NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Regorafenib for treating advanced gastrointestinal stromal tumours [ID1056]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Regorafenib for treating advanced gastrointestinal stromal tumours [ID1056]

Final Scope and Final Matrix

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3. **Clarification letters**
   - NICE request to the company for clarification on their submission
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4. **Patient group, professional group and NHS organisation submission** from:
   - GIST Support UK
   - Sarcoma UK

5. **Expert statements** from:
   - Charlotte Benson, Consultant Medical Oncologist – clinical expert, nominated by GIST Support UK
   - Venkata Ramesh Bulusu, Consultant Clinical Oncologist – clinical expert, nominated by GIST Support UK
   - Vicky Rockingham – patient expert, nominated by GIST Support UK
   - Emma Tennant – patient expert, nominated by GIST Support UK

6. **Evidence Review Group report** prepared by Peninsula Technology Assessment Group (PenTAG)
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13. **Updated analyses including new PAS price,** provided by Bayer

14. **Evidence Review Group addendum 2,** prepared by Peninsula Technology Assessment Group (PenTAG)

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Pre-meeting briefing

Regorafenib for previously treated unresectable or metastatic gastrointestinal stromal tumours [ID1056]

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

1

Key issues: clinical effectiveness

- GRID trial compared regorafenib with best supportive care
  - Does committee agree that BSC is the most appropriate comparator?
- In GRID 58% of people were from Europe, regorafenib was allowed after disease progression in both arms and only people with performance status 0-1 were included
  - Does committee agree that GRID is generalisable to clinical practice?
- Company and ERG agree that given high cross over from placebo to regorafenib, analyses for overall survival need to be adjusted
  - Does committee agree that cross over adjusted OS is appropriate?
- GRID results show improvements in PFS and OS after cross over correction
  - Does committee agree that regorafenib is clinically effective compared with BSC?

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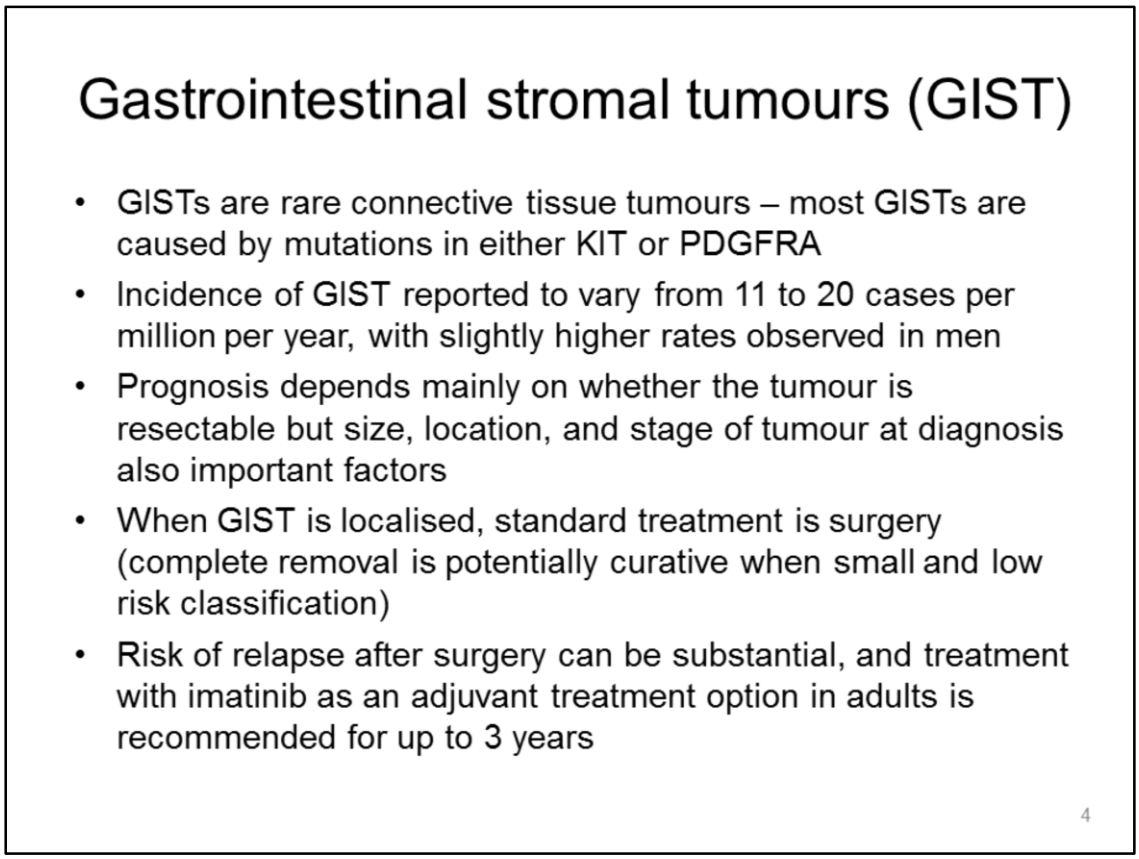
Key issues: cost-effectiveness

