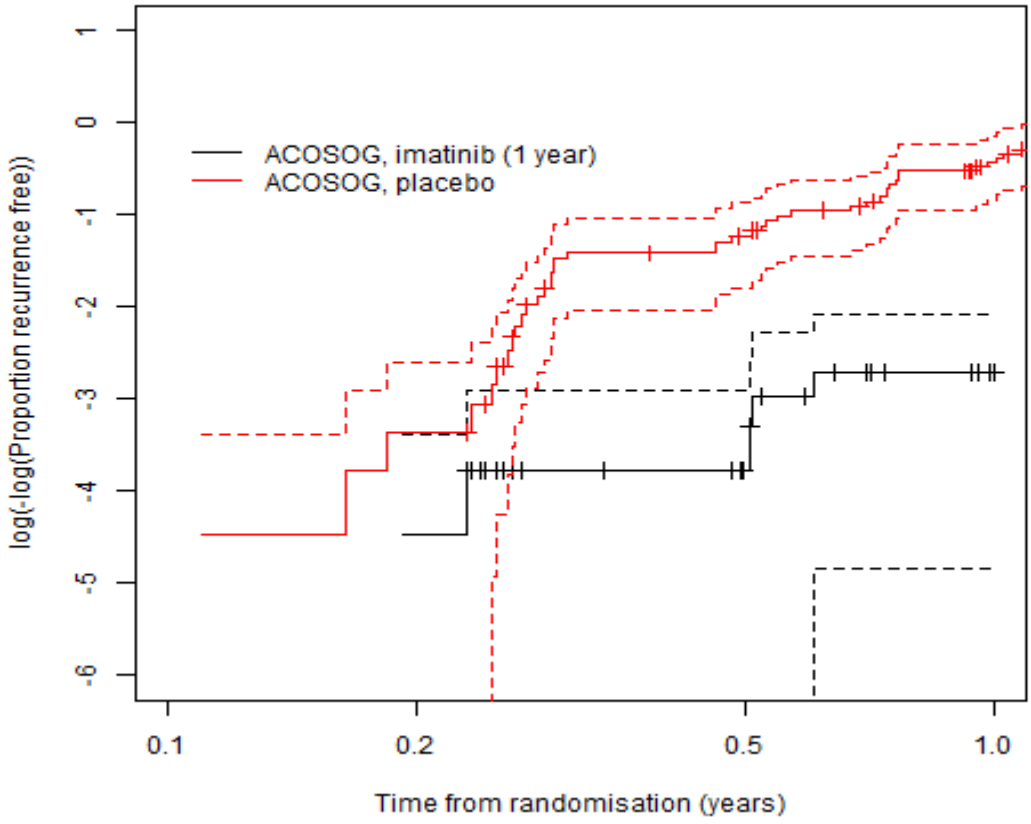
For patients on treatment it was assumed that the hazard for recurrence in the first year of imatinib treatment was the same regardless of whether or not the patient was to receive 1 or 3 years of treatment. Assuming that the hazard in the first year of treatment differs according to the planned treatment duration was judged to be not credible as treatment effectiveness at the time of the treatment onset should not be influenced by future events (i.e. continuing treatment after 1 year recurrence free survival). Whilst some differences were observed in the SSGXVII/AIO trial in the first year for patients randomised to 1 year of adjuvant imatinib and 3 years of adjuvant imatinib, the confidence interval was wide, and the differences in the first year is likely to be due to chance. However, it may be possible that the hazard is different in year 2 and 3 for patients treated with 3 years of adjuvant imatinib.

A treatment effect between no treatment vs. adjuvant imatinib treatment was required for the on-treatment period. Since it is assumed that the hazard is independent of planned treatment duration for the first year, an indirect comparison based on both randomised trials (No treatment vs. 1 year, 1 year vs. 3 year) was deemed to be not valid because in the SSGXVII/AIO trial all patients are on-treatment for this period and so there is no treatment comparison to be made.

Consequently, the analysis was based on data from the ACOSOG Z9001 trial alone. Of note, this may introduce some selection bias and overestimate the uncertainty in model estimates as it excludes evidence from the SSGXVII/AIO trial. However, including data from the SSGXVII/AIO trial into this analysis was deemed to be less robust and likely to introduce more biases to the analysis (and break randomisation). It would need to be assumed that the “missing” placebo arm in the SSGXVII/AIO would be the same as in the ACOSOG Z9001 trial.

The hazard ratio for RFS for the “on treatment” period is estimated from the hazard ratio for this outcome between the 1-year imatinib and placebo arms of the ACOSOG Z9001 trial, calculated using the Cox proportional hazards model truncating the data at 12 months (events and censoring that had occurred *after* 12 months were, instead, censored *at* 12 months). The validity of the proportional hazards assumption in the first 12 months after surgery is assessed by considering the complementary log log plot of the Kaplan-Meier estimate of the survival curves (Figure B-15). Although subject to substantial uncertainty, the curves are roughly parallel, suggesting that the proportional hazards assumption may hold, and therefore a HR can be estimated.

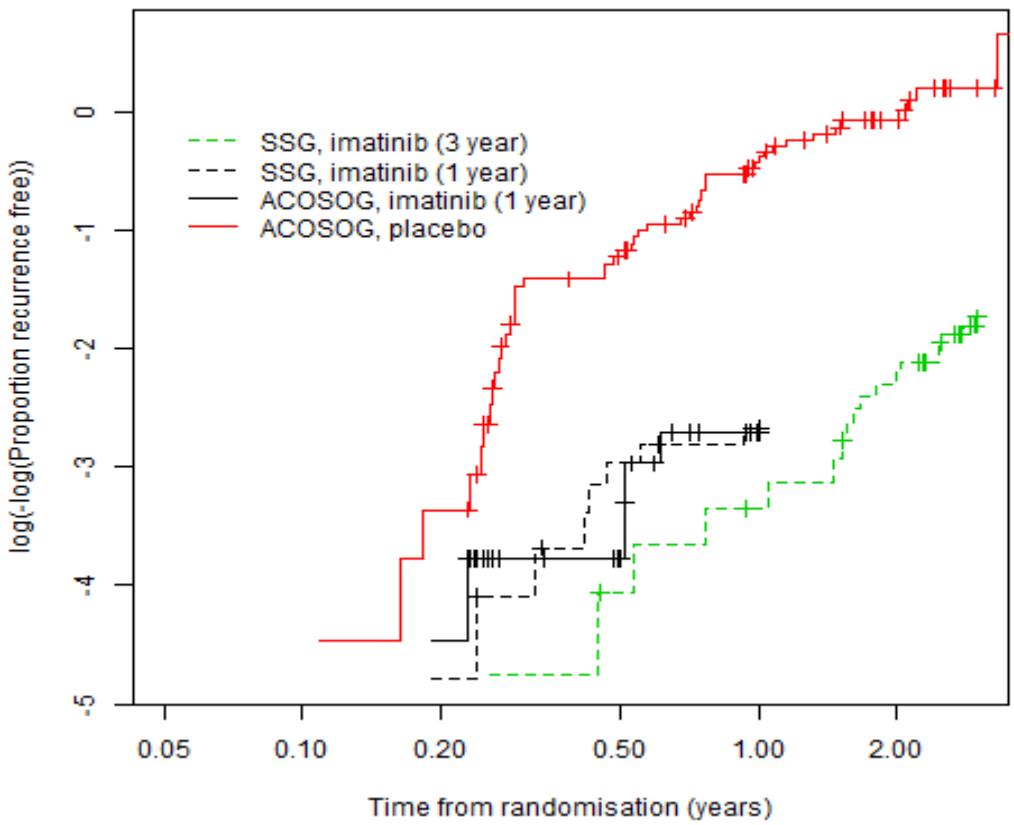
Figure B-15. Complementary log log plot of Kaplan-Meier estimate of recurrence free survival with 95% confidence bands - ACOSOG Z9001 trial, on treatment only



The HR for adjuvant imatinib compared with placebo was estimated to 0.111 (0.043 – 0.281) during the "*on treatment*" period.

The hazard of recurrence after the first year of imatinib therapy for patients treated for 3 years is modelled pragmatically because a direct comparison with no treatment is unavailable. The hazard ratio for the first year is applied for the whole 3-year period to the placebo curve. This ensures that the treatment effect is based on a direct comparison but requires the assumption that the treatment effect is not time dependent. Figure B-16 shows the complementary log log plot of each trial arm for the first 3 years post randomisation (treatment arms truncated at end of treatment period). The plot shows no evidence of a change in the behaviour of the hazard function after 1 year for patients on treatment in the 3 year arm of the SSGXVII/AIO trial relative to placebo. This suggests that treatment effect in the 3 year arm is not time dependent over the course of the treatment period, which is consistent with the above assumption.

Figure B-16. Complementary log log plot of Kaplan-Meier estimate of recurrence free survival - on-treatment period only



Therefore a HR of 0.111 (0.043 – 0.281) for adjuvant imatinib compared with placebo was was used the "*on treatment*" period for 1 year and 3-year treatment.

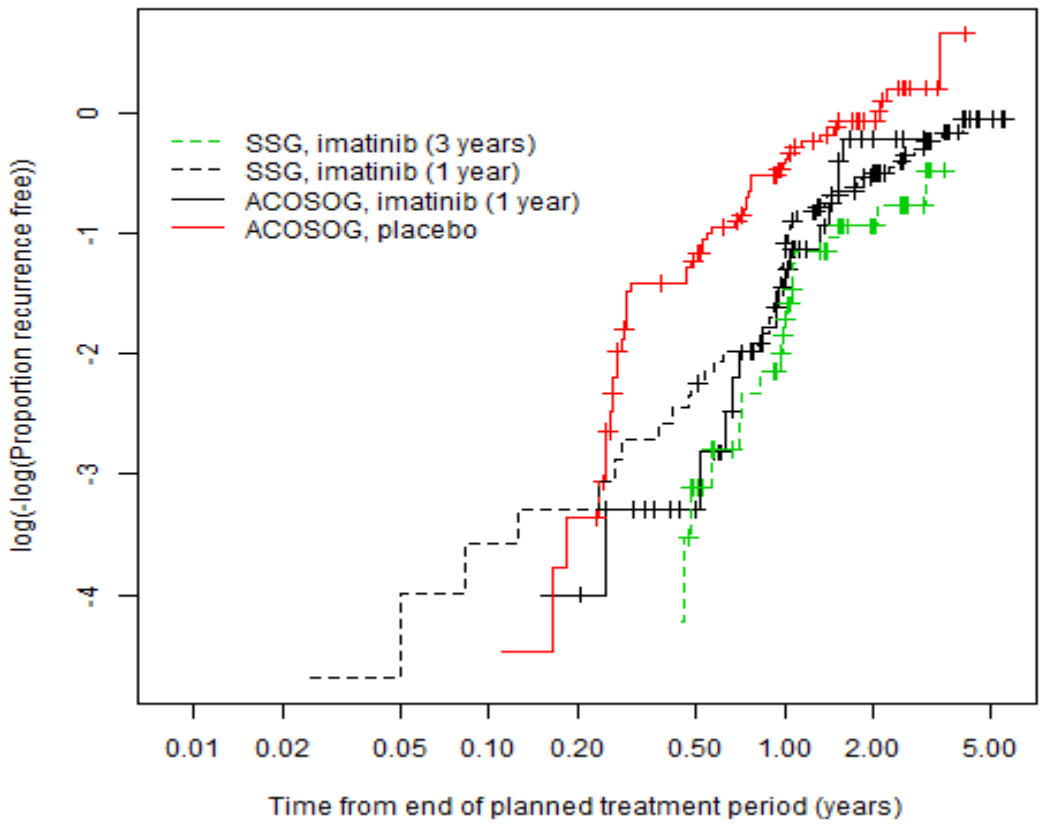
Estimation of the hazard (risk) of recurrence during the period off-treatment period (at the end of the planned treatment duration of 1 or 3 year)

Around the time at which the intended treatment period ends it is apparent that there is a sharp increase in the hazard of recurrence events in each of the imatinib arms of the trials. Intuitively, this suggests that the effect of imatinib therapy is, at least in part, to delay recurrence during the treatment period, after which the recurrence hazard increases towards the level of that experienced by patients immediately after initial surgery who receive no treatment. Note that the economic model is a cohort rather than an individual patient model, and so even if the hazard for individual patients were to increase to that of patients immediately after surgery who do not receive imatinib, the population hazard would be

expected to be lower because some patients at risk of early recurrence will have already experienced an event and left the risk set.

Figure B-17 shows the complementary log log plot of the hazard of recurrence free survival events for the data from each trial for the off-treatment period only, calculated by removing patients from the treatment arms who have an event or are censored whilst on treatment, and subtracting 12 or 36 months from the event and censor times for the remaining patients in the 1 year and 3 year imatinib arms respectively. Within each trial, the curves for each arm are approximately parallel (log log plot), suggesting the hazards are approximately proportional. In each case, the hazard is slightly higher in the arm with shorter treatment duration (placebo for ACOSOG Z9001, 1 year imatinib for SSGXVII/AIO). This is consistent with the above interpretation.

Figure B-17. Complementary log log plot of Kaplan-Meier estimates of recurrence free survival - off-treatment period



This motivates the approach to modelling recurrence hazard post-treatment period.

The approach can be described in the following steps:

- Step one: estimating the Kaplan-Meier curves for the post-treatment phase
    - For each trial and treatment considered, the data for the treatment arms is truncated on the left. This is achieved by removing patients who have experienced an RFS event or are censored within 1 or 3 years (as appropriate) and recalculating event and censor times for the remaining patients by subtracting 1 or 3 years from the original reported times. The dataset therefore contains information on RFS after the end of planned adjuvant imatinib after surgery for patients who are recurrence-free for the duration of the treatment period. Of note, data were not truncated for patients treated with surgical resection only (placebo arm) in the ACOSOG Z9001 trial.

- Step two: estimating the hazard ratio (for the post-treatment phase) from the new curves calculated in step one
    - Using this modified dataset, the hazard ratio for RFS (post-treatment phase only) is calculated
        - HR1: adjuvant imatinib 1 year vs. surgery only using the "modified" data from ACOSOG Z9001 trial
        - HR2: adjuvant imatinib 3 year vs. adjuvant imatinib 1 year using the "modified" data from the SSGXVII/AIO

- Step three: estimating the treatment effect of 3 years of adjuvant imatinib vs. surgery only using indirect comparison (HR3)
    - The hazard ratios calculated above (HR1 and HR2) are then combined using a frequentist indirect treatment comparison via a fixed effects model,[95] using the following formulae:
        - Log(adj3 vs. noT) = log(HR1) – log(HR2)
        - $SE[\log(\text{adj3 vs. noT})] = \sqrt{(SE[\log(HR1)^2] + SE[\log(HR2)]^2)}$

      adj3 = adjuvant 3 year imatinib;; noT = no treatment

    - This provides a hazard ratio for RFS for the comparison of 3 years of adjuvant imatinib versus surgery alone (HR3) for the post-treatment period.

The HR for RFS for the "off treatment" period for patients receiving 1 year of adjuvant imatinib vs. placebo (HR1) was estimated to be 0.519 (0.297 – 0.906) using data from the ACOSOG Z9001 trial. The HR for the "off treatment" period for patients receiving 1 year of adjuvant imatinib vs. 3 years of adjuvant imatinib (HR2) was estimated to be 0.663 (0.392 – 1.123) based on data from the SSGXVII/AIO trial.

The HR for the “off treatment” period for patients receiving 3 years of adjuvant imatinib vs. placebo was estimated to be 0.344 (0.160 – 0.741) using the frequentist indirect comparison approach.

The HR was applied in the adjuvant imatinib arm from the end of the planned adjuvant treatment duration (1 or 3 year). The HR was applied to the “no treatment” curve from baseline.

c) Other transition probabilities used in the economic model

Other event probabilities were assumed to be follow an exponential distribution and were estimated from published studies, using the following formula:

$p\ (event) = 1\text{-}r^{(1/t)}$

where r is the rate of occurrence and t is the time factor.

There are summarised below in Table B-29.

Table B-29. Monthly probabilities of events used in the economic model

	Mean	SE	Distribution	Source/comments
Monthly probability of death following				
Best supportive care	0.043	0.0043 (assumed to be 10% of the point estimate)	Beta	Huse et al. 2007[83] Tran et al. 2005[84] Demetri et al. 2012[94]
Imatinib 400 mg once daily	0.013	0.005	Beta	Verweij et al. 2004[73]
Sunitinib second-line treatment	0.040	0.014	Beta	Demetri et al. 2012[94]
Death due to non-GIST causes			Beta	Published government life tables for England[96]
Monthly probability of discontinuation				
Discontinuing 1-year adjuvant imatinib owing to AE (months 0−6)	1.36%	CI (0.77%-2.12%)	Beta	SSGXVIII/AIO study
Discontinuing 1-year adjuvant imatinib owing to AE (months 7−12)	0.09%	CI(0.06% - 0.10%)	Beta	SSGXVIII/AIO study
Discontinuing 3-year adjuvant imatinib owing to AE (months 0−6)	0.97%	CI(0.49% - 1.62%)	Beta	SSGXVIII/AIO study
Discontinuing 3-year adjuvant imatinib owing to AE (months 7−36)	0.41%	CI(0.31% - 0.45%)	Beta	SSGXVIII/AIO study
Discontinuing imatinib treatment for recurrence owing to AE	0.003	0.002	Beta	Verweij et al. 2004[73]
Discontinuing imatinib treatment for recurrence owing to progression	0.034	0.008	Beta	Verweij et al. 2004[73]
Discontinuing sunitinib second-line treatment (owing to AE and/or progression)	0.167	0.026	Beta	Demetri et al. 2012[94] Demetri et al. 2006[71]

GIST, gastrointestinal stromal tumour; SE, standard error ; AE, adverse event; SSGXVIII/AIO, Scandinavian Sarcoma Group and the Sarcoma Group of the Arbeitsgemeinschaft Internistische Onkologie

Mortality in patients treated with BSC

The probability of death following GIST recurrence for patients treated with BSC (first and second-line) was derived from 3 studies (Tran et al, 2005; Demetri et al, 2012; Huse et al, 2007).[83,84,94]

Tran et al (2005) conducted a large retrospective study in the USA of 1,458 patients with a diagnosis of GIST between 1992 and 2000 using the Surveillance, Epidemiology, and End Results (SEER) registry from the National cancer Institute. The authors reported that the median survival time for patients with GIST was 2.97 years (1 year observed survival rate of

77% and 5-year survival rate of 38%). This equated to a monthly probability of death of 0.022 using data at 1 year and 0.016 using data at 5 year.

Demetri et al (2012) in a randomised, double blind placebo-controlled trial examined the long-term efficacy of sunitinib in unresectable cKIT +ve imatinib resistant patients (n=207) versus placebo (n=105).

In this trial, patients assigned to the placebo arm could cross over to sunitinib at disease progression/study unblinding. Therefore, the authors analysed overall survival using conventional statistical methods and the rank-preserving structural failure time (RPSFT) method to explore cross-over impact. The authors reported that using conventional statistical analysis, the median survival was 64.9 weeks. After adjusting for cross-over using RPSFT analysis, the median OS for placebo was estimated to be 39.0 weeks. Assuming a median survival of 39 weeks, the monthly probability of death was estimated to be 0.074.

Finally, Huse et al (2007) in an economic evaluation of imatinib for the treatment of advanced GIST estimated the median survival for untreated patients to be 20 months (mean 37 months) based on the survival for patients with unresectable c KIT +ve advanced GIST (n=102) who did not respond to imatinib derived from Demetri et al (2002). As the trial did not have a BSC control group, the survival for the subgroup of 102 patients who withdrew from imatinib was used. Assuming a median survival of 20 months, the monthly probability was assumed to be 0.034.

The population and method used was different between these three studies. These three studies had some limitations. In the basecase, we used the average estimated from these three studies (Huse et al, 2007; Tran et al, 2005 and Demetri et al, 2012).[83,84,94] Sensitivity analyses were conducted using data from each individual study.

Probability of death for patients treated with imatinib 400 mg/day

The probability of death for patients treated with imatinib 400 mg/day (first-line) was taken from Verweij et al (2004). 946 patients were randomly allocated to receive imatinib 400 mg either once or twice a day. The authors reported that the 1 year and 2 year survival for patients treated once daily was 85% and 69%, compared with 86% and 74% for patients treated twice daily. Data for patients treated once daily was used in the economic model and transformed into monthly probabilities using the formula described above. As the calculated monthly probability using data at one and two year was broadly similar (0.013 vs 0.015), data at 1 year was used in the basecase. A sensitivity analysis is conducted using data at 2 years (0.015)

Probability of death for patients treated with sunitinib

The probability of death following sunitinib (second-line) treatment was taken from Demetri et al (2012)[94] in unresectable cKIT +ve imatinib resistant patients treated with sunitinib. Using long-term follow-up data the authors reported that the median OS for patients enrolled in the sunitinib arm was 72.7 weeks, equating to a monthly probability of death of 0.0405.

Probability of death from other causes

Finally, age-related mortality was estimated using the published life table data for England, using the following formula:[96]

p (age-related death) = $1-(\exp^{-mx})$

Probability of discontinuation for patients receiving adjuvant imatinib treatment (from Health State B to Health state E or H)

The monthly discontinuation probability for patients receiving adjuvant treatment (1 or 3 year) was calculated from data from the SSGXVIII/AIO study. The discontinuation rate was assumed to be different the first 6 months of adjuvant imatinib treatment and next 6 months.
At 6 months and 12 months, 7.9% and 8.4% of patients receiving one year adjuvant imatinib discontinued adjuvant treatment. For patients receiving 3 year adjuvant imatinib, the discontinuation rate at 6 and 36 months was 5.7% and 16.6% respectively. Monthly probabilities of discontinuation for the first 6 months and thereafter were calculated based on these figures.

Probability of discontinuation for patients treated with first-line imatinib 400 mg/day (from Health State C to G to H)

The probability of discontinuation following imatinib 400 mg/day treatment was taken from Verweij et al (2004).[73] The study reported that 7% of patients discontinued imatinib due to toxicity at median follow-up of 760 days year, equating to a monthly probability of 0.0029.

The authors also reported that 44% of patients allocated to imatinib once a day progressed after 2 years, equating to a monthly discontinuation due to progression of 0.034.

Probability of discontinuation for patients treated with sunitinib (from health state E or G to H)

Finally, the probability of discontinuation from sunitinib was taken from Demetri et al (2006)[71] in unresectable cKIT +ve imatinib resistant patients treated with sunitinib.

The monthly discontinuation for patients treated with sunitinib (0.167) was calculated as the sum of the monthly discontinuation due to progression (0.117) and AEs (0.050).

Demetri et al (2006)[71] reported that the median duration of progression-free survival was 24.1 weeks for sunitinib equating to a monthly discontinuation rate of 0.117. Similarly, Demetri et al (2006)[71] reported that the median numbers of days on drug was 56.0 (range 1–236) and that 9% of patients in the sunitinib group discontinued treatment because of adverse events equating to a monthly discontinuation rate due to AE of 0.050.

7.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

Examination of trial outputs for RFS indicates varying transition probabilities over time (Figure B-14). The parametric survival models that have been employed allow for differences in probabilities over time. A number of alternative models were tested to allow for a variety of assumptions to be examined. These are described in section 7.3.2.

Discontinuation rates by treatment arm (1 or 3 year) were also varied with time assuming a different discontinuation rate between the first 6 months and thereafter (Table B-29).

For simplicity, the probability of death following BSC, imatinib 400 mg treatment, sunitinib was assumed to be constant with time and follow an exponential distribution.

7.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what

sources of evidence were used, and what other evidence is there to support it?

Recurrence was used as a surrogate outcome for death. Following recurrence, patients were assumed to follow the same treatment pathways, with the same probability of further progression and death. The benefit of delayed recurrence was, therefore, assumed to lead to a survival benefit. This was considered to be a reasonable assumption given the evidence available that patients receiving adjuvant imatinib had an improved survival and that response to imatinib treatment does not appear to be affected by whether or not patients received adjuvant therapy.

As described in section 6.5.3 the clinical evidence suggests that longer-term adjuvant imatinib therapy can confer OS benefits. In the SSGVII/AIO study, a statistically significant improvement in OS was observed for 3 years of imatinib adjuvant therapy compared with 1 year of therapy in the Miettinen high-risk subgroup (5-year OS rate 74.2% in the 1-year imatinib group and 89.5% in the 3-year imatinib group; HR 0.39; 95% CI 0.19 to 0.79, p = 0.007)[9]. In the ACOSOG Z9001 study comparing 1 year of imatinib therapy with no adjuvant treatment, a trend towards improved OS was noted for adjuvant therapy over placebo but the difference was not statistically significant. In the primary analysis, this reflects the low number of events and the short follow-up period; in the longer-term follow-up at five years, it is likely to be confounded by the fact that, after an interim analysis, accrual was stopped and patients on placebo could cross over to receive imatinib for 1 year.).[8,13]

Non-RCT evidence also supports the view that the RFS benefits of long-term adjuvant therapy in high-risk groups can be associated with survival benefits, with 2 to 3 years of adjuvant therapy reported to significantly extend survival compared with no therapy.[16,19] However, the preliminary results reported from the EORTC 62024 study of 2 years adjuvant therapy versus no adjuvant therapy does not allow any clear conclusions on the impact of treatment on OS in high-risk patient groups.[11]

Evidence to date also suggests that patients who have had imatinib in the adjuvant setting will continue to respond to imatinib in the metastatic setting, as demonstrated in analyses of data from the SSGXVII/AIO and ACOSOG Z9001 trials[8,10,54].

Reichardt et al (2012)[82] reported data on patients from the SSGXVII/AIO trial who were diagnosed with recurrent GIST after having received imatinib in the adjuvant setting. At a median follow-up of 54 months, 27.1% of patients randomised to the 1-year adjuvant imatinib arm had a recurrence vs. 13.6% in the 3-year adjuvant imatinib arm. These patients were retreated with imatinib (88% received 400 mg/day). No differences in benefit were observed between the 2 arms (p = 0.385 for response and p = 0.289 for TTP). 32.6% had CR, 30.4%

had partial response, and 21.7% had stable disease. The median time to progression was 35.7 months. This study suggests that the time to disease progression for patients retreated with imatinib following adjuvant imatinib was similar to the time to progression observed in patient populations that have not been exposed to imatinib in the adjuvant setting.[97] The results of this study also suggest that the duration of adjuvant treatment does not affect the future response to imatinib since differences between the two treatment arms were not reported.