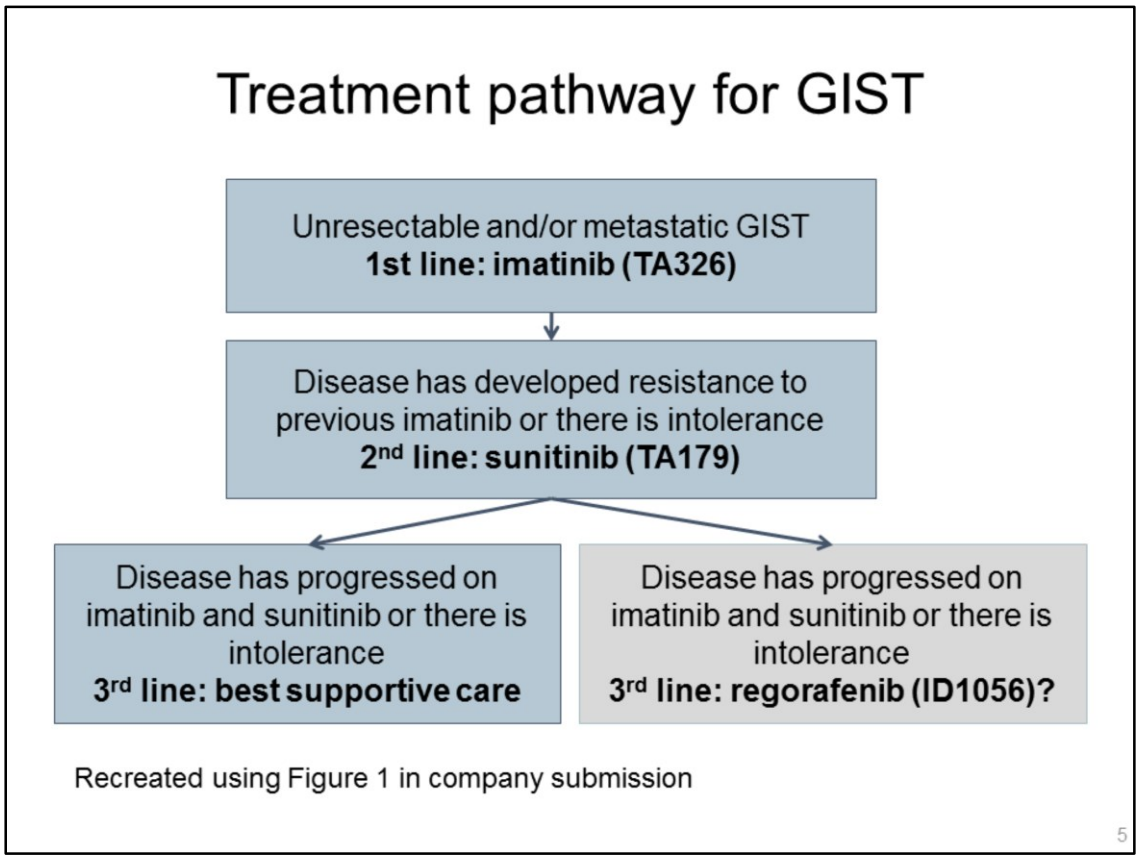
- Company and ERG agree treatment duration should be modelled in line with GRID and include cost of regorafenib post progression (regorafenib arm only)
  - Does committee agree with this approach?
- Company prefer to use 2017 data for OS while ERG use 2015 data (not able to validate 2017 data and some inconsistencies)
  - What is the committee's preferred data cut for overall survival?
- Choice of distribution for OS extrapolation has large impact on cost effectiveness results and ERG also suggest including additional general background mortality
  - Does committee agree with average of log logistic and Weibull models?
  - Does committee agree with adding general background mortality?
- ERG add age related utility decrements as utility often declines with age
  - Does committee agree with this approach?
- Does regorafenib meet the end of life criteria?

3

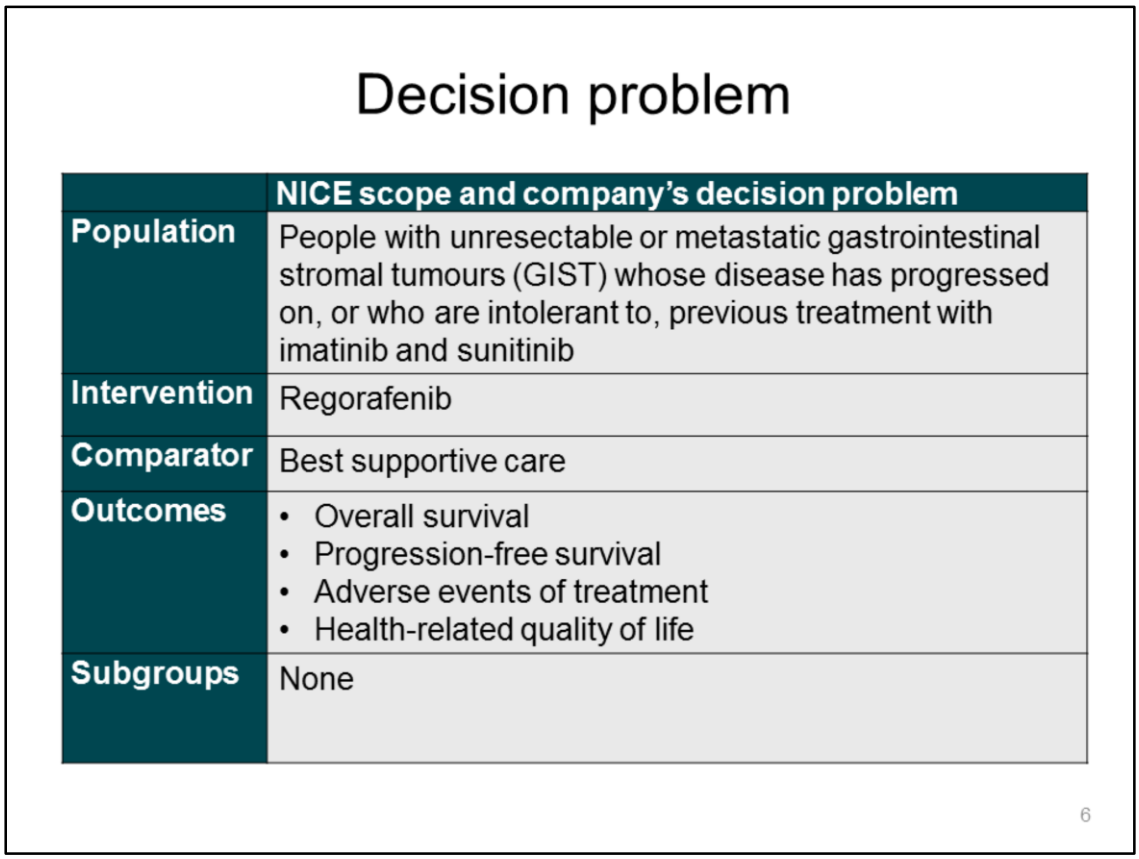


See section 3.1 of company submission

A less frequent mutation also exists, known as PDGFRA (platelet-derived growth factor receptor A), which causes the cell to overproduce a different protein (also called PDGFRA), but which has the same effect as KIT.



See section 3.3 (figure 1 on page 40) of company submission



See section 1.1 (table 1 on page 16) of company submission

Regorafenib

UK Marketing authorisation	Treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib.
Mode of administration	Administered as an oral therapy.
Mechanism of action	Inhibits angiogenic kinase receptors, such as the vascular endothelial growth factor and the TIE2 receptor, which play a role in angiogenesis.
Dosage	The recommended dose of regorafenib is 160 mg (4 tablets of 40 mg) taken once daily for 3 weeks followed by 1 week off therapy. This 4-week period is considered a treatment cycle. Treatment should continue as long as benefit is observed or until unacceptable toxicity occurs.
Cost	• £3,744 per 28 day cycle (pack of 84 tablets at 40mg), list price (BNF, edition 72) • Approved patient access scheme (simple discount)
Eligible population	Company estimates 60 people in England may be eligible for further TKI treatment

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Company anticipates that regorafenib will be an option for this population of approximately 60 new patients per year (by 2021). The ERG considers this an appropriate figure, given approximately half of new cases of GIST are likely to be metastatic and/or unresectable on first presentation and will initially be treated with imatinib/sunitinib

The SPC for regorafenib states “Patients with performance status (PS) 2 or higher were excluded from clinical studies. There is limited data in patients with PS ≥2”

Cancer Drugs Fund (CDF)

- Regorafenib is currently available on the CDF for treatment of adults with advanced GIST after failure of at least previous imatinib and sunitinib where the following criteria are met:
  - Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
  - Histologically confirmed, metastatic or unresectable GIST
  - PS 0-1
  - Disease progression on or intolerance to previous imatinib
  - Disease progression on previous sunitinib

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Impact on patients and carers

Received submissions from 2 patient and 1 clinical expert and 2 organisations (GIST support UK and Sarcoma UK):

- People with GIST often present with anaemia and non-specific symptoms: nausea, indigestion, pain, black stools, difficulty swallowing, and fatigue
- 40% have advanced disease at diagnosis
- Lack of education as rare disease – worrying and unsettling
- Psychological impact of prognosis and physical symptoms impacts quality of life
- No 3rd line treatment options
- Life expectancy of patients without the option of regorafenib is less than a year

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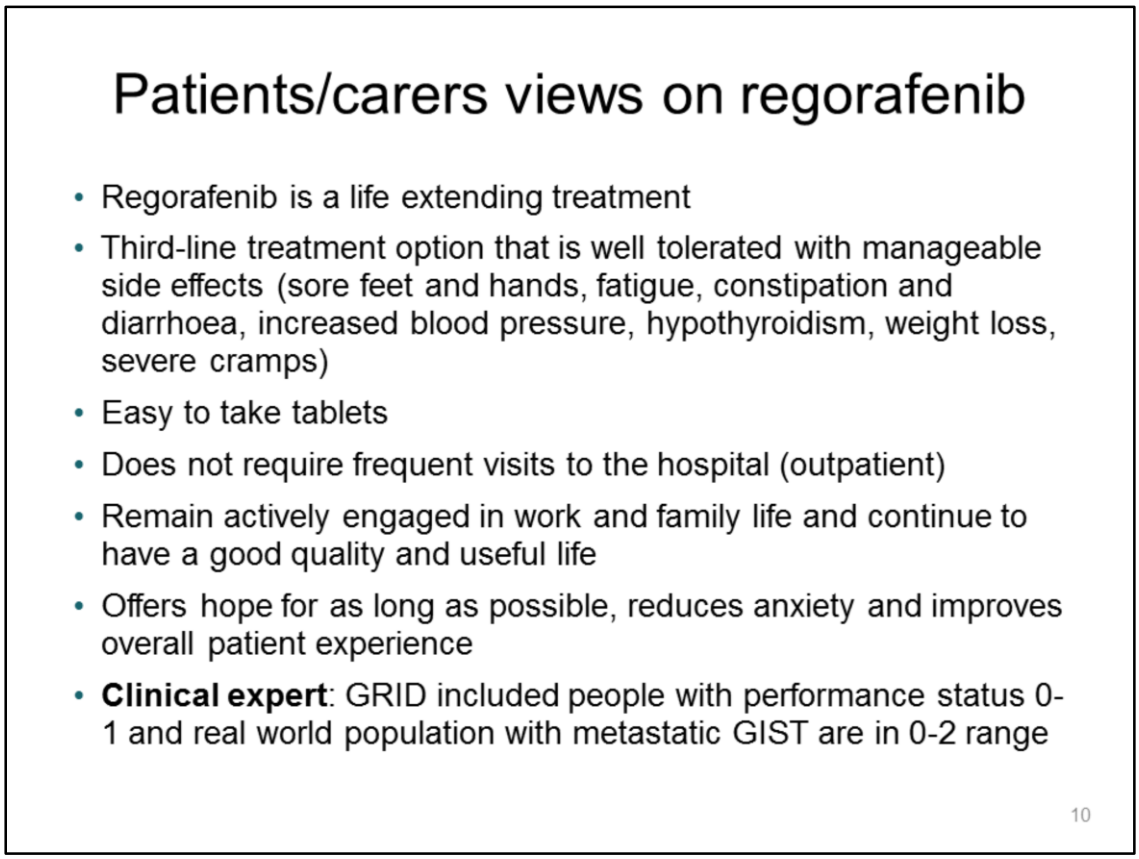