This is confirmed by a retrospective analysis of the ACOSOG Z9001 trial. Out of the 325 ITT population randomised to adjuvant imatinib, 25 patients developed a recurrence following completion of of adjuvant therapy in the period up to the data cut-off 12 April 07. Table B-30 presents the responses and duration of response when imatinib was re-administered for recurrent disease following completion of 1 year of adjuvant treatment (data from 23 out of the 25 patients). Data from 2 patients had not yet been obtained at the time of reporting.[60]

Table B-30. Results of re-challenge with imatinib following relapse after 1 year of adjuvant treatment for patients who had a relapse after adjuvant imatinib treatment in the ACOSOG Z9001 study

Randomi-sation number	Adjuvant treatment duration (months)	Time to relapse from adjuvant treatment, months	Imatinib dose at relapse, mg/day	Response[a] to re-challenge	Response[a] duration[b] (months)
[redacted]	12	26	400	Y	14
[redacted]	12	6	400	Y	48+
[redacted]	11	36	400	Y	14.5+
[redacted]	12	17.5	NA[c]	NA[c]	NA[c]
[redacted]	8	16	400	Y	30+
[redacted]	12	NA[d]	NA[c]	NA[d]	NA[d]
[redacted]	13.5	12	600[e]	-	4
[redacted]	12	11	400	N	NA
[redacted]	12	10	400	Y	14
[redacted]	12	17.5	400	Y	20[f]
[redacted]	2	5	300	Y	4.5[g]++
[redacted]	1.5	0	NA[h]	NA[h]	NA[h]
[redacted]	12	18.5	400	Y	10+
[redacted]	12	18	400	Y	21+
[redacted]	6	14	400	Y	22+
[redacted]	12	3	400	Y	14
[redacted]	6	NA[i]	800	NA[i]	NA[i]
[redacted]	12	12.5	400	NA[i]	16+[j]
[redacted]	12	11	300	NA[K]	19+[k]
[redacted]	13	7	800	Y	20.5+
[redacted]	12	7	600	Y	14+
[redacted]	7	6	400	Y	unknown[l]

[redacted]	1	5	400	Y	20

,[60]

Tx – treatment, Y – Yes, N – No,

[a]Response included objective response and stable disease.

[b]Time from start of re-challenge treatment to progression in patients who "responded" according to investigator.

[redacted]

+Patients still on imatinib treatment and responding at time of reporting.

++Patient responded for a minimum of 4.5 months; no information on response after August 2005.

In the majority of available cases (15/23), patients responded to a rechallenge of 400 mg imatinib which was the dose administered during adjuvant treatment.[60] In seven of these patients, the duration of response was in excess of 19 months and in most patients treatment was ongoing.

In summary, the additional data from the pivotal ACOSOG Z9001 and SSGXVII/AIO studies confirm that imatinib remains effective in treating recurrent GIST after previous adjuvant therapy. Patients who relapse following a period of imatinib adjuvant therapy at a dose of 400 mg will, in a majority of cases, respond to the same imatinib dose. These response rates and duration of response are comparable with those observed in patients who have not been exposed to prior adjuvant imatinib.[59,60]

Although not directly relevant to re-challenge following adjuvant treatment, further supportive evidence comes from the efficacy of imatinib re-challenge in patients with progressive disease after treatment interruption in the BFR14 trial[98] and a further study of reuse of imatinib in patients with metastatic disease failing imatinib or sunitinib.[58]

In the BFR14 trial, among the 26 patients who discontinued imatinib after 1 year and then progressed, all restarted imatinib treatment at 400 mg/day; the majority of these patients (92%) achieved tumour control.[98] Kang et al (2013)[58] reported results for a randomised, double-blind trial which included patients with metastatic or unresectable GIST who had experienced disease progression after treatment with at least sequential imatinib and sunitinib and were then treated with imatinib or placebo. Results suggested that re-use of imatinib can improve PFS in patients with advanced GIST who had previously received, responded to and then failed on imatinib and sunitinib.

7.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[3]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

The model structure is based on a model previously submitted to NICE,[61] informed by discussion with UK clinical experts.

Overall, five clinicians agreed to participate following invitations sent out to 12 clinicians from a list of leading UK clinicians, provided by Novartis UK. A telephone interview was conducted

[3] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

with each of the clinicians and their responses were recorded. These responses were used to validate the structure of the model and provide best estimates of the proportion of patients receiving surgery on recurrence, the type of surgery received and second-line treatment.[91]

Summary of selected values

7.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

The list of values used in the economic model is presented in Table B-31.

Table B-31. Summary of variables applied in the economic model

Variable	Value	CI (distribution)	distribution	Reference
Starting population	359	N/A	Fixed	
Starting age (of cohort)	61	N/A	Fixed	
Mortality from GIST (in no recurrence & on imatinib therapy)	–	N/A	Fixed	
Discontinuing 1-year adjuvant imatinib owing to AE (months 0−6)	1.36%	CI (0.77%-2.12%)	Beta	Table B-29; Section 7.3.2 Calculated from SSGXVIII/AIO trial
Discontinuing 1-year adjuvant imatinib owing to AE (months 7−12)	0.09%	CI(0.06% - 0.10%)	Beta	Table B-29; Section 7.3.2 Calculated from SSGXVIII/AIO trial
Discontinuing 3-year adjuvant imatinib owing to AE (months 0−6)	0.97%	CI(0.49% - 1.62%)	Beta	Table B-29; Section 7.3.2 Calculated from SSGXVIII/AIO trial
Discontinuing 3-year adjuvant imatinib owing to AE (months 7−36)	0.41%	CI(0.31% - 0.45%)	Beta	Table B-29; Section 7.3.2 Calculated from SSGXVIII/AIO trial
Probability of receiving sunitinib following recurrence in health state B (on adjuvant imatinib during	0.900	N/A	Fixed	Section 7.2.2 Based on assumption

treatment period)				
Probability of receiving BSC following recurrence in health state B (on adjuvant imatinib during treatment period)	0.100	N/A	Fixed	Section 7.2.2 Based on assumption
Mortality from GIST (in post-recurrence & imatinib 400 mg treatment)	0.013	SE: 0.0053 (0.0051-0.0257)	Beta	Table B-29; Section 7.3.2 Verweij et al. 2004[73]
Discontinuing imatinib treatment for recurrence owing to AE	0.003	SE: 0.0025 (0.0002-0.0094)	Beta	Table B-29; Section 7.3.2 Verweij et al. 2004[73]
Probability of sunitnib (in post-recurrence & imatinib 400 mg treatment)	0.900	N/A	Fixed	Section 7.2.2 Based on assumption
Probability of BSC (in post-recurrence & imatinib 400 mg treatment)	0.100	N/A	Fixed	Section 7.2.2 Based on assumption
Discontinuing imatinib treatment for recurrence owing to progression	0.034	SE: 0.0083 (0.0194-0.0517)	Beta	Table B-29; Section 7.3.2 Verweij et al. 2004[73]
Probability of sunitnib (in post-recurrence & imatinib 400 mg treatment)	0.900	N/A	Fixed	Section 7.2.2 Based on assumption
Probability of BSC (in post-recurrence & imatinib 400 mg treatment)	0.100	N/A	Fixed	Section 7.2.2 Based on assumption
Mortality from GIST (in post-recurrence & sunitinib 2nd line treatment)	0.040	SE: 0.0137 (0.0182-0.0715)	Beta	Table XX; Section 7.3.2 Based on Demetri et al. 2012[94]
Discontinuing sunitinib second-line treatment (owing to AE and/or progression)	0.167	SE: 0.0259 (0.1201-0.2216)	Beta	Table B-29; Section 7.3.2 Based on Demetri et al. 2012[94]
Mortality from GIST (in best supportive care)	0.043	SE: 0.0043 (0.0352-0.0521)	Beta	Table B-29; Section 7.3.2 Huse et al. 2007[83] Tran et al. 2005[84] Demetri et al. 2012[94]
Utility weights				
Age	61	N/A	Fixed	
Utility for Health state A :	0.822	NA	Beta	Table B-33; Section 7.4.8

Recurrence-free				Age-specific health utility from the general population values taken from Ara and Brazier (2009)[75] assuming a mean age of 61 years old
Utility for Health state B: No recurrence and on adjuvant imatinib treatment	0.741	N/A	Beta	Table B-33; Section 7.4.8 Derived from utility value used in health state A and assuming a decrement in utility of 0.081 for patients receiving adjuvant imatinib
Utility for Health state C, E: Recurrent GIST (1st recurrence) with treatment decrement	0.739	SE: 0.016 (0.706-0.771)	Beta	Table B-33; Section 7.4.8 Assumed to be the same as Health State E and G
Health state D: No recurrence and completed adjuvant imatinib therapy	0.822	NA	Beta	Table B-33; Section 7.4.8 Assumed to be the same as Health State A
Utility for Health state E : Post recurrence and on sunitinib	0.739	SE: 0.016 (0.706-0.771)	Beta	Table B-33; Section 7.4.8 Based on Chabot et al (2008)[76]
Utility for Health state G : sunitinib second-line treatment	0.739	SE: 0.016 (0.706-0.771)	Beta	Table B-33; Section 7.4.8 Based on Chabot et al (2008)[76]
Utility for Health state H : BSC (Progressive disease)	0.577	SE: 0.029 (0.520-0.635)	Beta	Table B-33; Section 7.4.8 Based on Chabot et al (2008)[76]

Drug acquisition costs				
Imatinib monthly drug acquisition cost	£1,750	N/A	Fixed	Based on bnf (2013) [4]
Sunitinib monthly drug acquisition cost (incorporating PAS agreement)	£1,615	N/A	Fixed	Derived from bnf (2013)[4] and assumption
Management costs				
Recurrence-free GIST (First 3 months)	£102.00	SE: 10.2 (82.99-122.94) SE assumed to be 10% of the point estimate	Gamma	Estimated from UK clinical guideline, assumption, and UK unit costs[6]
Recurrence-free GIST (0.25 to 2.25 years)	£94.83	SE: 9.48 (77.16-114.30) SE assumed to be 10% of the point estimate	Gamma	Estimated from UK clinical guideline, assumption, and UK unit costs[6]
Recurrence-free GIST (2.25 to 4.25 years)	£51.00	SE: 5.1 (41.49-61.47) SE assumed to be 10% of the point estimate	Gamma	Estimated from UK clinical guideline, assumption, and UK unit costs[6]
Recurrence-free GIST (4.25 years +)	£29.08	SE: 2.91 (23.66-35.05) SE assumed to be 10% of the point estimate	Gamma	Estimated from UK clinical guideline, assumption, and UK unit costs[6]
Adjuvant Imatinib 400 mg/day (First 3 months)	£102.33	SE: 10.233 (83.26-123.34) SE assumed to be 10% of the point	Gamma	Estimated from UK clinical guideline, assumption, and UK unit costs[6]

		estimate		
Adjuvant Imatinib 400 mg/day (0.25 to 2.25 years)	£51.17	SE: 5.11 (41.63-61.67) SE assumed to be 10% of the point estimate	Gamma	Estimated from UK clinical guideline, assumption, and UK unit costs[6]
Adjuvant Imatinib 400 mg/day (2.25 to 5 years)	£29.25	SE: 2.95 (23.79-35.25) SE assumed to be 10% of the point estimate	Gamma	Estimated from UK clinical guideline, assumption, and UK unit costs[6]
Adjuvant Imatinib 400 mg/day (5 years +)	£18.00	SE: 1.8 (14.64-21.69) SE assumed to be 10% of the point estimate	Gamma	Estimated from UK clinical guideline, assumption, and UK unit costs[6]
Imatinib 400 mg/day for recurrence (medical cost)	£105.67	SE: 10.57 (85.97-127.36) SE assumed to be 10% of the point estimate	Gamma	Estimated from UK clinical guideline, assumption, and UK unit costs[6]
Sunitinib for recurrence (medical cost)	£105.67	SE: 10.57 (85.97-127.36) SE assumed to be 10% of the point estimate	Gamma	Estimated from UK clinical guideline, assumption, and UK unit costs[6]
Cost in BSC	£783	SE: 78.34 (637-944) SE assumed to be 10% of the point estimate	Gamma	Table B-35; Section 7.5.6
One-off Cost of	£1 430.69	SE: 143	Gamma	Table B-35; Section

Recurrence		(1164-1724) SE assumed to be 10% of the point estimate		7.5.6
Average cost of treating AEs	£418.57	SE: 41.86 (340.57-504.50) SE assumed to be 10% of the point estimate	Gamma	Table B-35; Section 7.5.6
Discount rate	0.035	N/A (fixed)		
Baseline risk of recurrence				
Gompertz distribution (placebo arm), mu	-0.019		Multivariate normal	
Gompertz distribution (placebo arm), sigma	0.054		Multivariate normal	
Treatment effect				
HR on-treatment – adjuvant Imatinib vs. placebo	0.111	CI[95%]: 0.043 – 0.281		Section 7.3.2
HR off-treatment – 1 year adjuvant imatinib vs. placebo	0.519	CI[95%]: 0.297 – 0.906		Section 7.3.2
HR off-treatment – 3 year adjuvant imatinib vs. placebo	0.344	CI[95%]: 0.160 – 0.741		Section 7.3.2
CI, confidence interval				

7.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.

Outcomes were extrapolated beyond the follow-up period of the trials. The RFS curve for the no treatment arm of the model was derived from patient-level data from the placebo arm of the ACOSOG Z9001 dataset. A parametric survival model was fitted to the data.

7.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Table B-32 summarises the assumptions used in the economic model.

Table B-32 Summary of assumptions used in the economic model.

Assumptions		
Topic	**Assumption**	**Rationale**
MODEL STRUCTURE		
Markov model	Markov-state transition approach was used	Markov modelling approach is appropriate in order to allow modelling of disease progression over time.
	Transitions between health states occur at one month intervals.	Monthly transitions are appropriate to capture accurately recurrence and the discontinuation of treatment.
	The model runs over a 50-year time horizon	All patients will have died of GIST or other causes within this period. In accordance with NICE reference case[92]
Length of adjuvant treatment	Adjuvant therapy is given for 1 or 3 years	The ACOSOG Z9001 study was designed based on a conservative treatment period of 1 year, since this study was designed at a time when imatinib in the advanced setting was itself under investigation. It was the first large study to explore the use of imatinib in the adjuvant setting. More recently the SSGXVIII/AIO study comparing 3 years of adjuvant imatinib therapy to 1 year of imatinib adjuvant therapy observed an OS advantage for high-risk patients given the longer-term therapy.[10] One year of adjuvant treatment with imatinib was included as there are no direct comparison available between patients treated with surgical resection followed by 3 years of adjuvant imatinib and patients treated with surgical resection only.
Recurrence rates	The risk of recurrence for patients treated with surgical resection only (comparator arm) and patients treated with surgical resection followed by 1 or 3 years of adjuvant Imatinib therapy was derived from an analysis of the SSGXVIII/AIO and ACOSOG Z9001 trials.	Recurrence rates are taken from the two pivotal trials.
	The baseline risk of recurrence for patients treated with surgical resection only was taken from the ACOSOG Z9001 trial	

	The treatment effect was estimated for two distinct periods: the period patients received adjuvant imatinib ("*on treatment*" period) and the period immediately after cessation of adjuvant imatinib ("*off-treatment*" period).	This approach was employed as the assumption of proportional hazard was deemed to be inappropriate for the whole duration of the observed data. The treatment effect was estimated from the pivotal trials – further details are provided in section 7.3.2
	For patients treated for 3 years the hazard ratio for the first year is applied for the whole 3-year period to the placebo curve.	Assumption given that direct comparison with no treatment is unavailable.
	Patients who discontinue adjuvant therapy (before the end of the planned treatment duration) due to adverse events (AEs) move to the "No recurrence and no treatment" state (Health state A). These patients are assumed to have the same rate of recurrence as patients remaining on adjuvant imatinib	Patients who discontinued treatment were not censored when calculating the RFS and therefore the RFS used in the economic model is for all patients randomised to the adjuvant treatment arm (therefore a mix of patients who discontinued and did not discontinue).
Utilities	GIST patients who are surgically resected and recurrence-free have the same utility as healthy individuals in the same age	This is an assumption based on the fact that, following the immediate post-surgery period, these patients are recurrence-free with no symptoms; to all intents and purposes "well". A reduced utility for these patients is tested in sensitivity analysis
	Utilities associated with the no recurrence health state were multiplied by age-specific healthy utility values.	This takes account of the average utility of a given population of aged 61;[75] Assuming a baseline of perfect health over time ignores the natural decline in quality of life associated with co-morbidities, potentially over-estimating the benefits of treatment.
	Utility values for second line treatment and for progressive disease were taken from Chabot et	Assumption, due to lack of relevant utility study for imatinib.

	al,[76] which reported utilities for health states associated with sunitinib treatment and progression on BSC, valued using the EQ-5D.	
	It was assumed that all patients receiving adjuvant imatinib treatment have a lower utility during the entire treatment period due to adverse effects of treatment. A utility decrement of 0.081 for patients on adjuvant treatment is assumed in the basecase.	Assumption, due to lack of relevant utility study for imatinib. The utility decrement was taken from Chabot *et al*, who demonstrated a 0.081 difference in the mean utility for patients receiving sunitinib compared to those who were not receiving treatment. [76]
Costs	The one-off onset cost of recurrence is assumed to include one GP visit, one specialist outpatient visit, one CT scan, and for those suitable for resection (assumed to be 15% of patients) cost of surgical resection of the tumour or distant metastases	The frequency of follow-up visits and tests was estimated from the UK guidelines for GIST[6] patients and is therefore considered appropriate for a UK evaluation. UK clinicians provided estimates of the proportion of patients likely to receive surgery on recurrence.[91]
	Costs of continuing phase of cancer (defined as the period between the first year after diagnosis and the last year of life) are estimated assuming, on average, two GP visits per year, five outpatient visits per year and 0.5 CT scans.	The frequency of visits and tests was estimated from the UK guidelines for GIST patients[6] and is therefore considered appropriate for a UK evaluation.

Current practice		
	Patients who enter BSC are assumed to have progressive disease and are no longer being actively treated with either imatinib or sunitinib. Once in this state, patients remain there until death	This is in line with treatment pathway
	it is assumed that patients on adjuvant imatinib therapy do not have regular CT scans on the basis that scans would be undertaken only if a patient began displaying symptoms.	This is based on current UK practice

7.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

The purpose of a primary resection of a KIT-positive GIST (with or without imatinib) is to surgically remove the tumour, leaving no margins, and minimising the risk of recurrence with the objective of extending the period that the patient is disease-free and able to enjoy as near to normal health-related quality of life (HRQL) as possible.

GIST has been shown to have an impact on performance status.[38] Key symptoms include fatigue, which has a similar impact on patients as experienced in other cancers, and pain, with the majority of patients requiring analgesic therapy.[38] Additional symptoms include GI bleeding, malaise, decreased weight, nausea and vomiting, all of which will impact on HRQL.[38]

7.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

Patients who are disease-free following surgery are able to enjoy a near to normal health-related quality of life (HRQL).

Recurrence is associated with a reduced quality of life, as described in section 7.4.1. Patients experiencing metastatic recurrence which has failed to respond to imatinib or sunitinib are

treated with best supportive care. They are assumed to have progressive disease, and experience significant worsening of HRQL until death.

HRQL data derived from clinical trials

7.4.3 If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

No quality of life data was collected in from the ACOSOG Z9001 or SSGXVIII/AIO studies.

Mapping

7.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

Not applicable.

HRQL studies

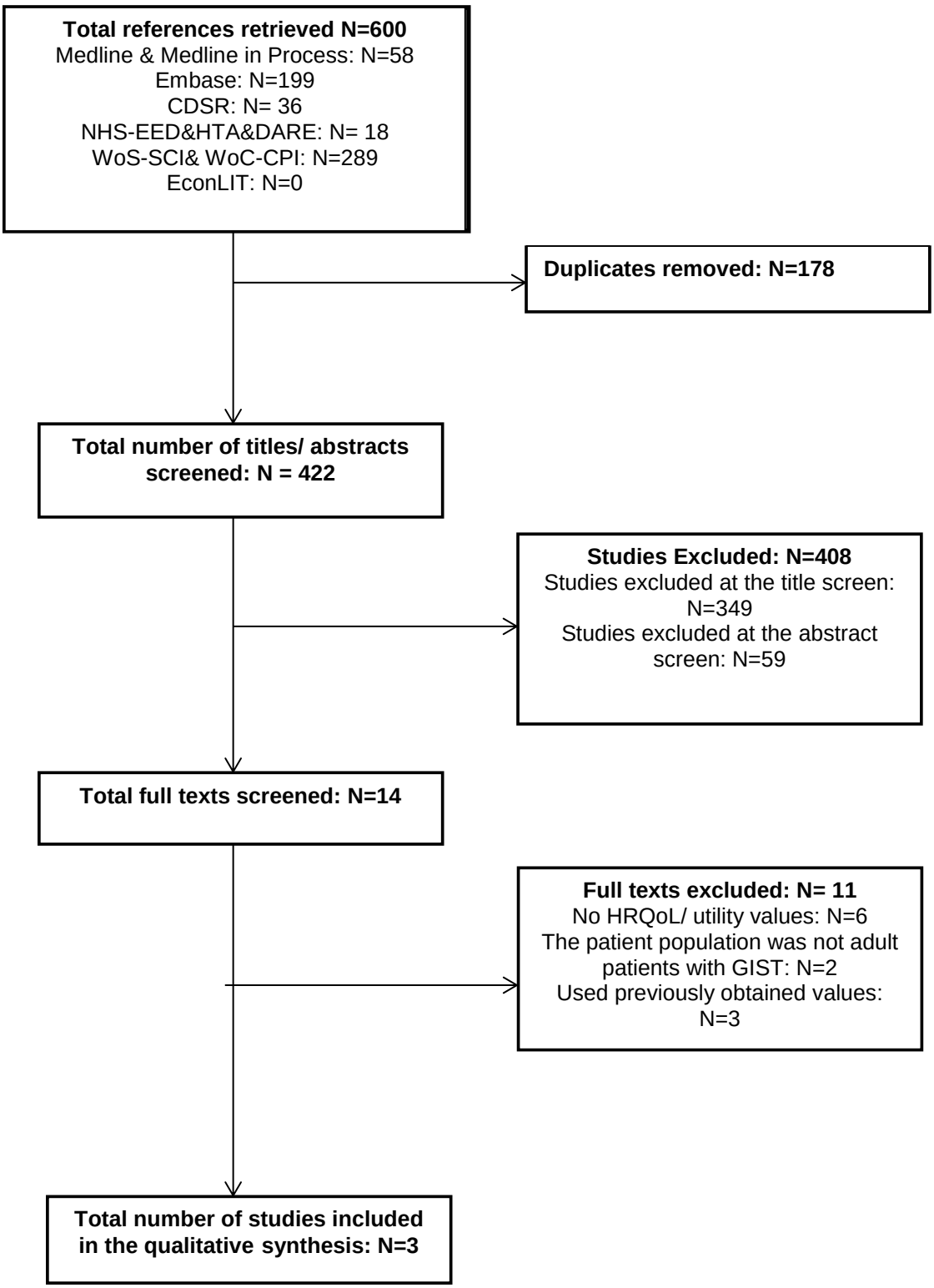
7.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria

used. The search strategy used should be provided in section 10.12, appendix 12.

Systematic searches were carried out between the 13th and 18th December 2013 to retrieve studies reporting health utility values. See section 7.1.1 for the list of database sources searched. The population terms for GIST (e.g. statements 1–33 in Medline strategy) were combined with a health utilities filter (e.g. statements 70–93 in the Medline strategy) in the search strategy. The search strategy was translated across all databases. No date limits were applied in these searches. All search strategies are provided in Appendix Section 10.12.

The flow diagram of included and excluded HRQL studies is presented in Figure B-18.

Figure B-18. Flow diagram of included and excluded HRQL publications from the review



Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.

- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

Overall, three studies met our inclusion criteria.[63,76,77]

Chabot et al (2008)[76] reported health utilities estimated using the EQ-5D from the A6181004 trial for patients free of progression (0.712 ± 0.2 during the 4 weeks on sunitinib treatment and an improvement of 0.081 ± 0.02 during the 2 weeks off sunitinib treatment), patients with no progression on BSC (0.781 ± 0.2) and for progression (0.577 ± 0.3). However, little detail is reported in the paper on how the EQ-5D was valued in the trial.[71] It is also unclear from the paper whether the UK tariff was used. Thus it is unclear whether EQ-5D values reported in this study are consistent with the NICE reference case.

In a previous health technology appraisal (HTA) of imatinib, Wilson et al (2005)[77] reported utility values used by the manufacturer in his submission to NICE. Utility values were elicited mapping ECOG performance status from the CST157I-B2222 trial to EQ-5D scores using 3 clinical experts. Using this approach, the manufacturer estimated the utility value for patients in the “progressive disease” health state to be 0.875 and 0.935 for patients in treated with imatinib.

Finally, a recent economic evaluation conducted by Sanon et al (2013)[63] used health utilities derived from Chabot et al (2008),[76] Wilson et al (2005)[77] and expert opinion. The authors

reported a utility weight of 0.87 for recurrent GIST based on Wilson et al (2005)[77] and expert opinion. The utility weight associated with a second recurrence was estimated to be 0.71 based on expert opinion. The utility weight for individuals in BSC was taken from the Chabot paper and assumed to be 0.58. Finally, the authors reported a utility decrement of 0.02 for patients receiving adjuvant imatinib, which was only applied in the month that patients discontinued treatment due to an adverse event. Details of the elicitation method were not provided.

In summary, only one study reported utility weights using EQ-5D as per NICE reference case. However, it is unclear from the study how the EQ-5D was valued and whether the UK tariff was used. Other studies used direct expert opinion or mapping from ECOG performance status to the EQ-5D based on expert opinion, and are thus of limited relevance.

7.4.6 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Not relevant.

Adverse events

7.4.7 Please describe how adverse events have an impact on HRQL.

Across the RCTs and non-RCTs assessing adjuvant imatinib therapy, long-term daily treatment with 400 mg/day has been shown to be well tolerated. No notable increase in adverse events during 3 years of treatment was observed in the SSGXVII/AIO trial when compared with 1 year of treatment (see section 6.10.1), suggesting that longer treatment durations are not associated with a greater incidence or severity of adverse events.

The extent of the decrement on quality of life for patients on imatinib is unknown but expected to be small. In the BFR14 French Sarcoma Group randomised phase III trial in patients with advanced GIST interruption of imatinib treatment after 1 year did not significantly improve patients' global health status, functional status, or symptom scores, as measured by the cancer-specific European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire (EORTC QLQ-C30)[98,99]Although the number of patients in this study was limited, treatment interruption was not associated with a major improvement of quality of life of patients.[98,99]

Quality-of-life data used in cost-effectiveness analysis

7.4.8 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

Within the economic model, utility values are used to weight years of life by the quality of life in any given health state in order to estimate QALYs.