Clinical expert submission: There is a UK experience of managed access program for regorafenib which confirmed treatment is well tolerated and side effects manageable in majority of patients (Kollar et al 2014) although some patients (55% in case series) did need dose reduction

GRID trial

Parameter	Description
Trial details	Double-blind, placebo-controlled trial with 2 arms: Regorafenib 160mg + BSC (N=133) vs. placebo + BSC (N=66)
Inclusion criteria	Histologically confirmed metastatic and/or unresectable GIST, with failure of at least: (1) prior imatinib (due to either disease progression or intolerance) and (2) prior sunitinib (due solely to progression to reduce heterogeneity). ECOG performance status 0-1.
Exclusion	Prior treatment with any VEGFR inhibitor except sunitinib, use of any approved tyrosine kinase inhibitors in past 1 week
Location	57 study centres in 17 countries including UK
Outcomes	**Primary**: Progression free survival (PFS) **Secondary**: Overall survival (OS), time to progression (TTP), disease control rate (DCR), tumour response rate (RR), duration of response (DOR), and safety. Exploratory: HrQoL, pharmacokinetics, secondary PFS during open label treatment, and biomarker analysis
Pre-specified subgroups	Based on geographic region, prior line of treatment, age, sex, baseline BMI, duration of imatinib treatment, ECOG performance status, and mutational status

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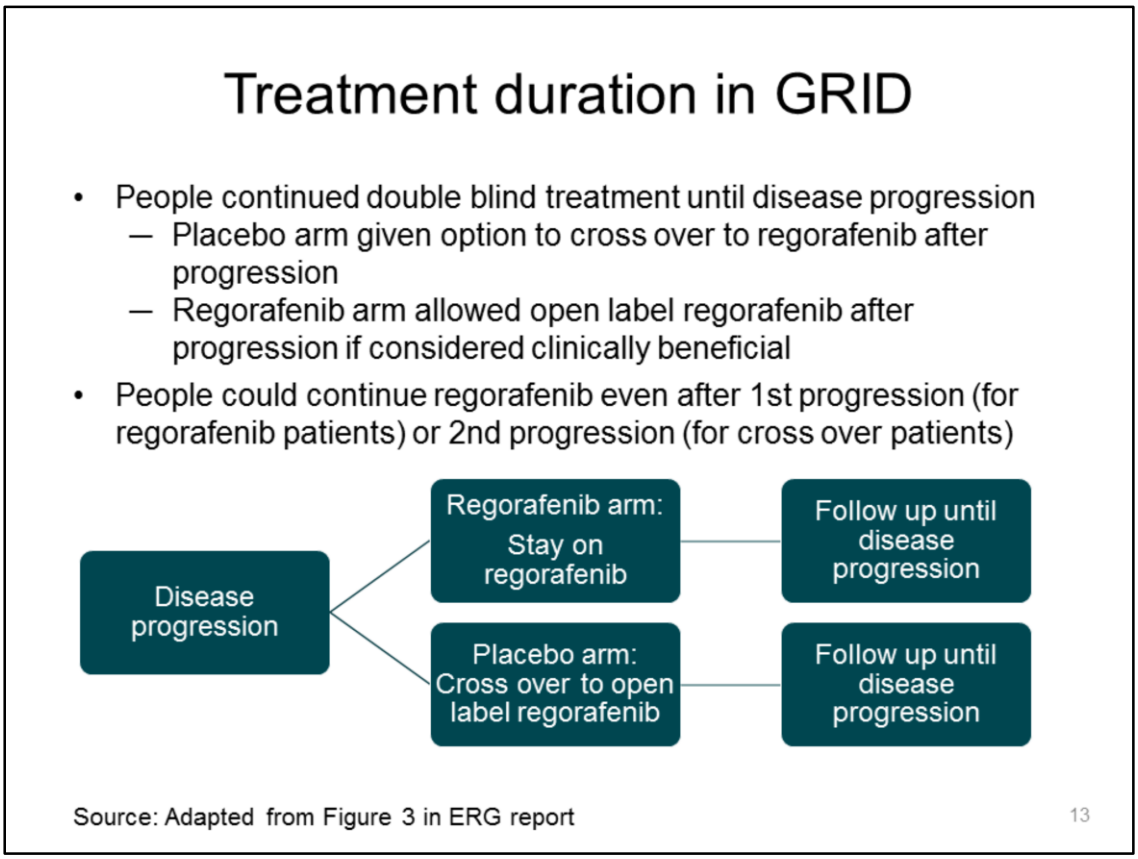
Table 16 company submission and table 7 ERG report

See section 4.3 (table 16 from page 72) of company submission and table 7 (page 41) of ERG report

At randomisation, patients were stratified by treatment line (3rd vs. 4th line therapy or beyond) and geographical region (Asia vs. rest of the world). Patients continued masked study treatment until disease progression, unacceptable toxicity or withdrawal of patient from the study. Upon progression, patients receiving placebo were offered open-label regorafenib (cross-over option).
Inclusion criterion for prior sunitinib due solely to progression was used to decrease heterogeneity, as definition of intolerance is more variable with this agent

See section 4.3 (page 61) of company submission for details on best supportive care

All medication necessary for the patient's welfare, and not expected to interfere with the evaluation of the study drug, could be given at the discretion of the principal investigator. These included standard therapies for concurrent medical conditions, prophylactic anti-emetics, bisphosphonates and treatment with non-conventional therapies (e.g. herbs or acupuncture) and vitamin/mineral supplements.



See section 4.2.1.2 (page 40 and figure 3 on page 38) of ERG report for details on treatment duration

Baseline characteristics in GRID

Baseline characteristic	Regorafenib + BSC (n=133)	Placebo + BSC (n=66)
Median Age	60 (51-67)	61 (48-66)
Male	85 (64%)	42 (64%)
Time since initial diagnosis to randomisation in weeks (mean, range)	296.4 (32.3 to 774)	310.6 (47.0 to 657)
Time since recent progression / relapse to randomisation in weeks (mean, range)	13.29 (0.7 to 145)	16.7 (0.4 to 421)
Metastatic disease at baseline	90 (67.7%)	38 (57.6%)
Unresectable disease at baseline	5 (3.8%)	10 (15.2%)
Metastatic & unresectable disease at baseline	35 (26.3%)	14 (21.2%)
2 lines of previous systemic anti-cancer therapy	74 (56%)	39 (59%)
≤ 6 months previous imatinib therapy	18 (14%)	4 (6%)
6–18 months previous imatinib therapy	26 (20%)	7 (11%)
> 18 months previous imatinib therapy	89 (67%)	55 (83%)

Source: Table 20 in company submission

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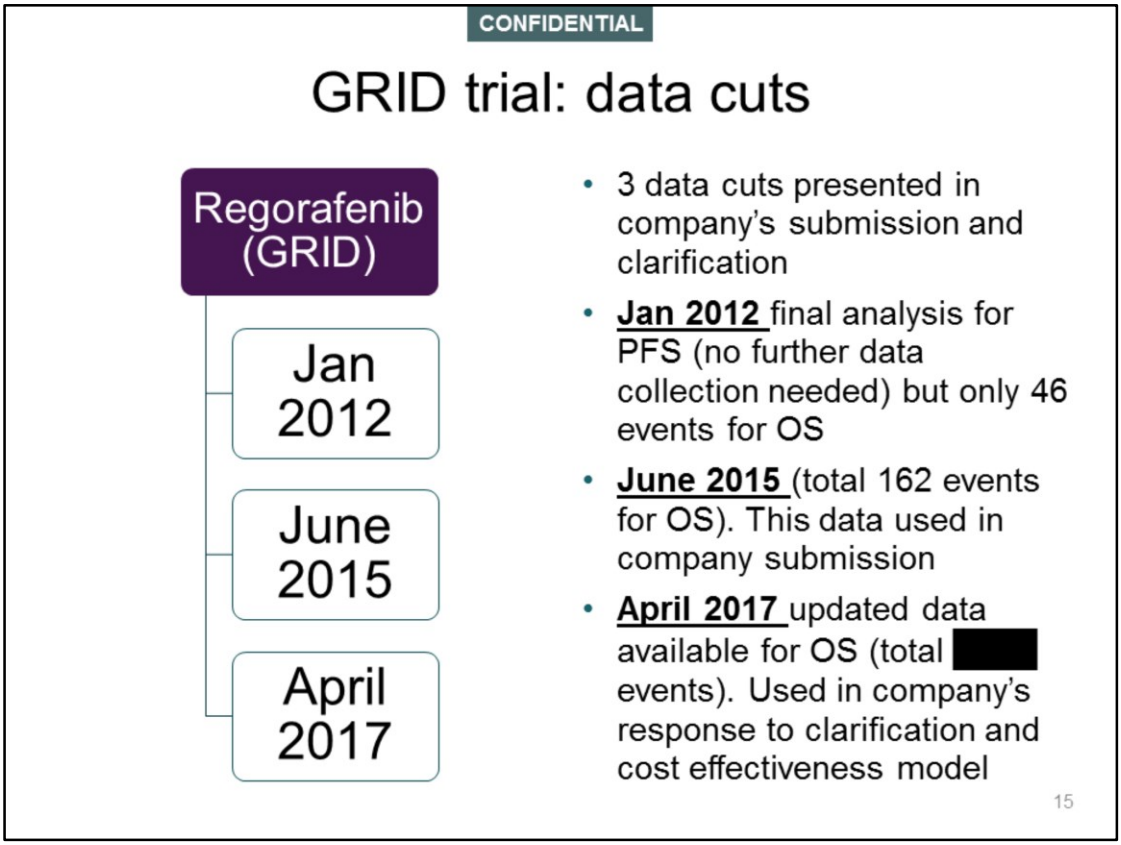
See table 20 (page 86) of company submission for details on baseline characteristics