Utility values are assigned for patients in different phases of disease – recurrence-free, recurrent GIST (first recurrence), recurrent GIST (second recurrence) and best supportive care. Utility values used in the economic model are presented in Table B-33.

Table B-33. Utility values used in the economic model

	Mean	SE	Distribution	Justification
Health State				
Health state A : Recurrence-free	0.822	NA	Beta	Age-specific health utility from the general population values taken from Ara and Brazier (2010) assuming a mean age of 61 years old[75]
Health state B: No recurrence and on imatinib treatment	0.741	N/A	Beta	Derived from utility value used in health state A and assuming a decrement in utility of 0.081 for patients receiving adjuvant imatinib
Health state C, E: Recurrent GIST (1st recurrence) with treatment decrement	0.739	SE: 0.016 (0.706-0.771)	Beta	Assumed to be the same as Health State E and G
Health state D: No recurrence and completed adjuvant	0.822	NA	Beta	Assumed to be the same as Health State A

imatinib therapy				
Health state E : Post recurrence and on sunitinib	0.739	SE: 0.016 (0.706-0.771)	Beta	Based on Chabot et al (2008)[76]
Health state G : sunitinib second-line treatment	0.739	SE: 0.016 (0.706-0.771)	Beta	Based on Chabot et al (2008)[76]
Health state H : BSC (Progressive disease)	0.577	SE: 0.029 (0.520-0.635)	Beta	Based on Chabot et al (2008)[76]

Utility weights used in the economic model were identified through a systematic review of the literature (section 7.4.5) and based on assumption when appropriate. There is a lack of published data on quality of life using EQ-5D in patients with GIST. As previously described, only Chabot et al (2008) reported utility weights calculated using the EQ-5D.[76] The authors reported the quality of life for patients resistant to or intolerant of imatinib free of progression treated with sunitinib (0.712 ± 0.2 during the 4 weeks on sunitinib treatment and an improvement of 0.081 ± 0.02 during the 2 weeks off sunitinib treatment), patients with no progression on BSC (0.781 ± 0.2) and patients with progressive disease (0.577 ± 0.3).

The utility value for patients in health state G (*"sunitinib second-line treatment"*), E (*"post-recurrence and on sunitinib"*), and H (*"BSC"*) was taken directly from Chabot et al (2008) as this study presented utility weight for patients treated in second-line with sunitinib or with progressive disease.[76] The utility value for patients treated with sunitinib following recurrence after imatinib treatment (Health State G) or adjuvant imatinib (Health State E) was assumed to be 0.739. The utility value for patients on BSC with progressive disease was assumed to be 0.577.

Due to the lack of data, the utility value for patients free of recurrence following surgical resection (Health State A) was assumed to be similar to the age-adjusted utility value derived from the general population (0.822) assuming a mean age of 61 years old (mean age of patients entering the economic model.).[75] Of note, Chabot et al (2008) reported a utility value of 0.781 for patients resistant to or intolerant of imatinib free of progression treated with BSC, suggesting that the utility value for patients free of recurrence following surgical resection is somewhat above 0.781.[76] Consequently, assuming a utility value of 0.822 for patients free of recurrence is considered to be a reasonable assumption.

In the economic model it was assumed that all patients receiving adjuvant imatinib treatment have a lower utility during the entire treatment period because of the adverse effects of treatment. In the base case, we assumed a utility decrement of 0.081 for patients on adjuvant treatment. The decrement was taken from Chabot *et al*, (2008)[76] who demonstrated a 0.081 difference in the mean utility for patients receiving sunitinib, compared to those who were not receiving treatment. Consequently, a utility value of 0.741 (=0.822 – 0.081) was assumed for patients free of recurrence following surgical resection receiving adjuvant Imatinib.

This assumption that utility on sunitinib treatment and imatinib treatment is the same may be considered conservative given the relative adverse event profiles of sunitinib and imatinib.[100,101] The most common grade 3 and 4 events (imatinib versus placebo) were neutropenia (3% versus 1%), abdominal pain (3.6% versus 1.7%), dermatitis (3% versus 0), nausea (2.4% versus 1.2%) and elevated alanine aminotransferase (2.7% versus 0).[8,55] The AE rate was low and was consistent with imatinib use in CML and metastatic GIST.[8] The most common adverse events on sunitinib include hypertension and asthenia. Diarrhoea, anorexia, disgeusia, stomatitis and skin toxicity are other clinically relevant toxicities. A decrease in left ventricular ejection fraction is a rare but potentially life-threatening complication.

In the economic model, the decrement is applied to **all** patients on adjuvant treatment, not just those who suffer a grade 3 or 4 adverse event. It is therefore a “treatment-related” decrement rather than a specific decrement for patients with severe AEs. Applying it to only those patients in the imatinib arm effectively assumes that the placebo patients do not suffer any adverse events and/or that all the adverse events in the imatinib arm are treatment related. Neither of these statements is likely to be correct. Consequently, this is likely to be a conservative approach and not in favour of the imatinib arm since the model may be overestimating the utility in patients receiving placebo and hence increasing the cost per QALY for adjuvant imatinib.

Finally, in the base case, the utility value for patients treated with imatinib first-line was assumed to be the same as for patients treated with sunitinib second-line treatment due to the lack of data. Sensitivity analyses were conducted using different values.

7.4.9 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[4]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

7.4.10 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

HRQL is determined by the patient's current health state and is constant throughout that health state. Changes in HRQL only occur when a patient moves between health states.

7.4.11 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

Not applicable.

7.4.12 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Not applicable.

7.4.13 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

HRQL is assumed to be constant with time

7.4.14 Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

No further amendment/adjustment was made to the utility weights reported in section 7.4.8.

7.5 Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

7.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

Imatinib is administered orally and hence there are no particular requirements relating to its administration.

NHS reference costs were used to value the cost of outpatient attendances for follow-up (HRG code: 301 Outpatient Follow-up Medical Gastroenterology) and the cost of CT scans (HRG code: RA13Z (three area with contrast)).[102] Complete blood counts (HRG code: DAP823) are performed regularly during therapy with imatinib and liver function (transaminases, bilirubin, alkaline phosphatase) (HRG code: DAP 841) is monitored regularly.[1] The cost of surgery for recurrences was based on NHS reference costs (Average of HRG codes GA04Z Hemihepatectomy, GA05A Resection of segment of liver, GA07 Excision of lesion of liver, and GA13 Therapeutic operation on liver using laparoscope). See Table B-36 in section 7.5.6.

Adverse events requiring hospitalisation were also costed using NHS reference costs[102]. See Table B-40 in section 7.5.7.

7.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

NHS reference costs are considered appropriate for costing of outpatient appointments, CT scans, the cost of surgery for recurrence and treatment for adverse events requiring hospitalisation.

Resource identification, measurement and valuation studies

7.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

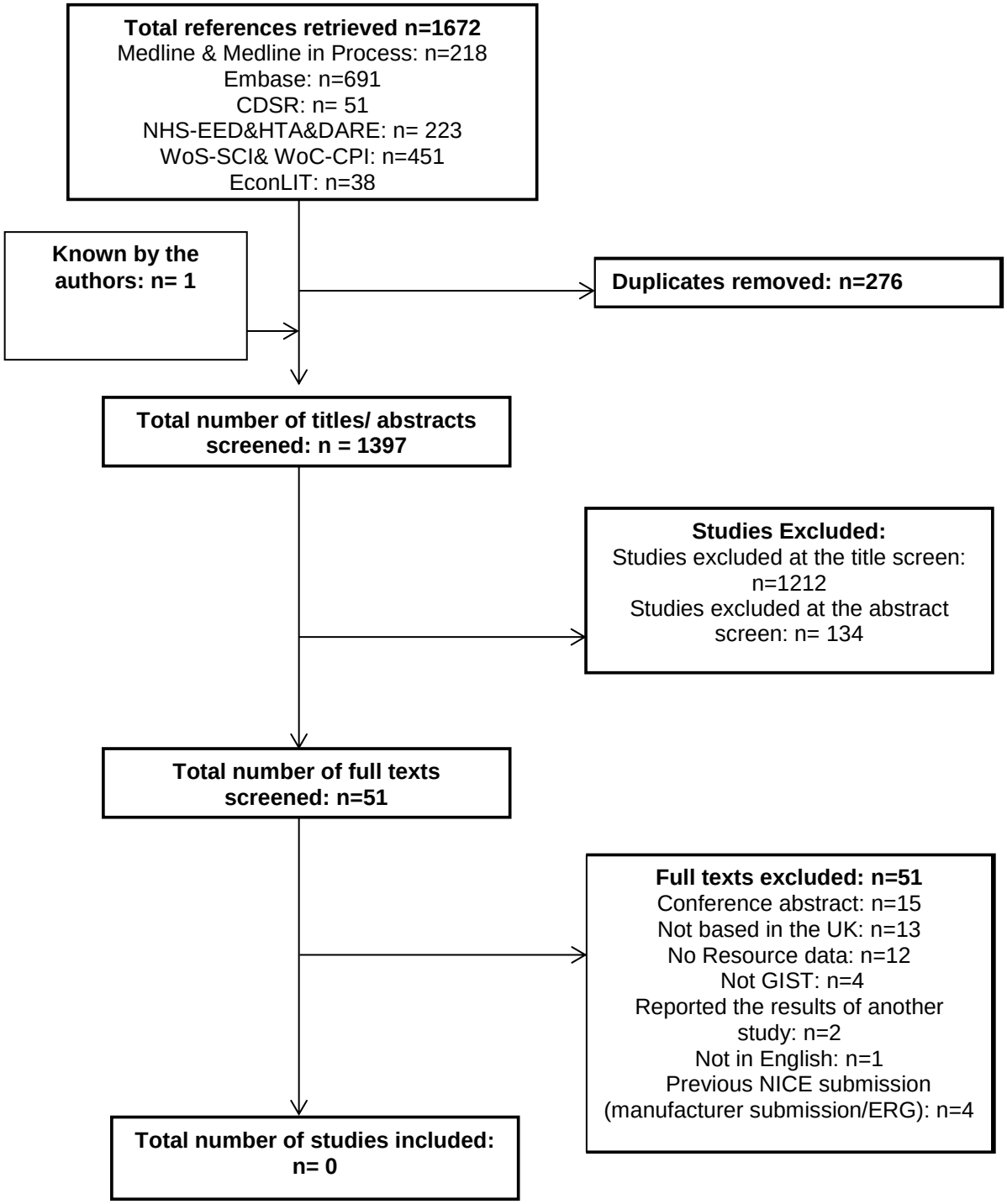
- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

Systematic searches were carried out to retrieve relevant resource allocation studies on 13th and 18th December 2013. See section 7.1.1 for the list of database sources searched. The population terms for gastrointestinal stromal tumours (e.g. statements 1–33 in Medline strategy) were combined with a cost filter (e.g. statements 34–64 in the Medline strategy) including resource allocation terms (e.g. statements 66–8 in the Medline strategy). The search strategy was translated across all databases. No date limits were applied in these searches.

All search strategies are provided in section 10.13, Appendix 13.

Only UK studies were considered since it was believed that resource use varies between countries. The flow diagram of the included resource use studies is included in Figure B-19

Figure B-19: Flow diagram of included and excluded resource publications from the review



The review did not identify any primary study estimating the resource use associated with the management of GIST in the UK.

Four UK studies were identified but not considered further. These studies were STA submissions made to NICE. In some cases, these included the manufacturer submission as well as report from the evidence review group (ERG). Resource uses were estimated from guidelines and/or expert opinion and were used to populate previous economic models submitted to NICE.

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Not applicable

[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Intervention and comparators' costs

7.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

The drug acquisition costs used within the model are presented in Table B-34. Drug acquisition costs for adjuvant imatinib treatment, imatinib as treatment for recurrence (imatinib 400 mg once daily), and sunitinib were taken from the BNF (October 2013).[4]

Imatinib is administered orally at a starting dose of 400 mg once daily for use as adjuvant therapy or for treatment on recurrence and hence there are no particular requirements relating to its administration. Imatinib is available as 100 mg and 400 mg tablets packaged in blister packs. Blister packs contain either 30 x 400 mg tablets at a cost of £1,724.39, or 60 x 100 mg tablets costing £862.19. In the economic model, the cost associated with the 400 mg tablet was used.

Patients may have dose interruptions, dose reductions or dose escalations during treatment, where the clinician deems this appropriate. In the basecase, dose reductions and interruptions were not considered and patients treated with adjuvant imatinib therapy were assumed to receive the full recommended dose of adjuvant imatinib (400 mg/day) as per SPC. A sensitivity analysis was conducted assuming a mean dose intensity of 386.9 mg as seen in the ACOSOG Z9001 study and 393.73 mg from the SSGXVII/AIO trial. Of note, these estimate only account for dose reductions and do not account for dose interruptions.

Table B-34. Drug prices, Wholesale Acquisition Cost (WAC)[4]

Drug	Cost/day	Cost/month	Source/Comments
Imatinib 400 mg once daily	£57.48	£1,749.54	Monthly cost for imatinib is calculated by 365.25 days in each year x daily cost and divided by 12 months

Monitoring whilst on imatinib includes outpatient follow-up visits, CT scans. Complete blood counts and liver function (transaminases, bilirubin, alkaline phosphatise) are performed regularly during therapy with imatinib and is monitored regularly by the GP. Resource use associated with the monitoring of Imatinib is presented in section 7.5.6.

For the second-line treatment of recurrences, the manufacturer of sunitinib has agreed a patient access scheme (PAS) with the Department of Health for GIST, in which the first

treatment cycle of sunitinib is free to the NHS. This is taken into account in the base case analysis, and the impact of full cost of sunitinib is considered in sensitivity analysis

Sunitinib 50 mg is given once daily for 4 weeks, followed by a 2-week treatment-free period to complete 6-week cycle. The cost for 28 Tablets (before reduction to the NHS) is £3,138.80. In order to accommodate the cost of sunitinib into the economic model adjustment was required as the model uses a monthly cycle length.

It was assumed that patients treated with sunitinib have a 21% probability of discontinuing sunitinib per month (owing due to progression, adverse events or death – section 7.3.2), equating to a mean duration of treatment of approximately 4.82 months (or 20.87 weeks). Assuming a mean duration of treatment of 20.87 weeks, patients treated with sunitinib are assumed to be treated for 3.48 6-week cycles. Assuming the first treatment cycle to be free to the NHS (as per PAS agreed with DH), patients would incur a total cost of £7,781 over the total treatment duration (20.87 weeks), equating to a cost per month of approximately £1,615. A sensitivity analysis was conducted assuming the full cost of sunitinib, assuming a cost per month of £2,267.

Monitoring whilst on sunitinib was assumed to include outpatient follow-up visits, CT scans and complete blood counts monitored regularly by the GP (section 7.5.6).

Health-state costs

7.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.

The cost associated with each health state is summarised in Table B-35.

Resource use was derived from the UK clinical guidelines and assumption when appropriate.[6] Monitoring includes outpatient follow-up visits, CT scans. Complete blood counts and liver function (transaminases, bilirubin, alkaline phosphatise) are performed regularly during therapy with imatinib and is monitored regularly by the GP. In some institutions, patients may receive a PET/CT scan rather than a CT scan, but given that this is not yet standard practice, this additional cost has not been included.

Table B-35. List of health states and associated costs in the economic model

Health states	Items	Value	Reference in submission
Recurrence-free GIST	First 3 months	£102.00	Table B-37
	0.25 to 2.25 years	£94.83	Table B-37
	2.25 to 4.25 years	£51.00	Table B-37
	4.25 years +	£29.08	Table B-37
Adjuvant imatinib 400 mg/day	Drug	£1 749.54	Table B-34
	First 3 months	£102.33	Table B-38
	0.25 to 2.25 years	£51.17	Table B-38
	2.25 to 5 years	£29.25	Table B-38
	5 years +	£18.00	Table B-38
Imatinib 400 mg/day for recurrence	Drug	£1 749.54	Table B-34
	Medical costs	£105.67	Table B-39
	Total	£1,855.21	
Sunitinib for recurrence	Drug	£1615.34	Table B-31
	Medical costs	£105.67	Table B-39
	Total	£1,721.01	
Best Supportive Care	Total	£783	
One-off Cost of Recurrence	Total	£1 430.69	Table B-39
Average cost of treating AEs	Total	£418.57	Table B-40

NHS reference costs were used to value the cost of outpatient attendances for follow-up and the cost of CT scans (Table B-36).[102] The cost of GP consultations, £40, was taken from Curtis (2012),[103] assuming a consultation lasting 11.7 minutes (with qualification costs, excluding direct care staff costs).The cost associated with complete blood count and liver blood count was taken from the NHS reference cost.

As described in section 7.2.3, a small proportion of patients are assumed receive further surgery following first recurrence (15%). The cost of surgery for recurrences was based on NHS reference costs (Average of HRG codes GA04Z Hemihepatectomy, GA05A Resection of segment of liver, GA07 Excision of lesion of liver, and GA13 Therapeutic operation on liver using laparoscope).[102]

Table B-36. Unit costs associated with monitoring and follow-up visits

	Mean £	**Source/Comments**
Complete blood count	3.00	NHS reference cost 2011/12. DAP823[102]
Liver function tests	1.00	NHS reference cost 2011/12. DAP841[102]
Routine OP visit	128	NHS reference costs 2011/12[102] HRG code: 301 Outpatient Follow-up Medical Gastroenterology
CT scan	135	NHS reference costs 2011/12[102] Tariff RA13Z (three area with contrast)
Surgery (on recurrence)	4,931	NHS reference costs 2011/12[102] Weighted average of G04 Complex Open Hepatobiliary or Pancreatic Procedures procedures (10%) GA05 Very Major Open Hepatobiliary or Pancreatic Procedures, (17.5%), GA07 Intermediate Open Hepatobiliary or Pancreatic Procedures, 20%), GA13 Minor Open or Laparoscopic, Hepatobiliary or Pancreatic Procedures (2.5%) and FZ12 Major General Abdominal Procedures (50%)
GP visit	40	Curtis 2012[103] Per surgery consultation lasting 11.7 minutes (with qualification costs, excluding direct care staff costs) Unit Costs of Health and Social Care published by the PSSRU. http://www.pssru.ac.uk/project-pages/unit-costs/2012/ Accessed 15 December 2013
CT, computed tomography; GP, general practitioner; HRG, Health Resource Group; OP, outpatient		

Management of recurrence-free with no adjuvant therapy

Resource use for high-risk patients free of recurrence not receiving adjuvant imatinib was derived from the UK Guidelines for the ManaGeMent of Gastrointestinal stroMal tuMours (GIST) and assumption when appropriate (Table B-37).[6] Based on the UK guideline, the number of CT scans was assumed to be one CT scan at 3 month following surgery, 3 monthly for 2 years, 6 monthly for 2 years, then annually.

The same number of outpatient follow-up visit was assumed. We further assumed that patients had 2 GP visits per year (including FBC).

Table B-37: Resource use for patients free of recurrence not receiving adjuvant imatinib

	Month 0 - 3	Year 0.25 – 2.25	Year 2.25 – 4.25	Year 4.25 +
Outpatient visits				
Number of visits	1 per 3 month	4 per year	2 per year	1 per year
CT Scans				
Number of CT scans	1 per 3 month	4 per year	2 per year	1 per year
GP				
Number of visits	1 per 3 month	2 per year	2 per year	2 per year
Cost per month	**£102.00**	**£94.83**	**£51.00**	**£29.08**

Management of recurrence-free with adjuvant therapy

Resource use for high risk patients free of recurrence receiving adjuvant imatinib was derived from the UK Guidelines for the ManaGeMent of Gastrointestinal stroMal tuMours (Gist) and assumption when appropriate (Table B-38).

The UK Guidelines suggested that patients taking adjuvant imatinib will require fewer follow-up CT scans. However, the guidelines do not suggest that monitoring costs are different according to the *duration* of adjuvant treatment and so the model applies the same monitoring costs in both the 1 and 3 year adjuvant imatinib arms.

Based on the UK guideline, the number of CT scans was assumed to be one CT scan at 3 month following surgery, 6 monthly for 2 years then annually to 5 years.

The same number of outpatient follow-up visit was assumed up to 5 years. No CT scan was assumed after 5 years but it was assumed that patients have one outpatient follow-up visit per year. We further assumed that patients had 2 GP visits per year.

Table B-38: Resource use for patients free of recurrence receiving adjuvant imatinib

	Month 0 - 3	Year 0.25 – 2.25	Year 2.25 – 5	Year 5 +
Outpatient visits				
Number of visits	1 per 3 months	2 per year	1 per year	1 per year
CT Scans				
Number of CT scans	1 per 3 months	2 per year	1 per year	0
GP				
Number of visits	1 per 3 months	2 per year	2 per year	2 per year
Cost per month	**£102.33**	**£51.17**	**£29.25**	**£18.00**

Management of recurrences

The ongoing monthly medical cost of recurrent disease (either first recurrence or second recurrence) was calculated as the sum of the cost of ongoing treatment with imatinib/sunitinib and the associated medical care costs. Medical costs are presented in Table B-39.

Table B-39: Medical costs associated with the management of recurrence

	One-off recurrence costs	**Ongoing medical cost**	**Unit cost**
Resource use			
GP visits	1	2 per year	£40 + FBC (£3) and LFT (£1)
Outpatient visits	4	5 per year	£128
CT scan	1	4 per year	£135
Surgery	15%		£4,931
One-off recurrence cost / Monthly medical cost (excluding drug costs)	£1 430.69	£105.67	

The frequency of follow-up visits and tests for patients in health state C, G and E were estimated from the UK guidelines. It is recommended that CT scanning should be performed 3 monthly, at least initially, to assess response to therapy for the treatment of unresectable and/or metastatic disease. In the model, we assumed that CT scanning is performed every 3 month for the whole duration of treatment. We further assumed 5 outpatients visits (including LFT and FBC counts) and 2 GP visits per year.

Patients were also assumed to incur a one-off cost at the onset of recurrence (£1,430.69). This cost was assumed to include one primary care visit (including FBC and LFT), four outpatient visits (including visits for initial assessment and further tests), one CT scan, and, where surgery was possible (assumed to be in 15% of patients), surgical resection of the tumour or metastases. The proportion of patients eligible for surgery and the cost of surgery for recurrence were based on advice given in the UK validation exercise on typical procedures undertaken used in a previous submission to NICE.[91]

Progressive disease (treated with Best Supportive Care)

Costs for progressive disease, treated with Best Supportive Care) were determined by estimating:

1. resource use in the period of progressive disease prior to the last 12 months of life
2. costs for the last year of life, based on the National Audit Office Report (2008) End of Life Care.[104]

Costs for the continuing phase of cancer (defined as the period between the first year after diagnosis and the last year of life) were estimated, assuming, on average, two primary care visits per year (including FBC), five outpatient visits per year and 0.5 CT scans, totaling £793.5 per annum.

Costs for the last year of life were estimated at £17,380 (based on £14,236 costs for 2007, inflated to 2012/13 costs), this being the average figure for patients with cancer reported by National Audit Office Report (2008) End of Life Care.[104]

In the economic model, patients on BSC remain in this health state for an average duration of 23.12 months (estimated from the probability of death in the BSC health state). Assuming an annual cost for the continuing phase of cancer of £793.5 for the first 11.12 month and a cost of £17,380 for the last 12 months, we estimated the average total cost for patients in BSC to be £18,116 for the average duration patients remain in the BSC health state. This equates to an average monthly cost of £783. Given the uncertainty, the cost of progressive disease was varied in sensitivity analysis.

Adverse-event costs

7.5.7 Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

The costs of AEs in the economic model were based on the most frequent grade 3 and 4 AEs experienced by patients in the SSGXVII/AIO trial in patients treated with surgical resection followed by 1 or 3 years of adjuvant imatinib. No cost was assumed for patients treated with surgical resection only (no treatment). This is conservative.

Table B-40. List of adverse events and summary of costs included in the economic model

Adverse events	Items	Value	Incidence (1yr imat)	Incidence (3yr imat)
Neutrophil count decreased	Hospital costs	118.6	9	10
	OP cost	384.0		
	Total	502.6		
White blood cell count decreased	Hospital costs	16.4	4	6
	OP cost	384.0		
	Total	400.4		
Infection	OP	384.0	3	5
	Total	384.0		
Dermatitis	OP	384.0	4	3
	Total	384.0		
Aspartate aminotransferase increased	OP	384.0	3	6
	Total	384.0		
Alanine aminotransferase increased	OP	384.0	4	6
	Total	384.0		
Chest pain	OP	384.0	2	6
	Total	384.0		
Diarrhoea	Hospital costs	34.3	1	4
	OP cost	384.0		
	Total	418.3		
Dyspnoea (shortness of breath)	OP cost	384.0	1	3
	Other	31.0		
	Total	415.0		
Nausea	Hospital costs	33.2		
	OP cost	384.0	3	1
	Total	417.2		
AVERAGE		**£418.57**		

Based on clinical advice, it was assumed that the AEs generated three additional outpatient appointments. Increased aspartate aminotransferase and alanine aminotransferase levels are assumed to result in treatment discontinuation if drug reduction/interruptions are unsuccessful. In addition to the outpatient appointments, decreased neutrophil count, fatigue, vomiting and diarrhoea are assumed to result in hospitalisation in 5% of cases. Dyspnoea is assumed to require an x-ray (see section 7.5.5). For dermatitis and infection the cost of three gastroenterology visits were applied. Other AEs were assumed to require minor tests or inexpensive medications, which were not costed.

Adverse events requiring hospitalisation were costed using NHS reference costs (Table B-41).[102] X-rays were costed at £31 based on the UCL Provider to provider Services Tariff 2012/13.[105]

Table B-41. Unit costs for adverse events

AE	Cost	Source
Neutropenia	£2,372.87	Average (weighted by activity levels) of: WA02W: disorders of immunity without HIV/AIDS without CC WA02Y: disorders of immunity without HIV/AIDS without CC National Schedule of Reference Costs, 2011/12[106]
Fatigue	£328.25	Average (weighted by activity levels) of: WA18V: Admission for unexplained symptoms with Major CC WA18X: Admission for unexplained symptoms with Intermediate CC WA18Y: Admission for unexplained symptoms without CC National Schedule of Reference Costs, 20111/12[106]
Nausea/ vomiting	£663.23	FZ43C: Non-Malignant Stomach or Duodenum Disorders with length of stay 1 day or less National Schedule of Reference Costs, 2011/12[106]
Diarrhoea	£685.21	FZ36F: Intestinal Infectious Disorders with length of stay 1 day or less National Schedule of Reference Costs, 2011/12[106]

The cost of treating each adverse event was calculated by multiplying the unit cost of each intervention by the respective resource use. The frequency of adverse event occurrence was taken into account to estimate the average monthly cost of treating an adverse event separately for imatinib 1 year and 3 year arms. The difference in the estimated average monthly costs for the two treatment groups was very small: £422.18 in the 1-year group and £414.96 in the 3-year group. An average cost of £418.57 was therefore used for both treatments in the cost-effectiveness model. The impact of an increase in these costs (twofold and fivefold) was tested in sensitivity analysis.