Demographics and baseline disease characteristics were comparable between the regorafenib and the placebo groups. All people in the placebo group (n=66) and 132 (99.2%) in the regorafenib group had prior surgical treatment for cancer. Most had been treated with imatinib for ≥18 months. However, a higher proportion of those in the placebo group had received imatinib therapy for more than 18 months than in the regorafenib group.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GRID trial: data cuts
Regorafenib (GRID)
Jan 2012
June 2015
April 2017
3 data cuts presented in company's submission and clarification
Jan 2012 final analysis for PFS (no further data collection needed) but only 46 events for OS
June 2015 (total 162 events for OS). This data used in company submission
April 2017 updated data available for OS (total [redacted] events). Used in company's response to clarification and cost effectiveness model
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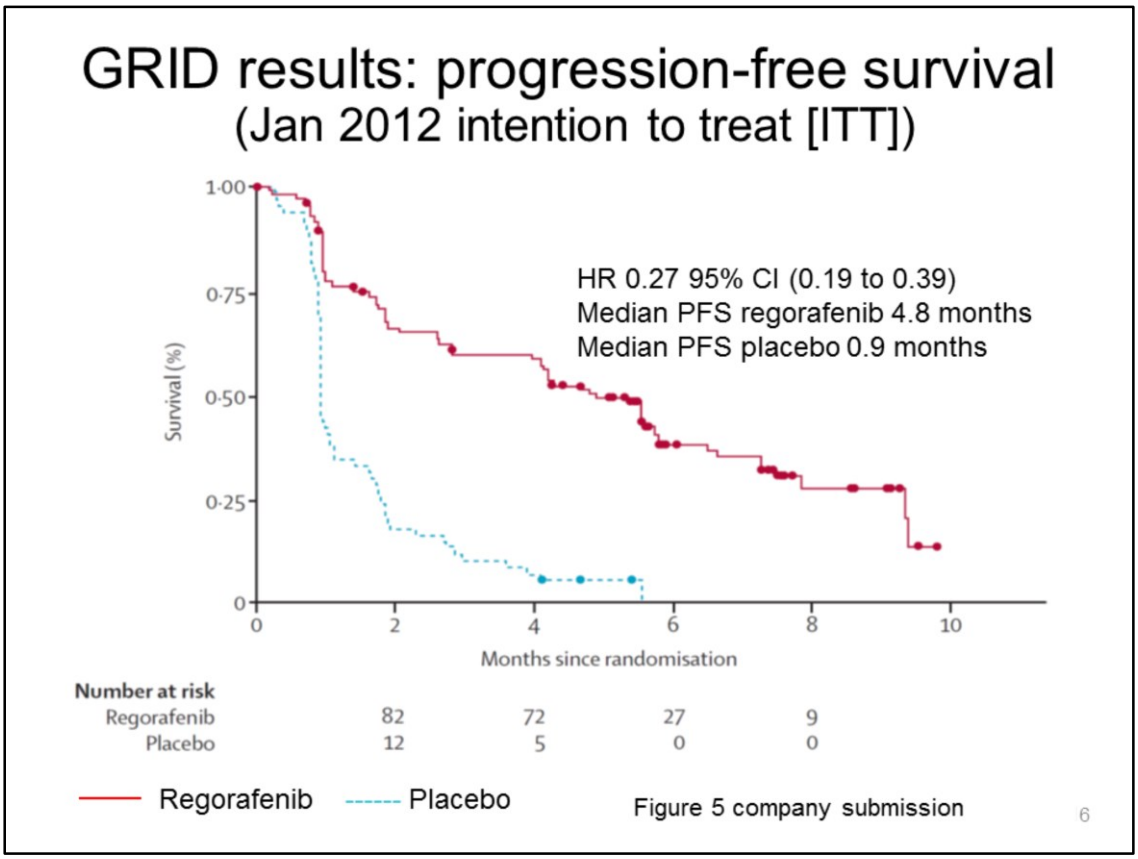
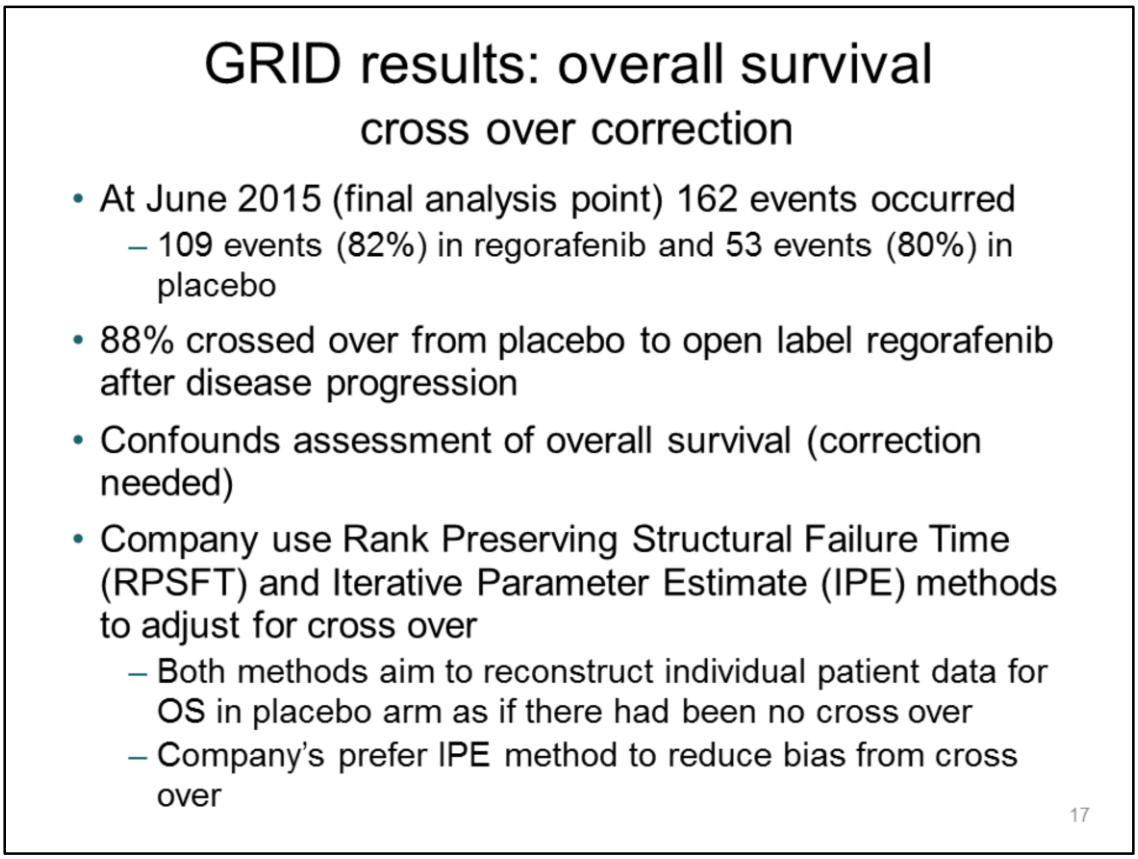


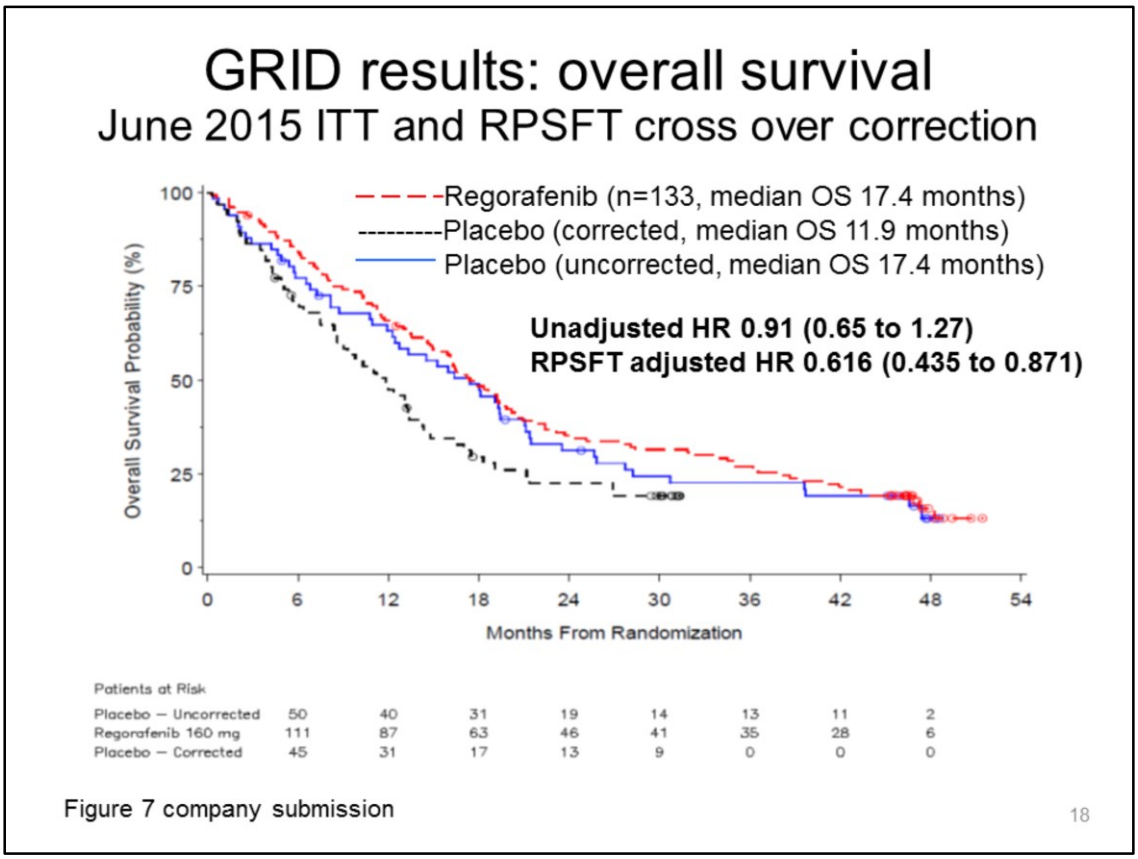
See figure 5 (page 95) of company submission for PFS analysis

The results of the sensitivity analyses were supportive of and consistent with the primary analysis of PFS, showing statistically significant improvement in the regorafenib group compared with the placebo group. Using the investigator's assessment, a significant improvement in median PFS of 7.4 months (interquartile range IQR 2.7–not calculable) in the regorafenib group compared to 1.7 months (0.9–2.7) in the placebo group (Hazard ratio [HR] 0.22, 95% CI 0.14–0.35; p<0.0001) was observed.