Miscellaneous costs

7.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

None.

7.6 Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

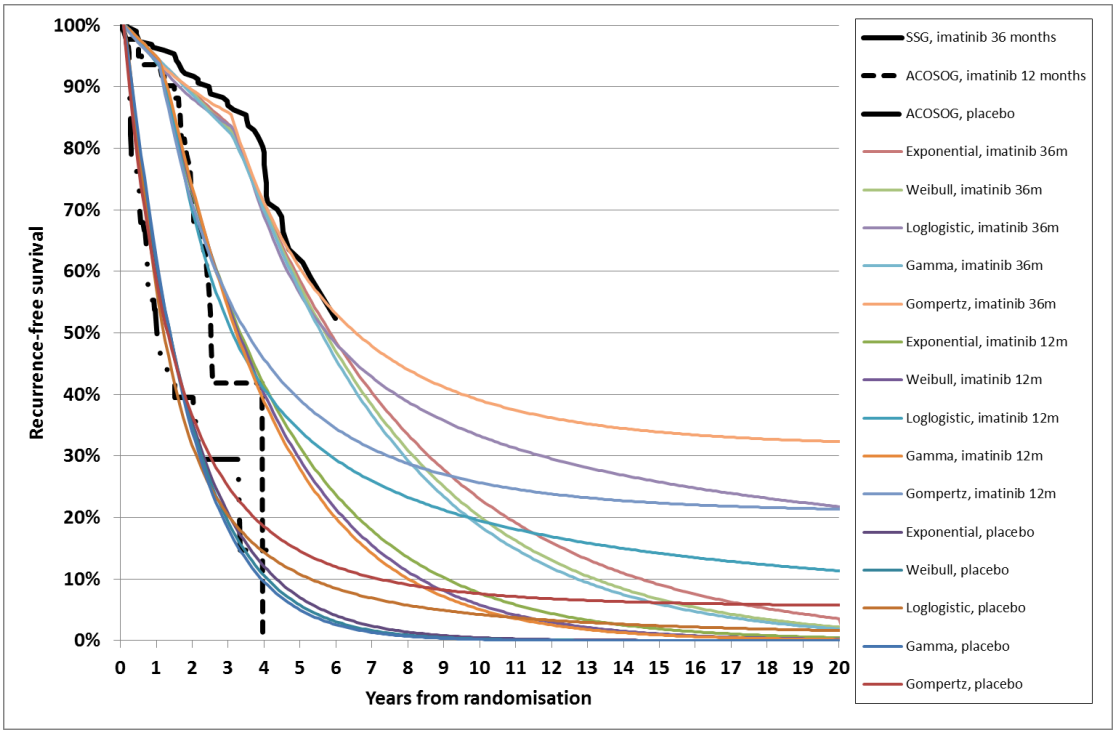
For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

7.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

Alternative survival models for extrapolation

Five parametric survival models (exponential, Weibull, gamma, loglogistic, Gompertz) were fitted to the RFS data for the no treatment arm. The Gompertz model was selected for the base case analysis (see section 7.3.2). The impact on the ICER of using the four remaining models was explored.

Figure B-20. Curve fitting graph using different parametric distribution



Dose escalation to 800 mg allowed in metastatic setting

Although not approved in NICE guidance (TA86), there is an option of patients switching to high-dose imatinib (800 mg) in the metastatic setting following progression on 400 mg. The model contains a health state for patients on high-dose imatinib (Health state F) and, in this SA, patients have the option to move to high dose imatinib (10%), sunitinib (80%), or BSC (10%), rather than sunitinib (90%) and BSC (10%) (basecase).

Proportion of patients moving to BSC following recurrence whilst on imatinib or adjuvant imatinib

In the basecase we assumed that 10% of patients with a recurrence whilst on treatment with imatinib or adjuvant imatinib move to BSC, with the remaining treated with sunitinib. Patients who are too ill/fragile are assumed to move to BSC rather than receiving further therapy. Sensitivity analysis was explored assuming everyone receives sunitinib or that only 80% receive sunitinib.

Extended post-recurrence survival

A scenario analysis in which patients were assumed to remain for a longer duration in post recurrence health states was considered to explore the impact of extended survival following recurrence on the ICER. For this scenario the probability of death whilst on BSC was taken from Tran et al (the most optimistic of the three available sources; and the lower confidence internval (LCI) of the probability of death whilst on sunitinib and whilst on imatinib was used.

7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

Multiple one-way sensitivity analyses were conducted to test the robustness of model results to changes in key parameters.

Sensitivity Analysis 1/2: Time horizon reduced to 5/10 years

In the base case analysis the costs and benefits of treatment were examined over the lifetime of patients. In these anlayses only the first five and first 10 years of costs and benefits were considered.

Sensitivity Analysis 3/4: HR for the "on-treatment" period

This was varied within the lower and upper confidence interval (CI)

Sensitivity Analysis 5/6: HR for the "off-treatment" period

This was varied within the lower and upper confidence interval (CI)

Sensitivity Analysis 7/8: HR for the "on treatment" and "off-treatment" period

This was varied within the lower and upper confidence interval (CI)

Sensitivity Analysis 9/10/11: Monthly probability death whilst in BSC

In the basecase, the monthly probability of death in BSC was calculated by combining evidence from three sources.[71,83,84] Sensitivity analyses were conducted using data from each individual study.

Sensitivity Analysis 12/13: Monthly probability death whilst on imatinib

This was varied within the lower and upper confidence interval (CI)

Sensitivity Analysis 14/15: Monthly probability death whilst on sunitinib

This was varied within the lower and upper confidence interval (CI)

Sensitivity Analysis 16/17: Probability of discontinuation whilst on adjuvant imatinib

This was varied within the lower and upper confidence interval (CI)

Sensitivity Analysis 18/19: Probability of discontinuation whilst on imatinib treatment for recurrence

This was varied within the lower and upper confidence interval (CI)

Sensitivity Analysis 20/21: Probability of discontinuation whilst on sunitinib treatment for recurrence

This was varied within the lower and upper confidence interval (CI)

Sensitivity Analysis 22/23/24: Varying utility values

There are considerable uncertainties around the utility values used in the economic model.

SA22 examined using a value of 0.7 for patients in BSC (other utility values remain the same)
SA23 examined using a value of 0.78 for recurrence-free (0.75 whilst on adjuvant imatinib) – other utility values remain the same
SA 24 examined using a value of 0.78 for recurrence-free (0.75 whilst on adjuvant imatinib) and 0.7 for BSC – utility values for recurrence (0.739) remain the same.

Sensitivity Analysis 25/26: Decrement in utility for patients treated with adjuvant imatinib

In the basecase analysis it was assumed that there is a utility decrement associated with adjuvant imatinib treatment which takes into account the effects of adverse events on quality of life. As the Chabot paper presents a 0.081 difference in the mean utility of sunitinib (not imatinib) patients being on treatment and off treatment, this value for the imatinib treatment might be too conservative.[76]

The extent of the decrement of imatinib on quality of life for patients on imatinib is unknown but may be limited. In the BFR14 French Sarcoma Group randomised phase III trial in patients with advanced GIST interruption of imatinib treatment after 1 year did not significantly improve patients' global health status, functional status, or symptom scores, as measured by

the cancer-specific European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire (EORTC QLQ-C30)[98,99] Although the number of patients in this study was limited, treatment interruption was not associated with a major improvement of quality of life of patients.

A SA was also conducted assuming no decrement and assuming half the decrement assumed in the basecase (i.e. 0.081/2 = 0.0405).

Sensitivity Analysis 27/28: Dose intensity reduction adjustment – using ACOSOG and SSG trial data

Mean dose intensities from the clinical trials were explored: Firstly, using the mean dose intensity from the ACOSOG Z9001, 386.9 mg in both the 1-year and 3- year treatment arms; secondly, using the mean dosage of 394.32 mg (98.6%) from the SSGXVII/AIO study in both the 1-year and the 3-year treatment arms. Mean dose intensity for imatinib in the recurrence/metastatic setting was also adjusted in the same way for consistency.

Sensitivity Analysis 29: Cost of sunitinib

SA was conducted assuming the full sunitinib price i.e. assuming no patient access scheme

Sensitivity Analysis 30/31: One-off cost of recurrence

In the basecase, it wasassumed that there is a one-off cost of recurrence (£1430.69), based on the cost of a GP appointment, outpatient visit, CT scan and surgery (for eligible patients – 15%).

SA was conducted varying the cost by +/- 50%

Sensitivity Analysis 32/33: Management costs in recurrence-free health state for patients not receiving adjuvant imatinib +/- 50%

SA was conducted varying the cost by +/- 50%

Sensitivity Analysis 34/35: Management cost in recurrence-free health state for patients treated with adjuvant imatinib +/- 50%

SA was conducted varying the cost by +/- 50%

Sensitivity Analysis 36/37: Management cost in recurrence health states +/- 50%

SA was conducted varying the cost by +/- 50%

Sensitivity Analysis 38/39: All management costs +/- 50%

SA was conducted varying the cost by +/- 50%

Sensitivity Analysis 40/41: Average cost of adverse events doubled/5x

Clinical advice suggests that the costs of treating adverse events are extremely variable depending on treatment requirements for individual patients and differences in practice. Therefore, the effect of increasing these costs has been tested in a sensitivity analysis. Costs have been increased twofold (to £837) and fivefold (to £2093).

Sensitivity Analysis 42/43: Cost of BSC +/- 50%

In the base case analysis an estimated cost of BSC of £7,860 per annum is used. This is based on a weighted average of the continuing phase costs (defined as the period between the first year after diagnosis and the last year of 12 months of life) and the end of life costs (defined as last 12 months of life). See section 7.2.6 for details.

Given the uncertainty surrounding these costs a sensitivity analysis has been undertaken varying the costs by +/-50%.

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

A probabilistic sensitivity analysis was conducted to take account of the simultaneous effect of uncertainty relating to model parameter values. A total number of 1,000 simulations were performed in order to provide sufficient information on uncertainty.

Uncertainty surrounding all important model parameters was described by probability distributions (Table B-29, Table B-31, Table B-33), and propagated through the model using Monte Carlo sampling techniques to produce distributions of expected costs and QALYs for each treatment group.

Uncertainty surrounding monthly recurrence, mortality and discontinuation rates and utility values was characterised using beta distributions. Gamma distributions were assigned to all cost parameters in the model. Lognormal distributions were used to describe the uncertainty surrounding hazard ratios. Multivariate normal distributions were assigned to all sigma, mu curve parameters in the model, in order to count for the covariance. Where standard errors were missing, the 10% of the parameter estimate was used as standard error.

The results of the probabilistic sensitivity analysis are presented as cost-effectiveness planes and acceptability curves. The mean simulated ICER was also calculated for each comparison. The probability of a certain treatment strategy being cost-effective at thresholds of £20,000 /QALY and £30,000/QALY is reported.

7.7 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

7.7.1 For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Predicted curves for RFS and OS are presented in Figure B-21 and Figure B-22, respectively. Predicted outcomes from the economic model were compared with clinical data from the SSG, ACOSOG trial and historical data when appropriate.

Recurrence free survival

At 5 years, the model predicted that 57% of patients receiving 3 year adjuvant imatinib were recurrence-free, compared with 37% of patients receiving 1 year adjuvant imatinib and 14% of patients treated with surgical resection only (Figure B-21)

Compared with the SSG data the model provides a good prediction of RFS in the 1-year arm, and in the 3-year arm, although there is an underestimation at 4 years for the latter.

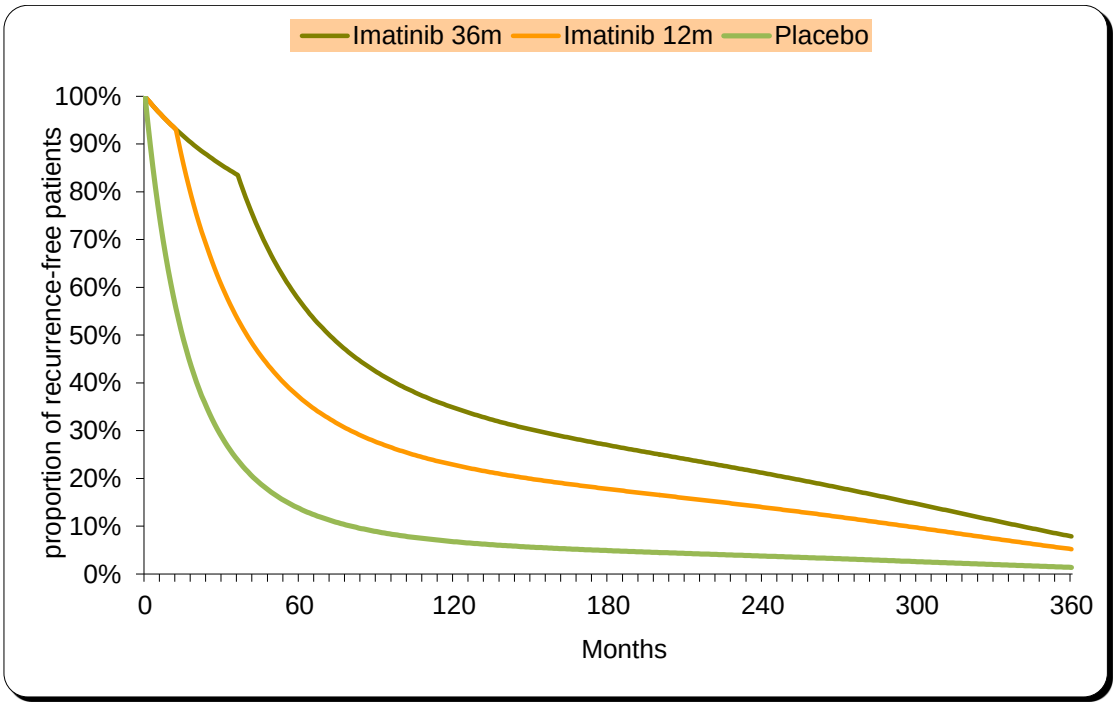
In the ACOSOG study, the *primary analysis* did not provide RFS out to five years, due to limited follow up. Compared with the ACOSOG primary analysis, the placebo arm and 1 year arms slightly underpredict RFS at 2 years. Predicted RFS in the 1-year arm is relatively close to the the *5-year update analysis* of ACOSOG, except for year 2.

RFS (%)									
	Placebo		**1-year arm**				**3-year arm**	
Year	**Model**	ACOSOG *Primary **	**Model**	SSG**	ACOSOG *Primary **	ACOSOG *5 yr update*	**Model**	SSG**
1	**56**	52.2	**93**	91.3	93.6	94.8	**93**	96.6
2	**35**	39.5	**68**	68.0	74.1	76.0	**88**	89.6
3	**24**	-	**53**	49.6		57.2	**84**	83.8
4	**18**	-	**44**	40.2		44.7	**68**	71.6
5	**14**	-	**37**	35.1		37.9	**57**	58.8
OS (%)								
	Placebo		**1-year arm**				**3-year arm**	
Year	**Model**	ACOSOG *Primary*	**Model**	SSG	ACOSOG *Primary*	ACOSOG *5 yr update*	**Model**	SSG
1	**95**		**98**	98.6		98.9	**98**	100
2	**83**	94.7	**93**	94.1	100	98.9	**94**	97
3	**69**	-	**85**	91.7	-	94.2	**90**	95.5
4	**55**	-	**75**	83	-	86.9	**85**	94.5
5	**42**	-	**65**	74.2	-	82.0	**79**	89.5

Note: * AGOSOG primary: RFS is based on efficacy population, high risk, event type =21 **SSG RFS: is based on efficacy population, high risk (modified Miettinen rsik classification). ACOSOG 5–yr update: taken from clinical study report.

Historical data suggest that for patients at high risk of recurrence and undergoing resection, up to 90% have an adverse outcome – recurrence, metastasis or GIST-related death[35] – and these patients experience a 5-year RFS of around of 20%.[3,8] At 5 years the predicted RFS in the placebo arm is 14%, suggesting that the model may underpredict RFS at 2 years in the placebo arm.

Figure B-21: Predicted RFS from Model



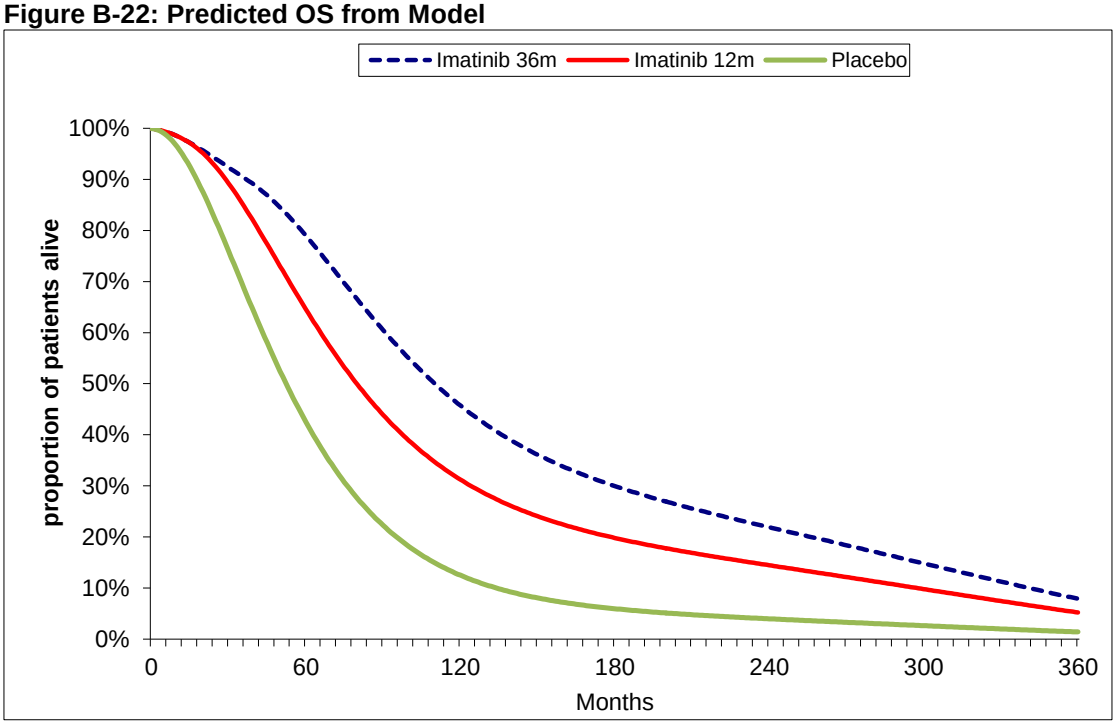
Overall Survival

The model predicted an overall survival at 5 years of 79% for patients receiving 3-year adjuvant imatinib, 65% for patients in the 1-yr arm, and 42% for patients treated with surgical resection only (Figure B-22)

The model underestimates overall survival for patients receiving adjuvant imatinib, compared with the datasets for 1 year and 3 year treatment. In the placebo arm arm, at 2 years , survival is also underpredicted.

This issue is explored further in scenario analysis (See section 7.7.9).

Figure B-22: Predicted OS from Model



7.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

The proportion of the modelled cohort in each health state over time for patients treated with surgical resection only is presented in Table B-42. The proportion of the modelled cohort for patients treated with surgical resection followed by 1 and 3 years of imatinib is presented in Table B-43 and Table B-44, respectively.

Table B-42. Proportion of patients in each health state over time – placebo arm

12th month of year…	No recurrence & no treatment (norecur_notx)	Post-recurrence & imatinib 400 mg treatment (Postrecur_imat400)	Post recurrence and on sunitinib	Second line sunitinib treatment	Post recurrent imatinib 800mg second line	Best Supportive Care (BSC)	Death from GIST (Death_GIST)	Death from Other (Death_Other)
1	218	108	0	11	0	8	11	2
2	134	120	0	19	0	34	48	5
3	90	96	0	17	0	51	97	7
4	66	70	0	13	0	55	146	9
5	51	48	0	9	0	51	189	11
6	41	33	0	6	0	42	223	13
7	35	22	0	4	0	33	250	14
8	30	15	0	3	0	25	270	15
9	27	10	0	2	0	19	285	16
10	25	7	0	1	0	13	296	17
11	23	5	0	1	0	10	303	18
12	21	3	0	1	0	7	308	19
13	20	2	0	0	0	5	312	19
14	19	2	0	0	0	3	315	20
15	18	1	0	0	0	2	317	20
16	17	1	0	0	0	2	318	21
17	16	1	0	0	0	1	319	22
18	15	1	0	0	0	1	320	22
19	14	0	0	0	0	1	320	23
20	14	0	0	0	0	0	321	24

Table B-43. Proportion of patients in each health state over time – imatinib 1 year arm

12th month of year…	No recurrence & on imatinib adjuvant therapy (Norecur_adj)	No recurrence & complete one year of imatinib therapy (Norecur_Adjcomp)	No recurrence & no treatment (norecur_notx)	Post-recurrence & imatinib 400 mg treatment (Postrecur_imat400)	Post recurrence and on sunitinib	Sunitinib second line	Best Supportive Care (BSC)	Death from GIST (Death_GIST)	Death from Other (Death_Other)
1	310	0	28	1	7	0	8	3	2
2	0	236	22	60	1	6	14	16	5
3	0	182	17	74	0	11	25	42	8
4	0	148	14	67	0	11	35	74	10
5	0	125	11	54	0	10	38	108	13
6	0	109	10	41	0	7	37	140	15
7	0	97	9	31	0	6	32	167	18
8	0	88	8	23	0	4	27	189	20
9	0	81	7	17	0	3	22	207	22
10	0	76	7	12	0	2	17	221	24
11	0	71	7	9	0	2	13	231	26
12	0	68	6	7	0	1	10	239	28
13	0	64	6	5	0	1	8	245	30
14	0	62	6	4	0	1	6	250	32
15	0	59	5	3	0	1	4	253	34
16	0	56	5	2	0	0	3	256	36
17	0	54	5	2	0	0	2	258	38
18	0	51	5	1	0	0	2	259	41
19	0	49	4	1	0	0	1	260	43
20	0	46	4	1	0	0	1	261	46

Table B-44. Proportion of patients in each health state over time – imatinib 3 year arm

12th month of year …	No recurrence & on imatinib adjuvant therapy (Norecur_adj)	No recurrence & complete one year of imatinib therapy (Norecur_Adjcomp)	No recurrence & no treatment (norecur_notx)	Post-recurrence & imatinib 400 mg treatment (Postrecur_imat400)	Post-recurrence & sunitinib treatment (Postrecur_sunit)	Sunitinib_second line	Best Supportive Care (BSC)	Death from GIST (Death_GIST)	Death from Other (Death_Other)
1	312	0	26	1	7	0	8	3	2
2	280	0	38	2	6	0	16	13	5
3	253	0	49	2	4	0	18	25	8
4	0	210	42	38	0	4	16	38	11
5	0	176	35	49	0	7	20	58	14
6	0	152	30	46	0	8	25	81	17
7	0	135	27	38	0	7	27	105	20
8	0	123	24	30	0	5	26	127	23
9	0	113	22	24	0	4	23	147	26
10	0	105	21	18	0	3	20	163	29
11	0	99	20	14	0	2	16	177	32
12	0	94	19	10	0	2	13	187	35
13	0	89	18	8	0	1	10	195	37
14	0	85	17	6	0	1	8	202	40
15	0	81	16	4	0	1	6	207	43
16	0	78	15	3	0	1	5	210	47
17	0	74	15	3	0	0	4	213	50
18	0	71	14	2	0	0	3	216	54
19	0	67	13	1	0	0	2	217	57
20	0	64	13	1	0	0	1	218	61

7.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

QALYs accrued in each health state over time for patients treated with surgical resection only are presented in Table B-45. QALYs accrued for patients treated with surgical resection followed by 1 and 3 years of imatinib are presented in Table B-45 to-B47.

Table B-45. QALYs accrued in each health state over time – placebo arm

12th month of year…	No recurrence & no treatment (norecur_notx)	Post-recurrence & imatinib 400 mg treatment (Postrecur_imat400)	Post recurrent and on sunitinib	Second line sunitinib treatment	Post recurrent imatinib 800mg second line	Best Supportive Care (BSC)
1	0.630	0.143	0.000	0.011	0.000	0.005
2	0.987	0.382	0.000	0.045	0.000	0.042
3	1.211	0.586	0.000	0.080	0.000	0.111
4	1.364	0.733	0.000	0.107	0.000	0.190
5	1.476	0.834	0.000	0.126	0.000	0.264
6	1.562	0.900	0.000	0.138	0.000	0.326
7	1.631	0.943	0.000	0.147	0.000	0.374
8	1.689	0.971	0.000	0.152	0.000	0.410
9	1.738	0.990	0.000	0.155	0.000	0.435
10	1.781	1.002	0.000	0.158	0.000	0.453
11	1.819	1.010	0.000	0.159	0.000	0.466
12	1.853	1.016	0.000	0.160	0.000	0.474
13	1.884	1.019	0.000	0.161	0.000	0.480
14	1.911	1.022	0.000	0.161	0.000	0.484
15	1.937	1.024	0.000	0.162	0.000	0.487
16	1.960	1.025	0.000	0.162	0.000	0.489
17	1.982	1.026	0.000	0.162	0.000	0.490
18	2.002	1.027	0.000	0.162	0.000	0.491
19	2.020	1.027	0.000	0.162	0.000	0.492
20	2.036	1.028	0.000	0.163	0.000	0.492
50	2.147	1.029	0.000	0.163	0.000	0.493

Table B-46. QALYs accrued in each health state over time – imatinib 1 year arm

12th month of year…	No recurrence & on imatinib adjuvant therapy (Norecur_adj)	No recurrence & complete one year of imatinib therapy (Norecur_Adjcomp)	No recurrence and no treatment	Post-recurrence & imatinib 400 mg treatment (Postrecur_imat400)	Post recurrence and on sunitinib	Sunitinib second line treatment	Best Supportive Care (BSC)
1	0.741	0.000	0.051	0.001	0.010	0.000	0.006
2	0.741	0.587	0.105	0.075	0.015	0.006	0.025
3	0.741	1.015	0.144	0.213	0.016	0.025	0.056
4	0.741	1.344	0.174	0.344	0.016	0.046	0.102
5	0.741	1.609	0.198	0.450	0.016	0.065	0.154
6	0.741	1.830	0.218	0.529	0.016	0.079	0.204
7	0.741	2.018	0.236	0.587	0.016	0.089	0.249
8	0.741	2.182	0.251	0.629	0.016	0.097	0.286
9	0.741	2.327	0.264	0.658	0.016	0.102	0.314
10	0.741	2.458	0.276	0.679	0.016	0.106	0.336
11	0.741	2.577	0.287	0.694	0.016	0.109	0.353
12	0.741	2.685	0.297	0.705	0.016	0.111	0.365
13	0.741	2.784	0.306	0.712	0.016	0.112	0.374
14	0.741	2.876	0.314	0.718	0.016	0.113	0.381
15	0.741	2.961	0.322	0.722	0.016	0.114	0.385
16	0.741	3.039	0.329	0.725	0.016	0.114	0.389
17	0.741	3.111	0.336	0.727	0.016	0.115	0.391
18	0.741	3.178	0.342	0.729	0.016	0.115	0.393
19	0.741	3.240	0.348	0.730	0.016	0.115	0.394
20	0.741	3.296	0.353	0.731	0.016	0.115	0.395
50	0.741	3.677	0.388	0.733	0.016	0.116	0.397

Table B-47. QALYs accrued in each health state over time – imatinib 3 year arm

12th month of year…	No recurrence & on imatinib adjuvant therapy (Norecur_adj)	No recurrence & complete one year of imatinib therapy (Norecur_Adjcomp)	No recurrence and no treatment	Post-recurrence & imatinib 400 mg treatment (Postrecur_imat400)	Post recurrence and on sunitinib	Sunitinib second line treatment	Best Supportive Care (BSC)
1	0.807	0.000	0.046	0.001	0.011	0.000	0.008
2	1.441	0.000	0.123	0.004	0.023	0.000	0.029
3	1.951	0.043	0.221	0.008	0.032	0.001	0.055
4	1.948	0.502	0.312	0.059	0.034	0.005	0.080
5	1.946	0.870	0.385	0.143	0.034	0.017	0.106
6	1.944	1.175	0.446	0.225	0.034	0.030	0.138
7	1.941	1.435	0.498	0.293	0.034	0.042	0.173
8	1.939	1.662	0.543	0.346	0.034	0.051	0.206
9	1.937	1.862	0.583	0.386	0.034	0.059	0.236
10	1.935	2.042	0.618	0.415	0.034	0.064	0.260
11	1.933	2.205	0.651	0.437	0.034	0.068	0.279
12	1.932	2.354	0.681	0.452	0.034	0.070	0.295
13	1.930	2.490	0.708	0.464	0.034	0.073	0.306
14	1.928	2.616	0.733	0.472	0.034	0.074	0.315
15	1.926	2.732	0.756	0.478	0.034	0.075	0.321
16	1.925	2.840	0.777	0.483	0.034	0.076	0.326
17	1.923	2.939	0.797	0.486	0.034	0.077	0.330
18	1.922	3.030	0.815	0.488	0.034	0.077	0.332
19	1.920	3.115	0.832	0.490	0.034	0.077	0.334
20	1.919	3.192	0.847	0.491	0.034	0.077	0.336
50	1.893	3.710	0.950	0.495	0.034	0.078	0.339

7.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

Total discounted life years and QALYs accrued by recurrence status (recurrence-free or post-recurrence) are presented in Table B-48 for patients treated with surgical resection only, Table B-49 for patients treated with surgical resection followed by one-year adjuvant imatinib and Table B-50 for patients treated with surgical resection followed by three-year adjuvant imatinib.

Table B-48. Model outputs by clinical outcomes – placebo

Outcome	LY	QALY
Recurrence-free survival	2.61	2.15
Post-recurrence survival	2.47	1.68
Overall survival	5.08	3.83

Table B-49. Model outputs by clinical outcomes – imatinib 1 year

Outcome	LY	QALY
Recurrence-free survival	5.85	4.81
Post-recurrence survival	1.86	1.26
Overall survival	7.71	6.07

Table B-50. Model outputs by clinical outcomes – imatinib 3 years

Outcome	LY	QALY
Recurrence-free survival	8.05	6.55
Post-recurrence survival	1.41	0.95
Overall survival	9.46	7.50

7.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Lifetime discounted costs, QALYs and life years by health states are presented in Table B-51, B-52 and B-53 for patients treated with surgical resection only and patients treated with surgical resection followed by 1 or 3 year adjuvant imatinib.

Table B-51: No Treatment vs 1 year

	No Treatment arm			Adjuvant Imatinib arm (1 year)			Incremental		
	LYG	QALY	Cost	LYG	QALY	Cost	LYG	QALY	Cost
State A No recurrence and no adjuvant treatment	2.6123	2.1472	£2,387	0.4719	0.3879	£518	-2.1405	-1.7594	-£1,870
State B No recurrence and on imatinib adjuvant therapy				0.9047	0.7409	£19,780	0.9047	0.7409	£19,780
State C Post-recurrence and on imatinib 400 mg once daily	1.3919	1.0286	£32,269	0.9914	0.7326	£22,986	-0.4006	-0.2960	-£9,283
State D No recurrence and completed adjuvant imatinib therapy				4.4733	3.6768	£1,591	4.4733	3.6768	£1,591
State E Post-recurrence and on sunitinib	0.0000	0.0000	£0	0.0213	0.0157	£514	0.0213	0.0157	£514
State G Sunitinib second-line treatment	0.2201	0.1627	£4,599	0.1566	0.1158	£3,273	-0.0635	-0.0469	-£1,326
State H Best supportive care	0.8548	0.4932	£8,036	0.6888	0.3974	£6,475	-0.1661	-0.0958	-£1,561
Total (discounted)	5.08	3.83	£47,292	7.71	6.07	£55,136	2.6287	2.2354	£7,844

Table B-52: No Treatment vs 3 year

	No Treatment arm			Adjuvant Imatinib arm (3 year)			Incremental		
	LYG	QALY	Cost	LYG	QALY	Cost	LYG	QALY	Cost
State A No recurrence and no adjuvant treatment	2.6123	2.1472	£2,387	1.1564	0.9505	£772	-1.4560	-1.1967	-£1,615
State B No recurrence and on imatinib adjuvant therapy				2.3831	1.8930	£51,756	2.3831	1.8930	£51,756
State C Post-recurrence and on imatinib 400 mg once daily	1.3919	1.0286	£32,269	0.6693	0.4946	£15,522	-0.7226	-0.5340	-£16,747
State D No recurrence and completed adjuvant imatinib therapy				4.5139	3.7103	£1,164	4.5139	3.7103	£1,164
State E Post-recurrence and on sunitinib	0.0000	0.0000	£0	0.0466	0.0344	£1,125	0.0466	0.0344	£1,125
State G Sunitinib second-line treatment	0.2201	0.1627	£4,599	0.1056	0.0781	£2,207	-0.1145	-0.0846	-£2,392
State H Best supportive care	0.8548	0.4932	£8,036	0.5874	0.3389	£5,522	-0.2674	-0.1543	-£2,514
Total (discounted)	5.08	3.83	£47,292	9.46	7.50	£78,068	4.3831	3.6680	£30,776

Table B-53: 3 year Treatment vs 1 year

	Adjuvant Imatinib arm (1 year)			Adjuvant Imatinib arm (3 year)			Incremental		
	LYG	QALY	Cost	LYG	QALY	Cost	LYG	QALY	Cost
State A No recurrence and no adjuvant treatment	0.4719	0.3879	£518	1.1564	0.9505	£772	0.6845	0.5626	£254
State B No recurrence and on imatinib adjuvant therapy	0.9047	0.7409	£19,780	2.3831	1.8930	£51,756	1.4784	1.1521	£31,976
State C Post-recurrence and on imatinib 400 mg once daily	0.9914	0.7326	£22,986	0.6693	0.4946	£15,522	-0.3220	-0.2380	-£7,464
State D No recurrence and completed adjuvant imatinib therapy	4.4733	3.6768	£1,591	4.5139	3.7103	£1,164	0.0406	0.0334	-£427
State E Post-recurrence and on sunitinib	0.0213	0.0157	£514	0.0466	0.0344	£1,125	0.0253	0.0187	£611
State G Sunitinib second-line treatment	0.1566	0.1158	£3,273	0.1056	0.0781	£2,207	-0.0510	-0.0377	-£1,066
State H Best supportive care	0.6888	0.3974	£6,475	0.5874	0.3389	£5,522	-0.1014	-0.0585	-£953
Total (discounted)	7.71	6.07	£55,136	9.46	7.50	£78,068	1.75	1.43	£22,931

Base-case analysis

7.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

Basecase case results are presented in Table B-54. The model predicted that, over a lifetime, the total discounted QALYs for patients treated with surgical resection only would be 3.83. Patients treated with surgical resection followed by one or three years adjuvant imatinib accrued 6.07 and 7.50 discounted QALYs over a lifetime, respectively (i.e. gain of 2.24 and 3.67 QALYs compared with no treatment, respectively).

The model predicted the total discounted costs for patients treated with surgical resection only to be £47,292. The total discounted costs predicted for patients treated with surgical resection followed by one or three years adjuvant imatinib was £55,136 and £78,068 (i.e. an increment of £7,844 and £30,776 compared with no treatment, respectively).

Compared with no treatment, the ICER for adjuvant one year imatinib was £3,509 per QALY gained. The ICER for 3 year adjuvant imatinib compared with no treatment was £8,390.

An incremental analysis was conducted comparing the least effective strategy to the next least effective strategy. The ICER for adjuvant one-year imatinib compared with no treatment (least effective strategy) remained the same and was £3,509 per QALY gained. Adjuvant imatinib 3 years was more effective than one adjuvant imatinib (gain of 1.43 in QALYs) but was associated with greater costs (increment of £22,931). The ICER for 3 year adjuvant imatinib compared with one year adjuvant imatinib was estimated to be £16,006 per QALY gained.

Table B-54. Base-case results

	Total Per Patient:				Incremental:				ICERs (compared with no treatment)		ICERs (incremental analysis)	
	Costs	QALYs	Life-Years		Costs	QALYs	Life-Years		Cost/QALY Gained	Cost/LY Saved	Cost/QALY Gained	Cost/LY Saved
No treatment	£47,292	3.83	5.08									
Adjuvant imatinib 1 yr tx	£55,136	6.07	7.71		£7,844	2.24	2.63		£3,509	£2,984	£3,509	£2,984
Adjuvant imatinib 3 yr tx	£78,068	7.50	9.46		£22,931	1.43	1.75		£8,390	£7,021	£16,006	£13,071

Sensitivity analyses

7.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

A range of sensitivity analyses was conducted to test the robustness of the model assumptions.

In particular, there was significant uncertainty around health state utility values used in the economic model. Therefore, sensitivity analyses were conducted examining different utility values for the recurrence-free health state and patients treated with progressive disease treated with BSC (SA22 to SA-26). Results were robust and were not sensitive to changes in health utility values (Table B-55).

As expected, reducing the time horizon increases the ICER as a shorter time horizon does not allow the benefit of adjuvant imatinib to be captured in the long-term. NICE recommends using a lifetime horizon, and therefore this analysis is presented for transparency only. However, this shows that even when using a 10 year time horizon, the ICER for adjuvant imatinib (one or 3 year) versus placebo remains below £20,000 per QALY gained.

We also varied the HR for the on and off treatment phase within the calculated confidence interval. As expected, results were less favourable when using the upper confidence interval and more favourable when using the lower CI. The ICERs when setting the HR for the “on-treatment” period to the upper CI remained below £20,000 per QALY gained when comparing 3 year adjuvant imatinib or 1 year adjuvant imatinib compared with no treatment. The ICER for 3 year adjuvant imatinib versus 1 year imatinib remained below £30,000 per QALY gained (£26,878 per QALY gained).

The ICERs for 1 year adjuvant imatinib and 3 year adjuvant imatinib compared with no treatment or 3 year imatinib vs. 1 imatinib remained below £30,000 per QALY gained varying the HR for the off-treatment period within the CI.

Results were robust to variation in costs and most transition probabilities.

Table B-55. Deterministic Sensitivity Analysis

	No treatment			Adjuvant imatinib 1 year			Adjuvant imatinib 3 years			ICERs (cost per QALYs)		
	Costs	QALYs	Life-Years	Costs	QALYs	Life-Years	Costs	QALYs	Life-Years	1 Yr vs. No treatment	3 Yr vs. No treatment	3 Yr vs. 1 Year
SA1 Time horizon reduced to 5 yrs	£36,229	2.70	3.55	£40,161	3.23	4.09	£60,331	3.46	4.30	£7,368	£31,718	£89,182
SA2 Time horizon reduced to 10 yrs	£45,519	3.39	4.52	£51,729	4.61	5.90	£73,242	5.35	6.74	£5,096	£14,184	£29,230
SA3 On treatment HR set to LCI	£47,292	3.83	5.08	£55,942	6.25	7.92	£80,840	8.03	10.09	£3,584	£7,982	£13,917
SA4 On treatment HR set to UCI	£47,292	3.83	5.08	£53,197	5.64	7.20	£71,770	6.33	8.08	£3,262	£9,787	£26,878
SA5 Off treatment HR set to LCI	£47,292	3.83	5.08	£47,187	7.78	9.71	£69,727	9.09	11.31	Dominant	£4,268	£17,265
SA6 Off treatment HR set to UCI	£47,292	3.83	5.08	£61,852	4.51	5.88	£87,066	5.68	7.33	£21,498	£21,557	£21,591
SA7 Both on&off treatment HR set to LCI	£47,292	3.83	5.08	£47,677	8.03	10.00	£71,670	9.78	12.13	£92	£4,098	£13,695
SA8 Both on&off treatment HR set to UCI	£47,292	3.83	5.08	£59,279	4.23	5.55	£78,836	4.90	6.41	£30,058	£29,496	£29,162
SA9 Probability of death whilst on BSC: Huse	£49,224	3.95	5.28	£56,686	6.16	7.87	£79,383	7.58	9.60	£3,373	£8,308	£16,003
SA10 Probability of death whilst on BSC: Demetri	£44,114	3.64	4.74	£52,581	5.91	7.44	£75,893	7.37	9.23	£3,724	£8,521	£16,011
SA11 Probability of death whilst on BSC: Tran	£54,041	4.25	5.80	£60,532	6.40	8.28	£82,637	7.78	9.95	£3,016	£8,091	£15,996
SA12 Probability death whilst on imatinib LCI	£55,128	4.14	5.53	£60,687	6.28	8.02	£81,785	7.64	9.67	£2,590	£7,599	£15,497
SA13 Probability death whilst on imatinib UCI	£39,256	3.52	4.62	£49,435	5.85	7.38	£74,241	7.35	9.24	£4,376	£9,131	£16,477
SA14 Probability death whilst on sunitinib LCI	£48,633	3.90	5.19	£56,087	6.12	7.79	£78,705	7.53	9.52	£3,365	£8,282	£15,971
SA15 Probability death whilst on sunitinib UCI	£45,783	3.75	4.95	£54,066	6.01	7.62	£77,350	7.46	9.40	£3,668	£8,510	£16,045
SA16 Probability of discontinuation on adjuvant	£47,292	3.83	5.08	£55,486	6.07	7.71	£79,755	7.50	9.46	£3,668	£8,859	£16,968

imatinib LCI															
SA17 Probability of discontinuation on adjuvant imatinib UCI	£47,292	3.83	5.08		£54,699	6.07	7.71		£76,323	7.50	9.47		£3,311	£7,906	£15,069
SA18 Probability of discontinuation whilst on imatinib treatment for recurrence LCI	£48,552	3.87	5.12		£56,028	6.09	7.74		£78,664	7.52	9.48		£3,361	£8,253	£15,895
SA19 Probability of discontinuation whilst on imatinib treatment for recurrence UCI	£44,743	3.76	4.99		£53,330	6.01	7.64		£76,858	7.46	9.42		£3,805	£8,663	£16,226
SA20 Probability of discontinuation whilst on sunitinib treatment for recurrence LCI	£48,023	3.84	5.08		£55,656	6.08	7.71		£78,417	7.51	9.46		£3,420	£8,301	£15,919
SA21 Probability of discontinuation whilst on sunitinib treatment for recurrence UCI	£46,766	3.82	5.08		£54,762	6.06	7.71		£77,816	7.50	9.46		£3,573	£8,454	£16,069
SA22 BSC utility set to 0.7	£47,292	3.94	5.08		£55,136	6.15	7.71		£78,068	7.57	9.46		£3,542	£8,466	£16,147
SA23 RecFree health state utility set to 0.78	£47,292	3.83	5.08		£55,136	6.07	7.71		£78,068	7.50	9.46		£3,509	£8,390	£16,006
SA24 BSC utility set to 0.7 & RecFree health state utility set to 0.78	£47,292	3.94	5.08		£55,136	6.15	7.71		£78,068	7.57	9.46		£3,542	£8,466	£16,147
SA25 Decrement in utility for patients treated with adjuvant imatinib set to 0	£47,292	3.83	5.08		£55,136	6.07	7.71		£78,068	7.57	9.46		£3,505	£8,242	£15,331
SA26 Decrement in utility for patients treated with adjuvant imatinib halved	£47,292	3.83	5.08		£55,136	6.07	7.71		£78,068	7.53	9.46		£3,507	£8,316	£15,662
SA27 Dose intensity reduction adjustment – using ACOSOG Z9001	£46,781	3.83	5.08		£54,150	6.07	7.71		£76,183	7.50	9.46		£3,297	£8,016	£15,379
SA28 Dose intensity reduction adjustment – using SSGXVII/AIO trial data	£47,292	3.83	5.08		£54,819	6.07	7.71		£77,232	7.50	9.46		£3,367	£8,162	£15,644

SA29 One-off cost of recurrence -50%	£45,775	3.83	5.08		£53,779	6.07	7.71		£76,753	7.50	9.46		£3,581	£8,445	£16,035
SA30 One-off cost of recurrence +50%	£48,809	3.83	5.08		£56,493	6.07	7.71		£79,383	7.50	9.46		£3,437	£8,335	£15,977
SA31 Management costs in recurrence-free health state for patients not receiving adjuvant imatinib -50%	£46,098	3.83	5.08		£54,877	6.07	7.71		£77,682	7.50	9.46		£3,927	£8,610	£15,917
SA32 Management costs in recurrence-free health state for patients not receiving adjuvant imatinib +50%	£48,486	3.83	5.08		£55,395	6.07	7.71		£78,454	7.50	9.46		£3,091	£8,170	£16,095
SA33 Management cost in recurrence-free heath state for patients treated with adjuvant imatinib - 50%	£47,292	3.83	5.08		£53,965	6.07	7.71		£76,655	7.50	9.46		£2,985	£8,005	£15,838
SA34 Management cost in recurrence-free heath state for patients treated with adjuvant imatinib + 50%	£47,292	3.83	5.08		£56,308	6.07	7.71		£79,480	7.50	9.46		£4,033	£8,775	£16,175
SA35 Management cost in recurrence health states - 50%	£46,270	3.83	5.08		£54,395	6.07	7.71		£77,547	7.50	9.46		£3,635	£8,527	£16,160
SA36 Management cost in recurrence health states + 50%	£48,314	3.83	5.08		£55,878	6.07	7.71		£78,588	7.50	9.46		£3,384	£8,254	£15,852
SA37 All management costs - 50%	£45,076	3.83	5.08		£52,965	6.07	7.71		£75,748	7.50	9.46		£3,529	£8,362	£15,903
SA38 All management costs + 50%	£49,508	3.83	5.08		£57,308	6.07	7.71		£80,387	7.50	9.46		£3,489	£8,419	£16,110
SA39 Average cost of adverse events 2x	£47,364	3.83	5.08		£55,222	6.07	7.71		£78,166	7.50	9.46		£3,515	£8,397	£16,015
SA40 Average cost of adverse events 5x	£47,581	3.83	5.08		£55,481	6.07	7.71		£78,460	7.50	9.46		£3,534	£8,418	£16,039
SA41 Cost of BSC - 50%	£43,274	3.83	5.08		£51,899	6.07	7.71		£75,307	7.50	9.46		£3,858	£8,733	£16,339
SA42 Cost of BSC + 50%	£51,310	3.83	5.08		£58,374	6.07	7.71		£80,829	7.50	9.46		£3,160	£8,048	£15,674

Notes: HR= hazard ratio, UCI = upper confidence interval , LCI = Lower confidence interval

7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

When the costs and effects are estimated with uncertainty, a Monte Carlo simulation can be used to generate the distribution of total costs and QALYs. The results of the probabilistic sensitivity analyses using 1,000 iterations is shown below (Table B-56). Again, the ICERs are presented compared with no treatment. Treatments are also compared using incremental analysis whereby the least effective is compared to the next least effective treatment.

Over a lifetime, patients receiving 3 years adjuvant imatinib accrue more QALYs compared with one year adjuvant imatinib (1.59 QALYs) and no treatment (3.89 QALYs), but at a greater cost (£22,583 and £30,958, respectively).

Compared with no treatment, the ICER for one-year adjuvant imatinib was £3,635 per QALY gained. The ICER for 3-year adjuvant imatinib compared with no treatment was £7,950 per QALY gained.

An incremental analysis was conducted comparing the least-effective strategy to the next least-effective strategy. The ICER for adjuvant one year imatinib compared with no treatment (least effective strategy) remained the same and was £3,635 per QALY gained. The ICER for 3 year adjuvant imatinib compared with one year adjuvant imatinib was estimated to be £14,205 per QALY gained.

Figure B-23 and Figure B-24 show the cost effectiveness plane and cost effectiveness acceptability curve using results generated over a lifetime horizon. The curves show the probability of being cost effective for different levels that the decision-maker may be willing to pay for an additional QALY. The CEAC shows that one is 41.70% and 58.30% confident that 1 year and 3 year adjuvant imatinib is a cost-effective strategy when using a threshold of £20,000 per QALY. The CEAC shows that one is 30.90% and 69.10% confident that 1 year and 3 year adjuvant imatinib is a cost-effective strategy when using a threshold of £30,000 per QALY.

Table B-56: PSA results

	Total Per Patient:				Incremental:				ICERs (compared with no treatment)		ICERs (incremental analysis)	
	Costs	**QALYs**	**Life-Years**		**Costs**	**QALYs**	**Life-Years**		**Cost/QALY Gained (vs no treatment)**	**Cost/LY Saved (vs no treatment)**	**Cost/QALY Gained**	**Cost/LY Saved**
No treatment	£48,256	5.27	2.27									
Adjuvant imatinib 1 yr tx	£56,631	7.57	4.62		£8,375	2.30	2.35		**£3,635**	**£3,570**	**£3,635**	**£3,570**
Adjuvant imatinib 3 yr tx	£79,214	9.16	6.21		£22,583	1.59	1.60		**£7,950**	**£7,853**	**£14,205**	**£14,148**

Table B-57: Net Monetary Benefit

	CE threshold = £20,000		CE threshold = £30,000	
	Expected Net Benefit	**Probability CE**	**Expected Net Benefit**	**Probability CE**
No treatment	-£2,862	0.00%	£19,835	0.00%
Imat 1yr	£35,680	41.70%	£81,836	30.90%
Imat 3yr	£45,022	58.30%	£107,140	69.10%

Figure B-23. Plot of incremental cost vs incremental QALY~: 3-year arm compared with no treatment and 1-year arm compared with no treatment

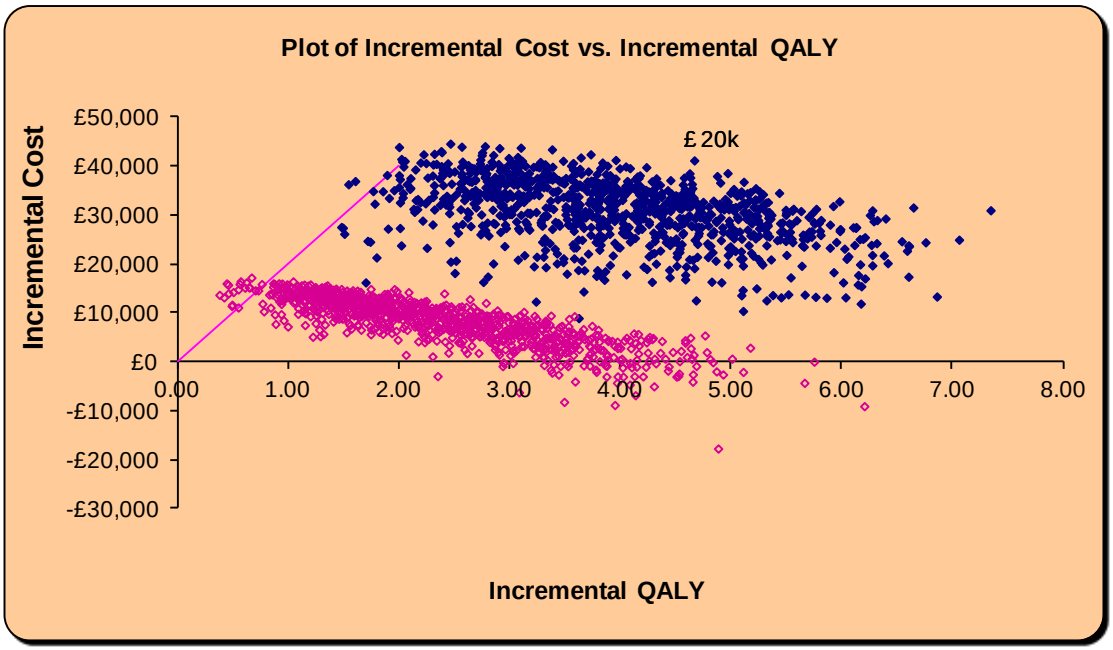
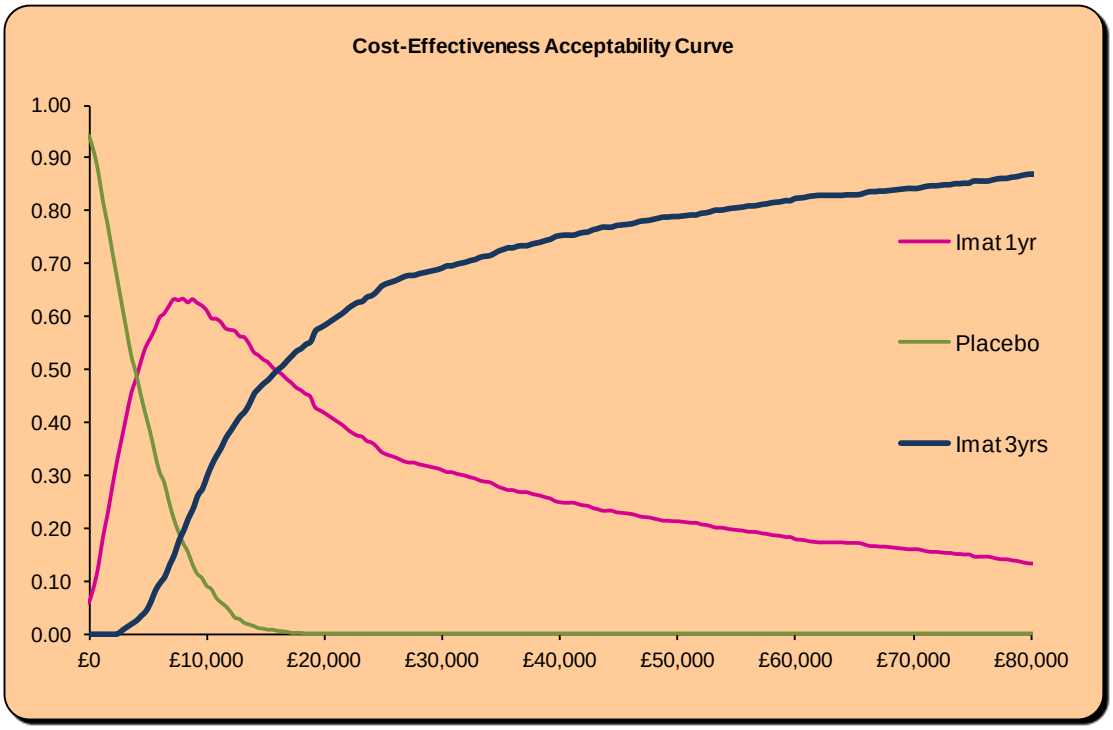


Figure B-24. Cost-effectiveness acceptability curves



7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Structural uncertainty was examined in terms of:

- the parametric distribution used to extrapolate RFS,
- assuming some patients may receive 800mg imatinib following recurrence, and
- assuming a different propoportion of patients moving to BSC (progressive disease) following recurrence.
- extended survival after recurrence

Results are presented in Table B-58.

The Gompertz distribution was used in the basecase to represent the risk of recurrence for patients treated with surgical resection only as this was deemed to provide the best fit to the observed data and was most consistent with historical data for patients receiving no treatment after surgical resection. However the impact of using other parametric curves was examined (exponential, Weibull, log-logistic and gamma). The exponential, Weibull and gamma models tended to overestimate the risk of recurrence for patients treated with surgical resection only, as well as overestimating the risk of recurrence for patients receiving adjuvant imatinib. The log-logistic provided a reasonable fit to the data and a reasonably credible long-term extrapolation. Overall, despite the differences in fit of the models, the ICERs were not unduly affected by changes in the baseline risk of recurrence and remained below £20,000 per QALY gained.

The ICERs were more favourable when we assumed that patients failing 400 mg imatinib could receive 800mg imatinib.

The ICERs were not affected when assuming 20% of or no (rather than 10%) patients move to BSC following recurrence on adjuvant imatinib or 400 mg imatinib treatment.

Assuming longer survival in post recurrence health states (on imatinib, sunitinib and BSC) had a limited impact on the ICERs. This suggests that the impact of the model underestimating survival in all three arms is limited. If patients survive longer in the post-recurrence health states they accrue additional costs – treatment on imatinib (400mg), sunitinib or BSC costs - as well as the additional survival benefits, albeit at a lower HRQL than in recurrence-free states. The 5 year overall survival for the 3-year , one year and no treatment arms are 85%, 77% and 63% in this analysis. This compares to 89.5% and 74.2% survival for the 3-year and 1-year arms, respectively, from the SSG study.

Table B-58: Scenario analysis

	No treatment				Adjuvant imatinib 1 year				Adjuvant imatinib 3 years				ICERs (cost per QALYs)		
	Costs	**QALYs**	**Life-Years**		**Costs**	**QALYs**	**Life-Years**		**Costs**	**QALYs**	**Life-Years**		**1 Yr vs. No treatment**	**3 Yr vs. No treatment**	**3 Yr vs. 1 Year**
Parametric distribution used															
Exponential	£49,812	3.26	4.41		£62,663	4.70	6.12		£86,563	6.03	7.76		£8,881	£13,266	£18,062
Weibull	£49,909	3.22	4.36		£63,091	4.60	6.00		£87,026	5.87	7.57		£9,551	£14,013	£18,866
Loglogistic	£48,948	3.46	4.64		£58,698	5.42	6.96		£80,932	6.87	8.73		£4,961	£9,382	£15,398
Gamma	£49,962	3.19	4.33		£63,312	4.55	5.94		£87,130	5.78	7.47		£9,886	£14,359	£19,239
Dose escalation to 800mg allowed in metastatic setting	£56 454	3,95	5,23		£61 440	6,15	7,80		£82 182	7,55	9,52		£2 274	£7 152	£14 764
Proportion of patients moving to BSC following recurrence whilst on imatinib or adjuvant imatinib															
• 20%	£46,997	3.83	5.08		£54,890	6.06	7.71		£77,847	7.50	9.46		£3,530	£8,407	£16,018
• 0%	£47,587	3.84	5.08		£55,382	6.07	7.71		£78,288	7.50	9.46		£3,489	£8,373	£15,995

Extended survival in post recurrence health states	£65,582	4.76	6.61		£68,684	6.76	8.85		£88,075	8.02	10.33		£1,551	£6,900	£15,390

7.7.10 What were the main findings of each of the sensitivity analyses?

Results were robust to most of the assumptions tested. Details are available in section 7.7.7.

7.7.11 What are the key drivers of the cost-effectiveness results?

Whilst results were robust to most parameters and assumptions tested (Table B-58), the ICERs were mainly affected by the predicted treatment effect over time and the time horizon of the analysis.

7.8 Validation

7.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

The validity of the model has been addressed through a variety of checks.

An independent health economist checked the internal validity of the model. Cell by cell verification of the model has been undertaken through:

- Check of sum of the health states = starting cohort at all times
- Check that the sum of each year's patient flow sum to the starting cohort

These tests ensure that patients are neither entering nor leaving the model – only changing from one state to another. An empirical validation was conducted by comparing the costs and effects and a number of alternative scenarios including plausible parameter values. Further testing of the model was conducted using a range of extreme parameter values.

7.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

7.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.

None undertaken

7.9.2 Please clearly define the characteristics of patients in the subgroup.

Not applicable

7.9.3 Please describe how the statistical analysis was undertaken.

Not applicable

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).

Not applicable

7.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.

Not applicable

7.10 Interpretation of economic evidence

7.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

The systematic review of the literature identified 2 cost-effectiveness studies evaluating surgical resection followed by 1 year adjuvant imatinib compared with 3 year adjuvant imatinib in the US and Dutch setting.[62,63]

These two studies used a similar structure and health states to our economic model, but different methodology was employed to model recurrence-free survival and overall survival. Indeed, neither of these studies evaluated surgical resection only compared with surgical resection followed with adjuvant imatinib, and therefore the methodology used to derive RFS and OS was different.

These two studies were non-UK based, therefore the generalisability of these studies to a UK setting may not be appropriate. However, these studies showed that 3 years of treatment may be considered cost effective. Majer et al (2013)[62] reported that the probability of 3 years of adjuvant imatinib being cost-effective compared with 1 year of adjuvant imatinib in the Dutch health care setting was 12.2%, 51.0%, 68.1% and 80.4% at willingness to pay thresholds of €20,000, €30,000, €40,000, €50,000 per QALY gained, respectively. Sanon et al (2013)[63] reported that in the US setting 3 years of adjuvant imatinib has a 100% probability of being cost effective compared with 1 year of adjuvant imatinib at a willingness to pay threshold of $100,000 per QALY gained.

Our study has similar findings and show that 3 year adjuvant imatinib may be considered cost-effective in the UK compared with one year adjuvant imatinib at a willingness to pay threshold of £30,000 per QALY gained. Our study also showed that both one year and three year adjuvant imatinib may be considered cost-effective in the UK compared with no treatment (current practice) at a willingness to pay threshold of £20,000 per QALY gained. Results were robust to most of the assumptions and parameters examined.

7.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?

The economic evaluation is relevant to adults who are at high risk of recurrence following resection of KIT (CD117)-positive GIST as defined in Section 5.

7.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The main strengths of the evaluation are:

- This is the first analysis to consider the cost effectiveness of one and three year adjuvant imatinib compared with no adjuvant treatment in the same economic model.
- A key driver of the model results is the extrapolation of treatment benefit over time. The Gompertz survival model was selected as the basecase analysis on the basis of goodness-of-fit to the trial data (examined visually and using AIC, BIC statistics), and the extrapolation beyond the period observed in the trial was assessed for face

validity with reference to published literature on long term recurrence rates. However results based on the four other models (exponential, Weibull, gamma, loglogistic, Gompertz) were also presented and showed that the impact on the ICER of using alternative models was limited.

- The decision to calculate hazard ratios for on and off treatment periods using data from the placebo arm of the ACOSOG Z9001 trial as the baseline was taken after careful assessment of the shape of the KM curves observed in all of the trial arms. This motivated the assumption that at the end of the treatment period the behaviour of the hazard of RFS was similar to that experienced immediately after surgery for patients not treated with adjuvant imatinib. It is recognised that this approach is unusual in the way that the data from one trial arm is used twice to estimate treatment effects. However, it was felt that this approach is more defensible than more traditional approaches. A proportional hazards model for the whole observation period is not suitable as the assumption of proportional hazards is clearly not appropriate. Simple parametric modelling of each trial arm was also considered inappropriate since it is necessary to assume that the hazard of recurrence free survival for the first year of imatinib treatment is independent of the decision to treat for 1 or 3 years.

The main weaknesses of the evaluation are:

- Lack of utility estimates from the imatinib clinical trials meant that utility values were taken from a range of other sources. However a range of sensitivity analysis has been undertaken and demonstrates the limited impact of utility on the ICERs

- A utility decrement for patients on adjuvant imatinib treatment is assumed, based on the decrement for patients on sunitinib treatment.[76] The actual extent of the decrement of imatinib on quality of life for patients on imatinib is unknown but may be lower than this. In the BFR14 French Sarcoma Group randomised phase III trial in patients with advanced GIST interruption of imatinib treatment after 1 year did not significantly improve patients' global health status, functional status, or symptom scores, as measured by the cancer-specific European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire (EORTC QLQ-C30).[98,99] Although the number of patients in this study was limited, treatment interruption was not associated with a major improvement of quality of life of patients, suggesting that imatinib therapy has a more limited impact of HRQL. This suggests that the ICER may be slightly lower than suggested in the basecase analysis

- The economic model under-predicts overall survival for all three arms. If patients were to survive longer in the post-recurrence health states they would accrue additional costs – treatment on imatinib (400mg), sunitinib or BSC costs - as well as the additional survival benefits, albeit at a lower HRQL than in recurrence-free states. The results of a scenario analysis assuming patients remain in post-recurrence health states for longer suggest that the impact on the ICER is limited.
- The high risk population considered in the model are subgroups of the trial populations. The ACOSOG Z9001 trial did not restrict recruitment to patients at high risk of recurrence. The SSGXVIII/AIO trial included patients with evidence of metastases although the protocol was subsequently amended to exclude them. Furthermore, it was subsequently discovered that some patients were at lower than high risk of recurrence. In an attempt to minimise these, and other, differences in the baseline populations whilst also presenting results which are in accordance with UK treatment guidelines, only the Miettinen high-risk sub-group is used in the analysis. This violates the randomisation of the studies, and therefore risks introducing bias into estimates of treatment effects. However, given the scope of the submission and the nature of the available data, this is unavoidable. It is considered that any bias introduced by this restriction is likely to be small in magnitude.
- As discussed in Section 2.1, mutations and tumour biological factors are associated with unfavourable outcomes. However, they are not considered established *independent* risk factors and are not included in the current risk-stratification schemes. Indeed, it is unlikely that a large enough study could be conducted to determine the effect on outcome of each of the 200-plus mutations.[44] As a result, we have not considered any further sub-grouping of the available data to take these factors in to account.

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

A cross-over analysis is currently being undertaken for the AGOSOG Z9001 five year update analysis but the results are not yet available. This work will use survival data to estimate an adjusted treatment effect that attempts to control for treatment switching, for both recurrence-free survival and overall survival. Results are anticipated in February 2014 and, once available, will be used in the economic model to produce a revised analysis.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

The prevalence for GIST is estimated to be 129 per million[26]. Based on a population of 56,600,000 in mid-2012,[96] at an annual growth rate of 0.7% (by 2014 implies a population of 56 996 200) this would suggest that there were 7,301 patients with GIST in England and Wales in 2014.

Following diagnosis of GIST, patients whose tumour is resectable will undergo surgery. It is only in these patients, in the immediate post-surgery period, that the use of adjuvant imatinib would be considered. Therefore, the pool of prevalent patients is not relevant when estimating the budget impact of adjuvant imatinib.

Based on an incidence of 14.5 per million,[107] the number of new patients presenting with GIST on an annual basis is given in Table C-1 below. Of these, it is assumed that two thirds are resectable.[38] Based on the ACOSOG Z9001 study the proportion of patients assigned to the high risk categories (Miettinen classification) is 29.7% respectively.[1] Therefore, in 2014 an estimated 164 patients are in the high risk category (based on the Miettinen 2006 criteria). This value increases slightly over time due to a small annual increase in the population of England and Wales.

Table C-1: Number of patients diagnosed with GIST in England and Wales

	2014	2015	2016	2017	2018
Population of England and Wales	56,996,200	57,395,173	57,796,940	58,201,518	58,608,929
No. of pts diagnosed with GIST : 14.5/million	826	832	838	844	850
No. of resectable pts	551	555	559	563	567
No of high risk	164	165	166	167	168
* due to rounding					

For patients prescribed 3 years of adjuvant imatinib treatment they will receive treatment for a maximum of 3 years. Each year, a proportion of patients will discontinue treatment due to adverse events, recurrence etc. This proportion will increase cumulatively over time, from 8.2% in year 1, to 19.2% in year 2 and 27.3% in year 3, reducing the number of patients receiving treatment over the 3-year period.

Each year a new cohort of patients will start treatment.

The number of patients receiving treatment in each year, taking into account discontinuations from 2014 to 2018 is shown in Table C-2.

Table C-2: Total number of patients receiving 3 years of treatment, taking into account discontinuations

Year	2014	2015	2016	2017	2018
Cohort 1	150	132	119		
Cohort 2		151	133	120	
Cohort 3			152	134	121
Cohort 4				153	135
Cohort 5					154
TOTAL	150	283	404	407	410

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

Adjuvant treatment in GIST is an innovative approach and imatinib is the only treatment licensed for use in this indication (marketing authorisation received 29 April 2009). Conventional chemotherapy and radiation are of limited benefit[11]. Consequently, it is assumed that there are currently no patients being treated post-surgical resection.

Predicted market uptake rates are shown in Table C-3. Based on these uptake rates, the number of patients prescribed adjuvant imatinib each year is as shown in Table C-3. It was estimated that, allowing for discontinuations, taken from the cost-effectiveness model, a net number of 150 (91.81%) will be treated in 2014. If 80% of the high risk patients (0.8 x 150) are prescribed imatinib in 2014, this gives a total predicted number of patients in 2014 of 120 Table C-3.

Table C-3: Percentage of eligible patients receiving imatinib (taking into account market uptake)

	2014	2015	2016	2017	2018
Market uptake	80%	85%	90%	90%	95%
No of patients:					
One year treatment	120	129	137	138	147
Three year treatment	120	241	364	367	390

Of note, between April and December 2013, inclusive, 70 patients were funded for adjuvant imatinib on the Cancer Drugs Fund (http://www.england.nhs.uk/ourwork/pe/cdf/), with monthly approvals of between 5 and 10 patients.

8.3 What assumption(s) were made about market share (when relevant)?

No assumptions are needed about market share because imatinib is the only therapy currently indicated for adjuvant therapy.

8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

As well as drug costs, follow-up costs and costs of treating adverse events are also taken into account in the budget impact calculations.

The total cost of treatment for patients on 1- and 3-year imatinib treatment from 2014 to 2018, estimated from the cost effectiveness model, is shown in Table C-4. This includes cost of the drug, administration and follow-up costs, and costs of treating adverse events.

Table C-4: Expected Total Costs of Patients receiving adjuvant imatinib therapy (£s)

	2014	2015	2016	2017	2018
Imatinib 1 yr treatment	2 694 996	2 883 477	3 074 465	3 095 987	3 290 862
Imatinib 3 yr treatment	2 694 996	5 225 883	7 644 247	7 976 089	8 335 909

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

Unit costs are based on the unit costs used in the cost effectiveness model. See Table B-34 and Table B-35.

8.6 Were there any estimates of resource savings? If so, what were they?

The direct savings relate to costs that would have been incurred if these patients had received no adjuvant therapy. These are presented in Table C-5.

The estimated savings are taken from the comparator arm of the cost-effectiveness model and comprise cost-savings related to reduced costs of recurrence: one-off costs, including surgery, plus on-going drug and medical costs relating to prescribing of 400 mg imatinib following recurrence.

Table C-5: Expected Direct Savings (£s)

	2014	2015	2016	2017	2018
BSC (1 year*)	815 334	872 357	930 137	936 648	995 605
BSC (3years*)	815 334	2 132 092	3 416 739	3 592 167	3 741 885

*3 yr BSC implies patients are not treated for 3 consecutive years. This allows comparison to the 3 yr treatment with imatinib. To compare to 1 yr treatment only the first year's BSC costs are taken into account.

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

The annual budget impact for the NHS in England and Wales is derived by subtracting the direct savings from the direct costs associated with imatinib. The net resource implications from 2014 to 2018 are shown in Table C-6.

Table C-6: Annual Budget Impact for NHS England and Wales (£s)

Year	2014	2015	2016	2017	2018
1 yr imatinib treatment	1 879 662	2 011 121	2 144 328	2 159 338	2 295 257
3 yr imatinib treatment	1 879 662	3 093 791	4 227 508	4 383 922	4 594 024

In summary, for the case of 1-year treatment, the cost impact on the NHS for England and Wales is expected to start at an estimated value of £1.9 million in 2014, rising slowly to £2.3 million by 2018. For the case of 3-year treatment the cost impact, compared with no treatment, is expected to be starting at an estimated value of £1.9 million in 2014, rising to £4.6 million by 2018.

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

None identified

9 References

Please use a recognised referencing style, such as Harvard or Vancouver.

1. Glivec (imatinib) Summary of Product Characteristics. Available at: http://www.medicines.org.uk/EMC/medicine/15014/SPC/GLIVEC+Tablets/. Updated 28 November 2013. Accessed 13 January 2014.
2. Demetri GD, von Mehren M, Antonescu CR, et al. NCCN Task Force report: update on the management of patients with gastrointestinal stromal tumors. J Natl Compr Canc Netw 2010;8 Suppl 2 S1-41; quiz S42-4.
3. Rutkowski P, Nowecki ZI, Michej W, et al. Risk criteria and prognostic factors for predicting recurrences after resection of primary gastrointestinal stromal tumor. Ann Surg Oncol 2007;14:2018-27.
4. BNF November 2013. http://www.bnf.org/bnf/index.htm. Accessed 1 December 2013.
5. Gastrointestinal stromal tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23 Suppl 7:vii49-55.
6. Guidelines for the management of gastrointestinal stromal tumours (GIST) in the UK and Ireland. 2009. Available at: http://www.augis.org/pdf/GIST_Management_Guidelines_180809.pdf. Accessed 25 August 2011. (Accessed at
7. Guidelines for the management of gastrointestinal stromal tumours (GIST) in Scotland. 2009. Available at: http://www.pathologyscotland.org/download/sgpg/guidelines/gist.pdf. Accessed 24 August 2011. (Accessed at
8. Dematteo RP, Ballman KV, Antonescu CR, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet 2009;373:1097-104.
9. Heintz D, Noronha-Jackson A, Green S, Scheuer N, Calderwood J, Gallagher N. Short (12 months) versus long (36 months) duration of adjuvant treatment with the tyrosine kinase inhibitor imatinib mesylate of perable GIST with a high risk for recurrence: A randomised Phase III study. Clinical Study Report STI571BF103.
10. Joensuu H, Eriksson M, Sundby Hall K, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. Jama 2012;307:1265-72.
11. Casali PG, Le Cesne A, Poveda Velasco A. Imatinib failure-free survival (IFS) in patients with localized gastrointestinal stromal tumors (GIST) treated with adjuvant imatinib (IM): The EORTC/AGITG/FSG/GEIS/ISG randomized controlled phase III trial. J Clin Oncol 2013;31:(suppl; abstr 10500).
12. Data on file. ACOSOG Z9001 Tables and Listings for High Risk Patients, Analysis performed by Novartis. Commercial in Confidence.
13. Data On File: Clinical Study Report 5-Year Follow-up for the ACOSOG trial.

14. Gong FJ, Li J, Wu WA, Shen L. Adjuvant therapy with imatinib in gastrointestinal stromal tumor (GIST) patients with intermediate or high risk: Analysis from a single-center contrast study. J Clin Oncol 2009; 27 10556.
15. Jiang WZ, Guan GX, Lu HS, Yang YH, Kang DY, Huang HG. Adjuvant Imatinib treatment after R0 resection for patients with high-risk gastrointestinal stromal tumors: A median follow-up of 44 months. J Surg Oncol 2011;104:760-4.
16. Li J, Gong JF, Wu AW, Shen L. Post-operative imatinib in patients with intermediate or high risk gastrointestinal stromal tumor. Eur J Surg Oncol 2011;37:319-24.
17. Nilsson BE, Sjolund K, Nilsson EP, Wangberg B, Nilsson O, Ahlman H. Neoadjuvant, adjuvant, and palliative treatment with imatinib in patients with gastrointestinal stromal tumors. J Clin Oncol 2010;28:10087.
18. Kang YK, Kang BW, Im SA, et al. Two-year adjuvant imatinib mesylate after complete resection of localized, high-risk GIST with KIT exon 11 mutation. Cancer Chemother Pharmacol 2013;71:43-51.
19. Conley AP, Guerin A, Sasane M, et al. Risk of disease recurrence and mortality in gastrointestinal stromal tumor (GIST) patients receiving short-term versus long-term imatinib adjuvant therapy: A chart review analysis. J Clin Oncol 2012;30:(Suppl): e20511.
20. Hatoum HT, Lin SJ, Sasane M, Trent JC. Effectiveness of adjuvant imatinib in patients with gastrointestinal stromal tumor: results of a population-based, matched-cohort study. Curr Med Res Opin 2012;28:805-14.
21. Kanda T, Nishida T, Wada N, et al. Adjuvant therapy with imatinib mesylate after resection of primary high-risk gastrointestinal stromal tumors in Japanese patients. Int J Clin Oncol 2013;18:38-45.
22. McCarter MD, Antonescu CR, Ballman KV, et al. Microscopically positive margins for primary gastrointestinal stromal tumors: analysis of risk factors and tumor recurrence. J Am Coll Surg 2012;215:53-9.
23. Nishida T, Kanda T, Wada N, et al. Phase II trial of adjuvant imatinib mesylate after resection of localized, primary high risk gastrointestinal stromal tumour (GIST) in Japan. Eur J Cancer 2009;7:594.
24. Wu XJ, Zhang RX, Chen G, et al. Prognostic factors in surgically managed gastrointestinal stromal tumours. J Int Med Res 2012;40:1904-11.
25. Yalcin S, Buyukberber S, Yilmaz U, et al. Phase II study of adjuvant imatinib mesylate (IM) in patients after resection of primary gastrointestinal stromal tumor (GIST): Efficacy and safety at one year. J Clin Oncol 2012 2012;30.
26. Maki RG. Recent advances in therapy for gastrointestinal stromal tumors. Curr Oncol Rep 2007;9:165-9.
27. von Mehren M. The role of adjuvant and neoadjuvant therapy in gastrointestinal stromal tumors. Curr Opin Oncol 2008;20:428-32.
28. Katz SC, DeMatteo RP. Gastrointestinal stromal tumors and leiomyosarcomas. J Surg Oncol 2008;97:350-9.
29. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 1998;279:577-80.

30. Sleijfer S, Wiemer E, Seynaeve C, Verweij J. Improved insight into resistance mechanisms to imatinib in gastrointestinal stromal tumors: a basis for novel approaches and individualization of treatment. Oncologist 2007;12:719-26.
31. European Medicines Agency Assessment report for Glivec. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000406/WC500022212.pdf; Accessed 30 January 2014.
32. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006a;23:70-83.
33. NCT01172548 Novartis Pharmaceuticals US. Safety and Efficacy Evaluation of Two Year Imatinib Treatment in Adjuvant Gastrointestinal Stromal Tumor (GIST) (INV555). Available at: http://clinicaltrials.gov/ct2/show/NCT01172548. Accessed 23 October 2013.
34. MacDuff E, Walsh S, Reid R. Royal College of Pathologists. Standards and datasets for reporting cancers: Dataset for gastrointestinal stromal tumours (GISTs) February 2011. Updated February 2012. Available from: https://www.rcpath.org/Resources/RCPath/Migrated%20Resources/Documents/G/G103_DatasetforGISTS_Feb12.pdf. Accessed 4 December 2013.
35. Eisenberg BT, Judson I. Surgery and imatinib in the management of GIST: emerging approaches to adjuvant and neoadjuvant therapy. Ann Surg Oncol 2004;11(5):465-75.
36. Blay JY, Le Cesne A, Cassier PA, Ray-Coquard IL. Gastrointestinal stromal tumors (GIST): a rare entity, a tumor model for personalized therapy, and yet ten different molecular subtypes. Discov Med 2012;13:357-67.
37. Demetri GD, Benjamin RS, Blanke CD, et al. NCCN Task Force report: management of patients with gastrointestinal stromal tumor (GIST)--update of the NCCN clinical practice guidelines. J Natl Compr Canc Netw 2007;5 Suppl 2:S1-29; quiz S30.
38. Reddy P, Boci K, Charbonneau C. The epidemiologic, health-related quality of life and economic burden of gastrointestinal stromal tumours. J Clin Pharm Ther 2007;32:557-65.
39. DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg 2000;231:51-8.
40. Nikfarjam M KE, Shereef S, Gusani NJ, Jiang Y, Liang J, Sehmbey M, Staveley-O'Carroll KF. Surgical outcomes of patients with gastrointestinal stromal tumours in the era of targeted drug therapy. J Gastointest Surg 2008;12:2023-31.
41. Miettinen M, Makhlouf H, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the jejunum and ileum: a clinicopathologic, immunohistochemical, and molecular genetic study of 906 cases before imatinib with long-term follow-up. Am J Surg Pathol 2006b;30:477-89.
42. Rutkowski P, Bylina E, Wozniak A, et al. Validation of the Joensuu risk criteria for primary resectable gastrointestinal stromal tumour - The

impact of tumour rupture on patient outcomes. Eur J Surg Oncol 2011;37:890-6.
43. Dematteo RP, Gold JS, Saran L, et al. Tumor mitotic rate, size, and location independently predict recurrence after resection of primary gastrointestinal stromal tumor (GIST). Cancer 2008;112:608-15.
44. Joensuu H, Vehtari A, Riihimaki J, et al. Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. Lancet Oncol 2012;13:265-74.
45. Chibon F, Lagarde P, Salas S, et al. Validated prediction of clinical outcome in sarcomas and multiple types of cancer on the basis of a gene expression signature related to genome complexity. Nat Med 2010;16:781-7.
46. Yen CC, Yeh CN, Cheng CT, et al. Integrating bioinformatics and clinicopathological research of gastrointestinal stromal tumors: identification of aurora kinase A as a poor risk marker. Annals of surgical oncology 2012;19:3491-9.
47. Lagarde P, Perot G, Kauffmann A, et al. Mitotic checkpoints and chromosome instability are strong predictors of clinical outcome in gastrointestinal stromal tumors. Clin Cancer Res 2012;18:826-38.
48. Linch M, Claus J, Benson C. Update on imatinib for gastrointestinal stromal tumors: duration of treatment. Onco Targets Ther 2013;6:1011-23.
49. von Mehren M, Benjamin RS, Bui MM, et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines ®). Soft Tissue Sarcoma. Version 1.2013. Available at: http://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf. Accessed 11 November 2013.
50. Fletcher CMD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumours: a consensus approach. Hum Pathol 2002;33:459-63.
51. Miettinen M, Lasota J, Sobin LH. Gastrointestinal stromal tumors of the stomach in children and young adults: a clinicopathologic, immunohistochemical, and molecular genetic study of 44 cases with long-term follow-up and review of the literature. Am J Surg Pathol 2005;29:1373-81.
52. SMC new product assessment form: Imatinib in GIST indication, Novartis Pharmaceuticals UK Ltd. August 2010.
53. NICE Single Technology Appraisal: Appendix D - NICE's response to consultee and commentator comments on the draft scope and provisional matrix. http://www.nice.org.uk/nicemedia/live/14205/65949/65949.pdf.
54. Corless CL, Ballman KV, Antonescu C, et al. Relation of tumor pathologic and molecular features to outcome after surgical resection of localized primary gastrointestinal stromal tumor (GIST): Results of the intergroup phase III trial ACOSOG Z9001. J Clin Oncol 2010;28:(suppl): 10006.
55. Data On File. Clinical Study Report: ACOSAG Z9001 primary analysis
56. Joensuu H, Eriksson M, Hatrmann J, et al. Twelve versus 36 months of adjuvant imatinib (IM) as treatment of operable GIST with a high risk of

recurrence: Final results of a randomized trial (SSGXVIII/AIO). J Clin Oncol 2011;29 (suppl; abstr LBA1)
57. Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumour. Hum Pathol 2008;39:1411-9.
58. Kang YK, Ryu MH, Yoo C, et al. Resumption of imatinib to control metastatic or unresectable gastrointestinal stromal tumours after failure of imatinib and sunitinib (RIGHT): a randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2013;14:1175-82.
59. Reichardt P HJ, Sundby Hall K, et al. Response to Imatinib Rechallenge of GIST That Recurs Following Completion of Adjuvant Imatinib Treatment − the First Analysis in the SSGXVIII/AIO Trial Patient Population. European Journal of Cancer 2011;47, Supp 2:15.
60. Data On File – GLI-006-09. 'Glivec remains effective in treating recurrent GIST after previous adjuvant therapy of patient after surgery' Commercial in confidence.
61. NICE Single Technology Appraisal Submission: The clinical and cost effectiveness of imatinib as adjuvant treatment for adult patients who are at significant risk of relapse following resection of KIT positive gastrointestinal stromal tumours. http://www.nice.org.uk/nicemedia/live/12178/48131/48131.pdf. 2009.
62. Majer IM, Gelderblom H, van den Hout WB, Gray E, Verheggen BG. Cost-effectiveness of 3-year vs 1-year adjuvant therapy with imatinib in patients with high risk of gastrointestinal stromal tumour recurrence in the Netherlands; a modelling study alongside the SSGXVIII/AIO trial. J Med Econ 2013;16:1106-19.
63. Sanon M, Taylor DC, Parthan A, Coombs J, Paolantonio M, Sasane M. Cost-effectiveness of 3-years of adjuvant imatinib in gastrointestinal stromal tumors (GIST) in the United States. J Med Econ 2013;16:150-9.
64. El OK, Pawar V, Coombs J, Rubin J. Cost-Effectiveness Of Imatinib As Adjuvant Treatment For Resected Gastrointestinal Stromal Tumors (Gist) Versus Best Supportive Care: Canadian Perspective. Value in Health 2010;13:A270.
65. Nagy B, Gray L, Ward SE. Cost-Effectiveness Analysis of Three Year Versus One Year Imatinib for the Treatment of Patients at High Risk of Disease Recurrence Following Surgical Resection of Kit (Cd117) Positive Gastrointestinal Stromal Tumours (GIST). Annals of Oncology 2012;23:235-6.
66. Parthan A, Sanon M, Coombs J, El KO. Cost-Effectiveness of Three-Years of Adjuvant Imatinib in Gastrointestinal Stromal Tumors (Gist) in Canada. Annals of Oncology 2012;23:235.
67. Pawar V, El OK, Rubin J, Coombs JH, Taylor D. Cost-effectiveness of adjuvant imatinib in patients with surgically resected localized gastrointestinal stromal tumors (GIST): Canadian societal perspective. Annals of Oncology 2010;21:232.
68. Raikou M, Boukovinas I, Geitona M. A Cost-Effectiveness Analysis of Three Years of Adjuvant Imatinib in Kit Plus Gastrointestinal Stromal Tumors (Gist) in Greece. Annals of Oncology 2012;23:236.
69. Rutkowski P, Gronchi A. Efficacy and economic value of adjuvant imatinib for gastrointestinal stromal tumors. The oncologist 2013;18:689-96.

70. Vetto JT. Role of imatinib in the management of early, operable, and advanced GI stromal tumors (GISTs). Onco Targets Ther 2009;2:151-9.
71. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patient with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006;368:1329-38.
72. Reichardt P, Blay JY, Gelderblom H, et al. Phase III study of nilotinib versus best supportive care with or without a TKI in patients with gastrointestinal stromal tumors resistant to or intolerant of imatinib and sunitinib. Annals of Oncology 2012;23:1680-7.
73. Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. Lancet 2004;364:1127-34.
74. Contreras-Hernandez I, Mould-Quevedo JF, Silva A, et al. A pharmaco-economic analysis of second-line treatment with imatinib or sunitinib in patients with advanced gastrointestinal stromal tumours. Br J Cancer 2008;98:1762-8.
75. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health 2010;13:509-18.
76. Chabot I, LeLorier J, Blackstein ME. The challenge of conducting pharmacoeconomic evaluations in oncology using crossover trials: the example of sunitinib for gastrointestinal stromal tumours. European Journal of Cancer 2008;44:972-7.
77. Wilson J, Connock M, Song F, et al. Imatinib for the treatment of patients with unresectable and/or metastatic gastrointestinal stromal tumours: systematic review and economic evaluation. Health technology assessment 2005;9:1-142.
78. Hanmer J, Lawrence WF, Anderson JP, Kaplan RM, Fryback DG. Report of nationally representative values for the noninstitutionalized US adult population for 7 health-related quality-of-life scores. Med Decis Making 2006;26:391-400.
79. Casali PG, Blay JY. Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21 Suppl 5:v98-102.
80. Polder JJ, Barendregt JJ, van Oers H. Health care costs in the last year of life--the Dutch experience. Soc Sci Med 2006;63:1720-31.
81. Yabroff KR, Lamont EB, Mariotto A, et al. Cost of care for elderly cancer patients in the United States. Journal for the National Cancer Institute 2008;100:630-41.
82. Reichardt P, Blay JY, Gelderblom H, et al. Phase III study of nilotinib versus best supportive care with or without a TKI in patients with gastrointestinal stromal tumors resistant to or intolerant of imatinib and sunitinib. Ann Oncol 2012;23:1680-7.
83. Huse DM, von Mehren M, Lenhart G, et al. Cost effectiveness of imatinib mesylate in the treatment of advanced gastrointestinal stromal tumours. . Clinical Drug Investigation 2007;27(2):85-93.

84. Tran T, Davila JA, El-Serag HB. The epidemiology of malignant gastrointestinal stromal umtours: an analysis of 1,458 cases from 1992 to 2000. Am J Gastroenterology 2005;100:162-8.
85. College voor Zorgverzekeringen, Medicijnkosten, 2012, College voor Zorgverzekeringen: Diemen. http://www.cvz.nl/binaries/content/documents/zinl-www/documenten/publicaties/gipeilingen/1310-gipeilingen-2012/GIPeilingen+2012.pdf. 2012.
86. Drug Topics Red Book. Montvale, NJ: Thomson Healthcare. 2010.
87. Nadler E, Eckert B, Neumann PJ. Do oncologists believe new cancer drugs offer good value? . Oncologist 2006;11:90-5.
88. National Institute for Health and Clinical Excellence Technology Appraisal 196. August 2010. Imatinib for the adjuvant treatment of gastrointestinal stromal tumours. Available at: http://www.nice.org.uk/nicemedia/live/13114/50447/50447.pdf. Accessed 16 January 2014.
89. National Institute for Health and Clinical Excellence Technology Appraisal 86. Updated November 2010. Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours. Available at: http://www.nice.org.uk/nicemedia/live/11548/32969/32969.pdf. Accessed 22 September 2011.
90. National Institute for Health and Clinical Excellence Technology Appraisal 179. September 2009. Sunitinib for the treatment of gastrointestinal stromal tumours. Available at: http://www.nice.org.uk/nicemedia/pdf/TA179Guidance.pdf. Accessed 16 January 2014.
91. Data On File – GLI-008-09: ‘ Clinical Validation Panel’ Commercial in confidence.
92. National Institute for Health and Clinical Excellence: Guide to the methods of technology appraisal 2013. Published April 2013. Available at: http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9/the-reference-case. Accessed 1 November 2013.
93. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. Med Decis Making 1993;13:322-38.
94. Demetri GD, Garrett CR, Schoffski P, et al. Complete longitudinal analyses of the randomized, placebo-controlled, phase III trial of sunitinib in patients with gastrointestinal stromal tumor following imatinib failure. Clin Cancer Res 2012;18:3170-9.
95. Trowman R, Collins R, Riemsma R, Palmer S. Implementing NICE guidance for evidence synthesis in technology appraisals: An overview of common methodological and analytic challenges.
96. ONS Interim Life Tables, Wales, 2010-2012. Available at: http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-325699 . Accessed 8 November 2013.
97. Blanke CD, Demetri GD, von Mehren M, Heinrich MC, Eisenberg B, Fletcher JA. Long-term results from a randomised Phase II trial of standard versus higher dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumours expressing KIT. Journal of Clinical Oncology 2008;26:620-5.

98. Blay JY, Le Cesne A, Ray-Coquard I, et al. Prospective multicentric randomized phase III study of imatinib in patients with advanced gastrointestinal stromal tumors comparing interruption versus continuation of treatment beyond 1 year: the French Sarcoma Group. J Clin Oncol 2007;25:1107-13.
99. Blay JY, Perol D, Le Cesne A. Imatinib rechallenge in patients with advanced gastrointestinal stromal tumors. Ann Oncol 2012;23:1659-65.
100. Theou-Anton N, Faivre S, Dreyer C, Raymond E. Benefit-risk assessment of sunitinib in gastrointestinal stromal tumours and renal cancer. Drug Saf 2009;32:717-34.
101. Adams VR, Leggas M. Sunitinib malate for the treatment of metastatic renal cell carcinoma and gastrointestinal stromal tumors. Clin Ther 2007;29:1338-53.
102. NHS Reference Costs 2011 /2012; Accessed 1 December 2013.
103. Curtis L. Personal Social Services Research Unit: Unit costs for health and social care. Available at: http://www.pssru.ac.uk/project-pages/unit-costs/2012/. Accessed 15 December 2013. 2012.
104. Hatzaindreu E, Archontakis F, Daly A. The potential cost savings of greater use of home- and hospice-based end of life care in England. National Audit Office report. 2008. Available at: http://www.nao.org.uk/publications/0708/end_of_life_care.aspx. Accessed 27th January 2010. 2008.
105. UCL Provider to provider Services Tariff. 2012/13. Available at: http://www.uclh.nhs.uk/aboutus/wwd/Documents/Provider%20to%20Provider%20Tariff%202012-13.pdf.Accessed 6 January 2014.
106. National Schedule of Reference Costs, 2011/12.
107. Nilsson B, Bumming P, Meis-Kindblom JM, et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era--a population-based study in western Sweden. Cancer 2005;103:821-9.

10 Appendices

10.1 Appendix 1

10.1.1 SPC/IFU, scientific discussion or drafts.

10.2 Appendix 2: Search strategy for section 6.1 (Identification of studies)

The following information should be provided.

10.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

A systematic literature review was performed in order to identify all studies reporting on the clinical effectiveness and safety of imatinib in the adjuvant setting of GIST. The review was an update of the original NICE submission (2010); consequently, similar search terms and sources were used.

Databases searched were Embase, MEDLINE and the Cochrane Library. Although the electronic databases contain information from a number of relevant conferences, these were supplemented by an electronic review of abstracts from the American Society of Clinical Oncology, European Society for Medical Oncology and European Crohn´s and Colitis Organisation conferences for 2010 to 21 June 2013.

10.2.2 The date on which the search was conducted.

The database searches were run on 8 April 2013 and the supplementary abstract search was run on 21 June 2013.

10.2.3 The date span of the search

The database searches were limited to studies published beginning in the year 2009 to the date that the search was run. Congress abstracts were searched from 2010 onwards.

10.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example,

MeSH) and the relationship between the search terms (for example, Boolean).

The search terms and numbers of hits are summarised below.

Embase

ID	Search	Hits
1	imatinib.tw.	12185
2	glivec.tw.	2342
3	gleevec.tw.	5356
4	imatinib mesilate.tw.	80
5	imatinib mesylate.tw.	3827
6	imatinib/	24765
7	1 or 2 or 3 or 4 or 5 or 6	25712
8	gastrointestinal stromal tumor/	8512
9	gastrointestinal stromal tumour*.tw.	1106
10	gastrointestinal stromal tumor*.tw.	5484
11	gastro-intestinal stromal tumour*.tw.	53
12	gastro-intestinal stromal tumor*.tw.	85
13	gist.tw.	5295
14	8 or 9 or 10 or 11 or 12 or 13	11115
15	adjuvant.tw.	113073
16	adjunct*.tw.	63694
17	post-resect*.tw.	691
18	post-surg*.tw.	13053
19	15 or 16 or 17 or 18	188695
20	7 and 14 and 19	536
21	limit 20 to yr="2009 -Current"	342

MEDLINE and MEDLINE In-Process

ID	Search	Hits
1	imatinib.tw.	8098
2	glivec.tw.	361
3	gleevec.tw.	850
4	1 or 2 or 3	8396
5	gastrointestinal stromal tumors/	3446
6	gastrointestinal stromal tumor*.tw.	4109
7	gastrointestinal stromal tumour*.tw.	831
8	gastro-intestinal stromal tumor*.tw.	47
9	gastro-intestinal stromal tumour*.tw.	36
10	gist.tw.	3505
11	5 or 6 or 7 or 8 or 9 or 10	6279

12	adjuvant.tw.	84227
13	adjunct*.tw.	50739
14	post-resect*.tw.	456
15	post-surg*.tw.	8055
16	12 or 13 or 14 or 15	142189
17	4 and 11 and 16	302
18	limit 17 to yr="2009 -Current"	182

Cochrane

ID	Search	Hits
#1	imatinib	425
#2	glivec	32
#3	gleevec	32
#4	imatinib mesilate	2
#5	imatinib mesylate	83
#6	#1 or #2 or #3 or #4 or #5	429
#7	MeSH descriptor: [Gastrointestinal Stromal Tumors] explode all trees	73
#8	gastrointestinal stromal tumor*	118
#9	gastrointestinal stromal tumour*	75
#10	gastro-intestinal stromal tumor*	13
#11	gastro-intestinal stromal tumour*	11
#12	gist	168
#13	#7 or #8 or #9 or #10 or #11 or #12	239
#14	adjuvant	13835
#15	adjunct*	8450
#16	post-resect*	27
#17	post-surg*	1281
#18	#14 or #15 or #16 or #17	22753
#19	#6 and #13 and #18	19

Although the electronic databases contain information from a number of relevant conferences, these were supplemented by an electronic review of abstracts from the American Society of Clinical Oncology, European Society for Medical Oncology and European Crohn´s and Colitis Organisation conferences for 2010 to 21 June 2013.

10.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

No additional searches were undertaken.

10.2.6 The inclusion and exclusion criteria.

Eligibility criteria used in the search strategy

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Populations	Patients with GIST (any risk)	Subgroups of GIST (eg rectal GIST)
Interventions	Adjuvant imatinib	Neoadjuvant imatinib, other TKIs
Outcomes	RFS (or equivalent), OS	None
Study design	Any (RCT and non-RCT, prospective and retrospective, case series)	1) Studies not specifically reporting data for adjuvant imatinib (eg reporting for neoadjuvant and/or adjuvant imatinib, or for with and without imatinib) 2) Studies reporting data for <20 patients receiving adjuvant imatinib
Language restrictions	English	Non-English languages
GIST, gastrointestinal stromal tumour; OS, overall survival; RCT, randomised controlled trial; RFS, recurrence-free survival; TKI, tyrosine kinase inhibitor		

10.2.7 The data abstraction strategy.

This process was fully compliant with the 2009 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines for the reporting of systematic reviews and meta-analyses.

An analyst screened articles for inclusion and a second researcher performed a random quality check of 30% of all articles selected. A third researcher resolved any disputes. All publications that met the inclusion criteria, based on titles and abstracts, were obtained as full documents and reassessed against the inclusion criteria. Data from relevant articles were subsequently used to populate predefined extraction tables, which corresponded to those required in the Single Technology Appraisal submission. All data extraction was fully validated by a second reviewer.

10.3 Appendix 3: Quality assessment of RCT(s) (section 6.4)

10.3.1 A suggested format for the quality assessment of RCT(s) is shown below.

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
ACOSOG Z9001[8]		
Was randomisation carried out appropriately?	“Patients were randomly assigned” to treatment via a web-	Yes

	bsed registration system	
Was the concealment of treatment allocation adequate?	No clear description of how treatment allocation was concealed	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Prognostic factors were well balanced between the two groups	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Study was double-blind, patients were assigned to imatinib or placebo and capsules looked alike	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	27% of patients in imatinib group and 25% of patients in placebo groups discontinued treatment	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No evidence of selective reporting	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	"Intention-to-treat analyses were done for both recurrence-free and overall survival" No clear indication of how missing data were accounted for	Yes Not clear
EORTC 62024[11]		
Was randomisation carried out appropriately?	Trial was randomised and stratified by certain criteria, but no further information provided	Not clear
Was the concealment of treatment allocation adequate?	Trial was open-label	N/A
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Prognostic factors were well balanced between the two groups	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Trial was open-label	No
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	17% of patients discontinued imatinib early; any further drop-out evidence not available	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No evidence of selective reporting	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?		Unclear Unclear Unclear
SSGXVIII/AIO[10]		

Was randomisation carried out appropriately?	"Randomisation was performed using computer-generated random numbers"	Yes
Was the concealment of treatment allocation adequate?	Trial was open-label; all patients received imatinib	N/A
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Prognostic factors were well balanced between the two groups	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Trial was open-label; all patients received imatinib	No
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	3.0% in each group were lost to follow-up	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No evidence of selective reporting	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	"The modified full population consisted of randomised patients who signed informed consent and the efficacy population of patients who signed informed consent; had centrally confirmed GIST, and did not have metastases resected prior to study entry… Efficacy analyses are based on the efficacy population… and the modified full population" "Patients lost to follow-up were censored on the date of the last follow-up visit"	Yes Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination DeMatteo et al. 2009;[8] Joensuu et al. 2012;[10] Casali et al. 2013.[11]		

10.4 Appendix 4: Search strategy for section 6.7 (Indirect and mixed treatment comparisons)

The following information should be provided.

10.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase

- Medline (R) In-Process
- The Cochrane Library.

No indirect treatment comparisons were performed as there is no accepted alternative to adjuvant therapy in patients at risk of relapse or recurrence after primary resection of GIST. Therefore, no searches were undertaken to identify studies for indirect and mixed treatment comparisons.

10.4.2 The date on which the search was conducted.

Not relevant; no searches were conducted.

10.4.3 The date span of the search.

Not relevant; no searches were conducted.

10.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Not relevant; no searches were conducted.

10.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not relevant; no searches were conducted.

10.4.6 The inclusion and exclusion criteria.

Not relevant; no searches were conducted.

10.4.7 The data abstraction strategy.

Not relevant; no searches were conducted.

10.5 Appendix 5: Quality assessment of comparator RCT(s) in section 6.7 (Indirect and mixed treatment comparisons)

10.5.1 A suggested format for the quality assessment of RCT(s) is shown below.

No indirect treatment comparisons were performed as there is no accepted alternative to adjuvant therapy in patients at risk of relapse or recurrence after primary resection of GIST. Therefore, no quality assessment was undertaken.

10.6 10.6 Appendix 6: Search strategy for section 6.8 (Non-RCT evidence)

The following information should be provided.

10.6.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Searches for non-RCT evidence were conducted simultaneously with the searches for RCT evidence. Please refer to section 10.2.1 for a description of the search strategy.

10.6.2 The date on which the search was conducted.

Please refer to section 10.2.2.

10.6.3 The date span of the search.

Please refer to section 10.2.3.

10.6.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Please refer to section 10.2.4.

10.6.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Please refer to section 10.2.5.

10.6.6 The inclusion and exclusion criteria.

Please refer to section 10.2.6.

10.6.7 The data abstraction strategy.

Please refer to section 10.2.7.

10.7 Appendix 7: Quality assessment of non-RCT(s) in section 6.8 (Non-RCT evidence)

10.7.1 Please tabulate the quality assessment of each of the non-RCTs identified.

Study question	**How is the question addressed in the study?**	**Grade (yes, no, not clear, NA)**
Conley et al. 2012[19]		
Is the study based on a representative sample selected from a relevant population?	Data was obtained from 248 US oncologists, but no further information provided in abstract to indicate whether or not this was a representative sample	Not clear
Are the criteria for inclusion explicit?	Study included “adult patients with primary resectable Kit positive GIST initiating imatinib 84 days after surgery”; no other criteria listed	Not clear
Did all individuals enter the survey at a similar point in their disease progression?	Not stated in abstract	Not clear
Was follow-up long enough for important events to occur?	Data was collected “for patients with short-term (6 months to1 year) and long-term imatinib use (2 years).”	Yes
Were outcomes assessed using objective criteria or was blinding used?	Not stated in abstract	Not clear
If sub-series compared, was there sufficient description of the series and distribution of prognostic factors?	Abstract describes mean age, proportion of males and Miettinen 2006 criteria risk scores for patients with short- versus long-term follow-up	Yes
Hatoum et al. 2012[20]		
Is the study based on a representative sample selected from a relevant population?	Patients were identified using ICD-9 and CPT-4 codes from the database of a large health plan covering more than 70 million patients in the USA	Yes

Are the criteria for inclusion explicit?	Step-wise algorithm used to identify patients from database; exclusion criteria explicit	Yes
Did all individuals enter the survey at a similar point in their disease progression?	Unclear; based on the baseline data presented there were large standard deviations and interquartile ranges for most variables	Not clear
Was follow-up long enough for important events to occur?	Median follow-up after surgery was 499 days (imatinib-treated) or 318 days (not imatinib-treated); median treatment duration was 270 days with 30% treated for more than 1 year	Not clear
Were outcomes assessed using objective criteria or was blinding used?	Treatment pattern criteria were objective and clearly defined; primary efficacy outcome (incidence of surgery) was objective and well defined	Yes
If sub-series compared, was there sufficient description of the series and distribution of prognostic factors?	Patients in imatinib-treated and non-imatinib-treated groups were compared by baseline characteristics and prognostic factors	Yes
Li et al. 2011[16]		
Is the study based on a representative sample selected from a relevant population?	Chinese patients in a single-centre trial, small patient group (n = 105)	Not clear
Are the criteria for inclusion explicit?	Inclusion and exclusion criteria are clearly stated	Yes
Did all individuals enter the survey at a similar point in their disease progression?	Patients were required to have a ECOG performance status of 0 to 2 and an intermediate or high risk of recurrence	Yes
Was follow-up long enough for important events to occur?	5-year follow up; treatment duration was 3 years	Yes
Were outcomes assessed using objective criteria or was blinding used?	RFS and OS, the primary outcomes, were clearly defined and objective	Yes
If sub-series compared, was there sufficient description of the series and distribution of prognostic factors?	Patients were assigned non-randomly to imatinib treatment or control; only some prognostic factors for each group were listed	Not clear
McCarter et al. 2012[22]		
Is the study based on a representative sample selected from a relevant population?	Data from two clinical trials; limited information available on representativeness of population	Not clear
Are the criteria for inclusion explicit?	Explicit inclusion and exclusion criteria are available on clinicaltrials.gov for the Z9000 clinical trial; criteria are less clear for the Z9001 clinical trial	Not clear
Did all individuals enter the survey at a similar point in their disease progression?	Both trials included patients who had resection of primary GIST; over 3/4 of patients had a performance status of 0	Yes
Was follow-up long enough for important events to occur?	Median follow-up was 49 months	Yes

Were outcomes assessed using objective criteria or was blinding used?	Risk factors assessed were objective but not clearly defined; recurrence criteria not clearly defined	Not clear
If sub-series compared, was there sufficient description of the series and distribution of prognostic factors?	Prognostic data for R0 and R1 resection groups not presented individually	Not clear
Nilsson et al. 2010[17]		
Is the study based on a representative sample selected from a relevant population?	Unclear based on abstract	Not clear
Are the criteria for inclusion explicit?	Criteria are not explicit in abstract	No
Did all individuals enter the survey at a similar point in their disease progression?	Unclear based on abstract	Not clear
Was follow-up long enough for important events to occur?	Actual follow-up unclear but 5-year outcomes were estimated	Yes
Were outcomes assessed using objective criteria or was blinding used?	PFS, RFS and OS were assessed	Yes
If sub-series compared, was there sufficient description of the series and distribution of prognostic factors?	Patient with R0-resection and adjuvant imatinib were compared with R2-resection with palliative imatinib and historic controls; very little information provided on prognostic factors between groups	Not clear
Gong et al., 2009[14]		
Is the study based on a representative sample selected from a relevant population?	Single-centre, non-randomised trial; unclear from abstract if representative of relevant population	Not clear
Are the criteria for inclusion explicit?	Criteria are not explicit in abstract	No
Did all individuals enter the survey at a similar point in their disease progression?	Unclear based on abstract	Not clear
Was follow-up long enough for important events to occur?	Median follow-up was 3 months	Yes
Were outcomes assessed using objective criteria or was blinding used?	Primary outcome (RFS) was objective	Yes
If sub-series compared, was there sufficient description of the series and distribution of prognostic factors?	Patients were assigned to imatinib treatment or no treatment; distribution of prognostic factors between the two groups unclear based on abstract	Not clear
Wu et al. 2012[24]		
Is the study based on a representative sample selected from a relevant population?	All patients who had undergone surgical treatment for GIST at a single centre in China were included; retrospective design; unclear if this is representative of the relevant population	Not clear

Are the criteria for inclusion explicit?	Criteria are not explicit	No
Did all individuals enter the survey at a similar point in their disease progression?	Unclear based on data provided	Not clear
Was follow-up long enough for important events to occur?	Median follow-up was 36.5 months	Yes
Were outcomes assessed using objective criteria or was blinding used?	Primary outcome (OS) was objective	Yes
If sub-series compared, was there sufficient description of the series and distribution of prognostic factors?	Patients were analysed based on tumour location and whether or not they had a complete resection; tumour stage compared between these patients	Yes
Jiang et al. 2011[15]		
Is the study based on a representative sample selected from a relevant population?	Study population was comprised of consecutive patients from a single centre in Japan, relatively small sample size (n = 90)	Not clear
Are the criteria for inclusion explicit?	Study included “90 consecutive patients with CD117 positive high-risk GISTs who had an R0 resection” at a single centre in Japan	Yes
Did all individuals enter the survey at a similar point in their disease progression?	All patients had undergone R0 resection and all patients were at a performance status of 0 or 1	Yes
Was follow-up long enough for important events to occur?	Median follow-up was 44.0 months	Yes
Were outcomes assessed using objective criteria or was blinding used?	Primary endpoint (RFS) was clearly defined and objective	Yes
If sub-series compared, was there sufficient description of the series and distribution of prognostic factors?	Patients were assessed based on imatinib treatment or no treatment; prognostic factors were shown for each group individually	Yes
Kanda et al. 2013[21]		
Is the study based on a representative sample selected from a relevant population?	Based on a patients from 17 hospitals in Japan; relatively small sample size (n = 64)	Not clear
Are the criteria for inclusion explicit?	Inclusion criteria are clearly stated	Yes
Did all individuals enter the survey at a similar point in their disease progression?	All patients had high-risk GIST; 87.5% of patients were at an ECOG performance status of 0	Yes
Was follow-up long enough for important events to occur?	Median follow-up was 109 weeks	Yes
Were outcomes assessed using objective criteria or was blinding used?	The primary endpoint (RFS) and secondary endpoint (OS) were well-defined and objective	Yes
If sub-series compared, was there sufficient description of	No sub-series was compared	NA

the series and distribution of prognostic factors?		
Kang et al. 2013[18]		
Is the study based on a representative sample selected from a relevant population?	Patients were enrolled from 4 centres in Korea; sample size relatively small (n = 47)	Not clear
Are the criteria for inclusion explicit?	Inclusion criteria are clearly stated	Yes
Did all individuals enter the survey at a similar point in their disease progression?	All patients underwent complete resection of a primary GIST and had an ECOG performance status of 2 or less (approximately half had a status of 0 and half had a status of 1)	Yes
Was follow-up long enough for important events to occur?	Median follow-up of 56.7 months	Yes
Were outcomes assessed using objective criteria or was blinding used?	The primary endpoint (RFS) and secondary endpoint (OS) were well-defined and objective	Yes
If sub-series compared, was there sufficient description of the series and distribution of prognostic factors?	No sub-series was compared	NA
Nishida et al. 2009[23]		
Is the study based on a representative sample selected from a relevant population?	Based on a patients from 17 hospitals in Japan; relatively small sample size (n = 64)	Not clear
Are the criteria for inclusion explicit?	Eligibility criteria are clearly defined	Yes
Did all individuals enter the survey at a similar point in their disease progression?	Unclear based on abstract	Not clear
Was follow-up long enough for important events to occur?	Median follow-up of 109 weeks	Yes
Were outcomes assessed using objective criteria or was blinding used?	Primary outcomes (RFS and OS) were objective	Yes
If sub-series compared, was there sufficient description of the series and distribution of prognostic factors?	No sub-series was compared	NA
Yalcin et al. 2012[25]		
Is the study based on a representative sample selected from a relevant population?	Phase 2 study conducted in several countries; no further information on representativeness of study population	Not clear
Are the criteria for inclusion explicit?	Inclusion criteria are clearly defined	Yes
Did all individuals enter the survey at a similar point in their disease progression?	All patients had resection of primary GIST within 70 days of enrollment; WHO PS ≤ 1	Yes

Was follow-up long enough for important events to occur?	Planned analysis at 1 year (full study was 2 years)	Yes
Were outcomes assessed using objective criteria or was blinding used?	Primary outcomes (RFS and OS) were objective	Yes
If sub-series compared, was there sufficient description of the series and distribution of prognostic factors?	No sub-series was compared	NA
CPT-4, Current Procedural Terminology, Version 4; ECOG, Eastern Cooperative Oncology Group; GIST, gastrointestinal stromal tumour; ICD-9, International Classification of Diseases, Ninth revision; OS, overall survival; PFS, progression-free survival; PS, performance status; RFS, recurrence-free survival; WHO, World Health Organization Hatoum et al. 2012;[20] Li et al. 2011;[16] Conley et al. 2012;[19] McCarter et al. 2012;[22] Nilsson et al. 2010;[17] Gong et al. 2009;[14] Jiang et al. 2011;[15] Wu et al. 2012;[24] Kanda et al. 2013;[21] Kang et al. 2013;[18] Nishida et al. 2009;[23] Yalcin et al. 2012.[25]		

10.8 Appendix 8: Search strategy for section 6.9 (Adverse events)

The following information should be provided.

10.8.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Specific searches for AE evidence were not conducted.

10.8.2 The date on which the search was conducted.

Not applicable

10.8.3 The date span of the search.

Not applicable

10.8.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Not applicable

10.8.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not applicable

10.8.6 The inclusion and exclusion criteria.

Not applicable

10.8.7 The data abstraction strategy.

Not applicable

10.9 Appendix 9: Quality assessment of adverse event data in section 6.9 (Adverse events)

10.9.1 Please tabulate the quality assessment of each of the non-RCTs identified.

No non-RCTs specifically assessing safety were identified

10.10 Appendix 10: Search strategy for cost-effectiveness studies (section 7.1)

The following information should be provided.

10.10.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

.

- MEDLINE and MEDLINE in Process: Ovid. 1946 to Present
- EMBASE: Ovid. 1974 to 2013 December 05
- Cochrane Library
    - Cochrane Database of Systematic Reviews (CDR): Wiley Interscience. 1996-present
    - Health Technology Assessment Database (HTA): Wiley Interscience. 1995-present
    - Database of Abstracts of Reviews of Effects (DARE)): Wiley Interscience. 1995-present
    - NHS Economic Evaluation Database (NHS EED): Wiley Interscience. 1995-present
- Science Citation Index: Web of Science. 1899-present
- Conference Proceedings Index: Web of Science. 1990-present
- EconLit: Ovid. 1961 to November 2013

10.10.2 The date on which the search was conducted.

The searches were conducted on the 13th and 18th December 2013

10.10.3 The date span of the search.

Searches were limited from 2009 onwards.

10.10.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Medline and Medline in Process: Ovid. 1946 to Present

1. Gastrointestinal Neoplasms/ 2. Gastrointestinal Stromal Tumors/ 3. gastrointestinal neoplasm$.tw. 4. gastrointestinal stromal tumor$.tw. 5. gastrointestinal stromal tumour$.tw. 6. gastrointestinal-stromal-tumor$.tw. 7. gastrointestinal-stromal-tumour$.tw. 8. gastro-intestinal tumor$.tw. 9. gastro-intestinal tumour$.tw. 10. GIST.tw. 11. cd117 positive tumor$.tw. 12. cd117 positive tumour$.tw. 13. gastrointestinal smooth muscle tumor$.tw. 14. gastrointestinal smooth muscle tumour$.tw. 15. gastrointestinal mesenchymal tumor$.tw. 16. gastrointestinal mesenchymal tumour$.tw.
17. Mesenchymoma/ 18. mesenchymal tumor$.tw. 19. mesenchymal tumour$.tw. 20. exp Leiomyoma/ 21. leiomyoma$.tw. 22. mesenchymoma$.tw. 23. Leiomyosarcoma/ 24. leiomyosarcoma$.tw. 25. leiomyoblastoma$.tw. 26. Leiomyoma, Epithelioid/ 27. Neurilemmoma/ 28. schwannoma$.tw.
29. or/1-16
30. exp Gastrointestinal Tract/ 31. or/17-28
32. 30 and 31
33. 29 or 32

34. Economics/
35. "costs and cost analysis"/
36. Cost allocation/
37. Cost-benefit analysis/
38. Cost control/
39. cost savings/
40. Cost of illness/
41. Cost sharing/
42. "deductibles and coinsurance"/
43. Health care costs/
44. Direct service costs/
45. Drug costs/
46. Employer health costs/
47. Hospital costs/
48. Health expenditures/
49. Capital expenditures/
50. Value of life/
51. exp economics, hospital/
52. exp economics, medical/
53. Economics, nursing/
54. Economics, pharmaceutical/
55. exp "fees and charges"/
56. exp budgets/
57. (low adj cost).mp.
58. (high adj cost).mp.
59. (health?care adj cost$).mp.
60. (fiscal or funding or financial or finance).tw.
61. (cost adj estimate$).mp.
62. (cost adj variable).mp.
63. (unit adj cost$).mp.
64. (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
65. or/34-64
66. Resource Allocation/
67. health care rationing/
68. (resource$ adj2 (allocat$ or utili$ or usage or use$)).tw.
69. or/65-68

70. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sfthirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti.
71. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti.
72. (sf6D or sf 6D or short form 6D or shortform 6D or sf sixD or sfsixD or shortform sixD or short form sixD).ti.
73. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti.
74. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti.
75. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti.
76. (euroqol or euro qol or eq5d or eq 5d or eq-5d).ti.
77. qol.ti.
78. (qaly$ or qald$ or qale$ or qtime$).ti.
79. quality adjusted life year/
80. quality adjusted life.ti.
81. (hye or hyes).ti.
82. health$ year$ equivalent$.ti.
83. health utilit$.ti.
84. (hui or hui1 or hui2 or hui3).ti.
85. quality of wellbeing.ti.
86. quality of well being.ti.
87. qwb.ti.
88. standard gamble$.ti.
89. time trade off.ti.
90. time tradeoff.ti.
91. tto.ti.
92. health state$ utilit$.ti.
93. utilit$.ti.
94. or/70-93
95. 33 and 65
96. limit 95 to yr="2009 -Current" (costs)
97. 33 and 94 (utility)
98. 33 and 69 (resource)
99. 98 not 96 (resource minus costs)

Embase 1974 to 2013 December 05

1. Gastrointestinal Tumor/
2. Gastrointestinal Stromal Tumor/
3. gastrointestinal neoplasm$.tw.
4. gastrointestinal stromal tumor$.tw.
5. gastrointestinal stromal tumour$.tw.
6. gastrointestinal-stromal-tumor$.tw.
7. gastrointestinal-stromal-tumour$.tw.
8. gastro-intestinal tumor$.tw.
9. gastro-intestinal tumour$.tw.
10. GIST.tw.
11. cd117 positive tumor$.tw.
12. cd117 positive tumour$.tw.
13. gastrointestinal smooth muscle tumor$.tw.
14. gastrointestinal smooth muscle tumour$.tw.
15. gastrointestinal mesenchymal tumour$.tw.
16. gastrointestinal mesenchymal tumor$.tw.

17. Mesenchymoma/
18. mesenchymal tumor$.tw.
19. mesenchymal tumour$.tw.
20. mesenchymoma$.tw.
21. Leiomyoma/
22. leiomyoma$.tw.
23. leiomyoma$.tw.
24. Leiomyosarcoma/
25. leiomyosarcoma$.tw.
26. leiomyoblastoma$.tw.
27. Leiomyoma/
28. Neurilemoma/
29. schwannoma$.tw.

30. or/1-16
31. gastrointestinal tract/
32. or/17-29
33. 31 and 32
34. 30 or 33
35. exp "costs and cost analysis"/
36. economics/
37. exp economics hospital/
38. exp economics medical/
39. exp economics nursing/
40. economics pharmaceutical/
41. exp "fees and charges"/
42. exp budgets/
43. budget$.tw.
44. cost$.ti.
45. (cost$ adj2 (effective$ or utilit$ or benefit$ or minim$)).ab.
46. (economic$ or pharmacoeconomic$ or pharmaco-economic$).ti.
47. (price or pricing$).tw.
48. (financial or finance or finances or finanaced).tw.
49. (fee or fees).tw.

50. or/35-49
51. resource allocation/
52. (resource$ adj2 (allocat$ or utili$ or usage or use$)).tw.
53. or/50-52

54. (value adj2 (money or monetary)).ti.
55. value of life/
56. quality adjusted life year/
57. quality adjusted life.ti.
58. (qaly$ or qald$ or qale$ or qtime$).ti.
59. disability adjusted life.ti.
60. daly$.ti.
61. health status indicators/
62. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti.
63. (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti.
64. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti.
65. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen).ti.
66. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti.
67. (euroqol or euro qol or eq5d or eq 5d).ti.
68. (hql or hqol or h qol or hrqol or hr qol).ti.
69. (hye or hyes).ti.
70. health$ year$ equivalent$.ti.
71. health utilit$.ti.
72. (hui or hui1 or hui2 or hui3).ti.
73. disutilit$.ti.
74. rosser.ti.
75. quality of wellbeing.ti.
76. qwb.ti.
77. willingness to pay.ti.
78. standard gamble$.ti.
79. time trade off.ti.
80. time tradeoff.ti.
81. tto.ti.
82. exp models economic/
83. *models theoretical/
84. *models organizational/
85. economic model$.ti.
86. markov chains/
87. markov$.ti.
88. monte carlo method/
89. monte carlo.tw.
90. exp decision theory/
91. (decision$ adj2 (tree$ or analy$ or model$)).ti.
92. utilit$.ti.
93. or/54-92
94. letter.pt.
95. editorial.pt.
96. comment.pt.
97. or/94-96
98. 93 not 97
99. 34 and 50
100. limit 95 to yr="2009 -Current" (costs)
101. 34 and 98 (utility)
102. 34 and 53 (resource)
103. 102 not 100 (resource minus costs)

Cochrane Database of Systematic Reviews (CDR): Wiley Interscience. 1996-present
Database of Abstracts of Reviews of Effects (DARE)): Wiley Interscience. 1995-present
Health Technology Assessment Database (HTA): Wiley Interscience. 1995-present
NHS Economic Evaluation Database (NHS EED): Wiley Interscience. 1995-present

#1	MeSH descriptor: [Gastrointestinal Neoplasms] this term only
#2	MeSH descriptor: [Gastrointestinal Stromal Tumors] explode all trees
#3	(gastrointestinal neoplasm*):ti,ab,kw or (gastrointestinal stromal tumor*):ti,ab,kw or (gastrointestinal stromal tumour*):ti,ab,kw or (gastrointestinal-stromal-tumor*):ti,ab,kw or (gastrointestinal-stromal-tumour*):ti,ab,kw
#4	(gastro-intestinal tumor*):ti,ab,kw or (gastro-intestinal tumour*):ti,ab,kw or (gist):ti,ab,kw or (cd117 positive tumor*):ti,ab,kw or (cd117 positive tumour*):ti,ab,kw
#5	(gastrointestinal smooth muscle tumor*):ti,ab,kw or (gastrointestinal smooth muscle
#6	tumour*):ti,ab,kw or (gastrointestinal mesenchymal tumor*):ti,ab,kw or (gastrointestinal
#7	mesenchymal tumour*):ti,ab,kw
	MeSH descriptor: [Mesenchymoma] explode all trees
#8	(mesenchymal tumor*):ti,ab,kw or (mesenchymal tumour*):ti,ab,kw or
#9	(leiomyoma*):ti,ab,kw or (mesenchymoma*):ti,ab,kw or (leimyoscarcoma*):ti,ab,kw
#10	MeSH descriptor: [Leiomyoma] this term only
#11	MeSH descriptor: [Leiomyosarcoma] explode all trees
#12	MeSH descriptor: [Leiomyoma, Epithelioid] explode all trees
#13	MeSH descriptor: [Neurilemmoma] explode all trees (leiomyoblastoma*):ti,ab,kw (schwannoma*):ti,ab,kw
#14	{or #1-#13} (resource)
#15	{or #1-#13} from 2009 to 2013 (costs)
#16	#14 not #15 (resource minus costs)
#17	(utilit*):ti,ab,kw
#18	(qol or qaly* or qald* or qale* or qtime*):ti,ab,kw
#19	MeSH descriptor: [Quality-Adjusted Life Years] explode all trees
#20	(quality adjusted life or hye or hyes or hui* or qwb):ti,ab,kw
#21	(health* year* equivalent*):ti,ab,kw
#22	(quality or wellbeing):ti,ab,kw
#23	(quality of well being):ti,ab,kw
#24	(standard gamble):ti,ab,kw
#25	(tto):ti,ab,kw or (time trade off):ti,ab,kw or (time tradeoff):ti,ab,kw
#26	(#17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25)
#27	(#14 and #26) (utility)

Science Citation Index: Web of Science. 1899-present
Conference Proceedings Index: Web of Science. 1990-present

1. TS= (gastrointestinal neoplasm* OR gastrointestinal stromal tumor* OR gastrointestinal stromal tumour* OR gastrointestinal-stromal-tumor* OR gastrointestinal-stromal-tumour$* OR gastro-intestinal tumor* OR gastro-intestinal tumour* OR GIST OR cd117 positive tumor* OR cd117 positive tumour* OR gastrointestinal smooth muscle tumor* OR gastrointestinal smooth muscle tumour* OR gastrointestinal mesenchymal tumor* OR gastrointestinal mesenchymal tumour*)
2.TS= (mesenchymoma* OR mesenchymal tumor* OR mesenchymal tumour* OR leiomyoma* OR mesenchymoma* OR leiomyosarcoma* OR leiomyoblastoma* OR neurilemmoma* OR schwannoma*)
3. TS= gastrointestinal
4. #2 AND #3
5. #1 OR #4

6. TS= (economics OR cost* OR expenditure* OR value of life OR fee* OR charge* OR budget* OR fiscal or funding or financial or finance OR economic* or pharmacoeconomic* or price* or pricing)
7. TS= (euroqol or euro qol or eq5d or eq 5d or eq-5d OR qol OR qaly* or qald* or qale* or qtime* OR quality adjusted life year* OR quality adjusted life OR hye or hyes OR health* year* equivalent* OR hui or hui1 or hui2 or hui3 OR quality of wellbeing* OR quality of well being OR qwb OR standard gamble OR time trade off OR time tradeoff OR tto OR utilit*)
8. TS= ((resource* NEAR/2 (allocat* or utili* or usage or use*)))
9. #5 AND #6 Timespan=2009-2013 (costs)
10. #5 AND #7 (utility)
11. #7 OR #8
12. #5 AND #11 (resource)
13. #12 NOT #9 (resource minus costs)

EconLit: Ovid. 1886 to November 2013
18th December 2013

1. gastrointestinal neoplasm$.tw.
2. gastrointestinal stromal tumor$.tw.
3. gastrointestinal stromal tumour$.tw.
4. gastrointestinal-stromal-tumor$.tw.
5. gastrointestinal-stromal-tumour$.tw.
6. gastro-intestinal tumor$.tw.
7. gastro-intestinal tumour$.tw.
8. GIST.tw.
9. cd117 positive tumor$.tw.
10. cd117 positive tumour$.tw.
11. gastrointestinal smooth muscle tumor$.tw.
12. gastrointestinal smooth muscle tumour$.tw.
13. gastrointestinal mesenchymal tumor$.tw.
14. gastrointestinal mesenchymal tumour$.tw.
15. mesenchymal tumor$.tw.
16. mesenchymal tumour$.tw.
17. leiomyoma$.tw.
18. mesenchymoma$.tw.
19. leiomyosarcoma$.tw.
20. leiomyoblastoma$.tw.
21. schwannoma$.tw.
22. or/1-21
23. limit 22 to yr="2009 -Current" (costs)
24. 22 not 23 (resource minus costs)

25. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sfthirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti. 26. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti. 27. (sf6D or sf 6D or short form 6D or shortform 6D or sf sixD or sfsixD or shortform sixD or short form sixD).ti. 28. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti. 29. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti. 30. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti. 31. (euroqol or euro qol or eq5d or eq 5d or eq-5d).ti. 32. qol.ti. 33. (qaly$ or qald$ or qale$ or qtime$).ti. 34. quality adjusted life.ti. 35. (hye or hyes).ti. 36. health$ year$ equivalent$.ti. 37. health utilit$.ti. 38. (hui or hui1 or hui2 or hui3).ti. 39. quality of wellbeing.ti. 40. quality of well being.ti. 41. qwb.ti. 42. standard gamble$.ti. 43. time trade off.ti. 44. time tradeoff.ti. 45. tto.ti. 46. health state$ utilit$.ti. 47. utilit$.ti.
48. or/25-47
49. 22 and 48 (utility)

10.10.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

None

10.11 Appendix 11: Quality assessment of cost-effectiveness studies (section 7.1)

This is provided in section 7.1.3

10.12 Appendix 12: Search strategy for section 7.4 (Measurement and valuation of health effects)

The following information should be provided.

10.12.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS Economic Evaluation Database (NHS EED)
- EconLIT

- MEDLINE and MEDLINE in Process: Ovid. 1946 to Present
- EMBASE: Ovid. 1974 to 2013 December 05
- Cochrane Library
    - Cochrane Database of Systematic Reviews (CDR): Wiley Interscience. 1996-present
    - Health Technology Assessment Database (HTA): Wiley Interscience. 1995-present
    - Database of Abstracts of Reviews of Effects (DARE)): Wiley Interscience. 1995-present
    - NHS Economic Evaluation Database (NHS EED): Wiley Interscience. 1995-present
- Science Citation Index: Web of Science. 1899-present
- Conference Proceedings Index: Web of Science. 1990-present
- EconLit: Ovid. 1961 to November 2013

10.12.2 The date on which the search was conducted.

The searches were conducted on the 13th and 18th December 2013

10.12.3 The date span of the search.

None

10.12.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example,

MeSH) and the relationship between the search terms (for example, Boolean).

See section 10.10.4

10.12.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

None

10.12.6 The inclusion and exclusion criteria.

Inclusion/exclusion criteria are described in Table C-7. Inclusion criteria were kept broad. However, economic evaluation reporting health utility values reported elsewhere were excluded, but we checked that the original reference was included in the review.

Table C-7 Eligibility criteria used for abstract screening and study selection

Selection Criteria	Inclusion	Exclusion
Population	Adult patients (>18 years) with a Gastrointestinal Stromal Tumour	–
Intervention	Any	–
Comparators	Any	–
Outcomes	Preference based-measure, SF-36, SF-12, EQ-5D, EQ-5D-5L, EURQOL, time trade off, standard gamble, utilities..	Absence of uitility weight
Study Type	Any	–
Language	English Only	–

10.12.7 The data abstraction strategy.

Titles and abstracts were screened by one reviewer in accordance with pre-defined inclusion/exclusion criteria in Table C-7.

10.13 Appendix 13: Resource identification, measurement and valuation (section 7.5)

The following information should be provided.

10.13.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

- MEDLINE and MEDLINE in Process: Ovid. 1946 to Present
- EMBASE: Ovid. 1974 to 2013 December 05
- Cochrane Library
  - Cochrane Database of Systematic Reviews (CDR): Wiley Interscience. 1996-present
  - Health Technology Assessment Database (HTA): Wiley Interscience. 1995-present
  - Database of Abstracts of Reviews of Effects (DARE)): Wiley Interscience. 1995-present
  - NHS Economic Evaluation Database (NHS EED): Wiley Interscience. 1995-present
- Science Citation Index: Web of Science. 1899-present
- Conference Proceedings Index: Web of Science. 1990-present
- EconLit: Ovid. 1961 to November 2013

10.13.2 The date on which the search was conducted.

The searches were conducted on the 13th and 18th December 2013

10.13.3 The date span of the search.

None

10.13.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See section 10.10.4

10.13.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

None

10.13.6 The inclusion and exclusion criteria.

The inclusion/ exclusion criteria are reported below in Table C-8. The inclusion criteria were again kept broad to allow any potentially relevant studies to be included. Studies were excluded if the resource use information was in a format that could not be used in a cost-effectiveness analysis. Studies were not excluded on the basis of location as it was not expected that a study using a primary data source in the UK would be found.

Table C-8 Eligibility criteria used for abstract screening and study selection

Selection Criteria	Inclusion	Exclusion
Population	Adult patients (>18 years) with a Gastrointestinal Stromal Tumour	–
Intervention	Any	–
Comparators	Any	–
Outcomes	Resource counts, unit costs	–
Study Type	Any	–
Language	English Only	–
Other	–	Non-UK resource use Previous NICE submissions

10.13.7 The data abstraction strategy.

Titles, abstracts and full texts were screened by one reviewer in accordance with the pre-defined inclusion/exclusion criteria in Table C-8.

Table C-9 Inclusion and exclusion criteria

11 Related procedures for evidence submission

11.1 Cost-effectiveness models

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission.

There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

11.2 Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential

information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and information submitted under 'academic in confidence' in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of 'academic in confidence' information. The 'stripped' version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE's website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the 'stripped' version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been

put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, NICE will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.