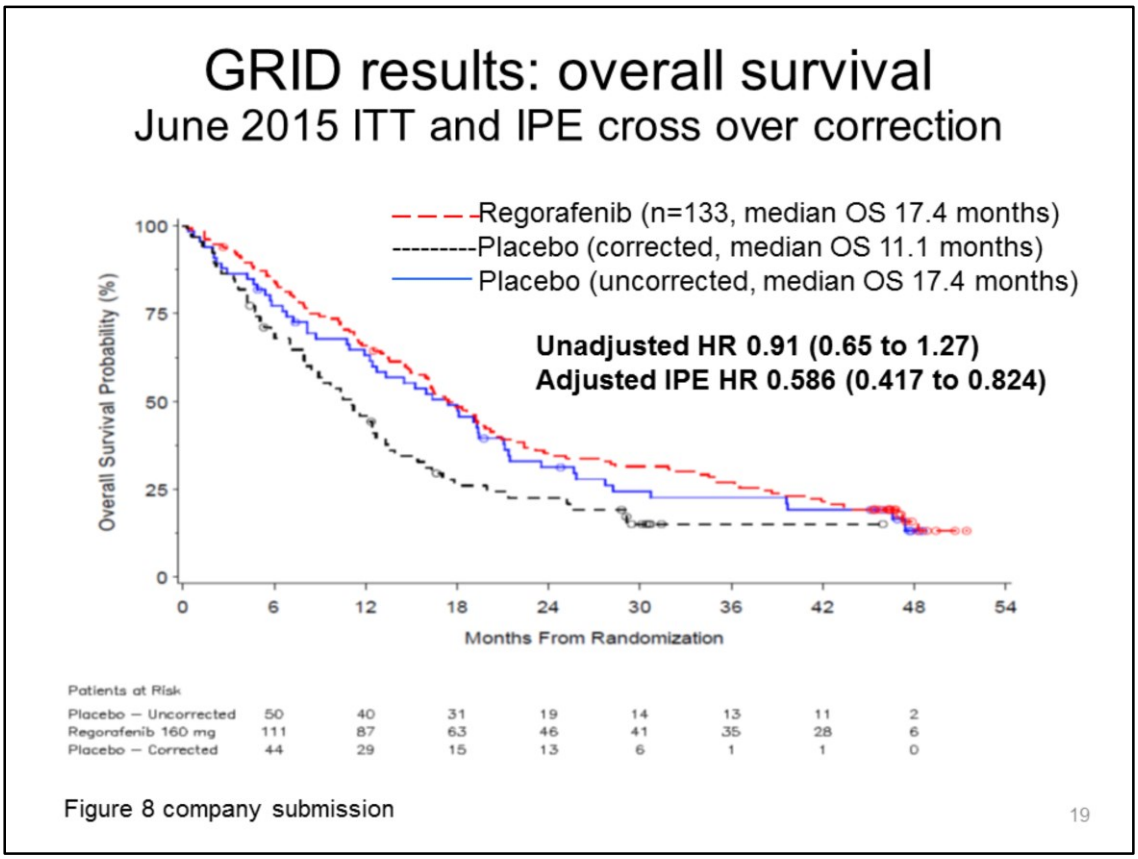


See section 4.4.3 (page 80, Statistical analysis – secondary, tertiary and other endpoints) of company submission and section 5.3.6.2 (page 79) of ERG report for details of cross over corrections

All medication necessary for the patient's welfare, and not expected to interfere with the evaluation of the study drug, could be given at the discretion of the principal investigator. These included standard therapies for concurrent medical conditions, prophylactic anti-emetics, bisphosphonates and treatment with non-conventional therapies (e.g. herbs or acupuncture) and vitamin/mineral supplements.



See figure 7 (page 96) and table 22 (page 92) of company submission for OS analysis using RPSFT correction for cross over



See figure 8 (page 97) and table 22 (page 92) of company submission for OS analysis using IPE correction for cross over

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GRID results: New 2017 data

- Company present updated 2017 data in response to clarification
- Company: adjusted OS outcomes slightly reduce for placebo (greater follow up time allows for longer potential censoring date)

Outcome	2015	2017*
PFS	HR 0.27 (0.19 to 0.39)	HR 0.27 (0.19 to 0.39)
Median OS; months†	Regorafenib: 17.4 months Placebo unadjusted: 17.4 IPE adjusted: 11.1 RPSFT adjusted: 11.9	Regorafenib: [redacted] Placebo unadjusted: [redacted] IPE adjusted: [redacted] RPSFT adjusted: [redacted]
OS unadjusted	HR 0.91 (0.65 to 1.27)	[redacted]
OS IPE adjusted	HR 0.59 (0.42 to 0.82)	[redacted]
OS RPSFT adjusted	HR 0.62 (0.44 to 0.87)	[redacted]

All analyses include stratification by prior anti cancer drug group and region. *Hazard ratios from 2017 data may include recensoring.
†Reported as days in Table 22 of company submission (2017 data from CSR)

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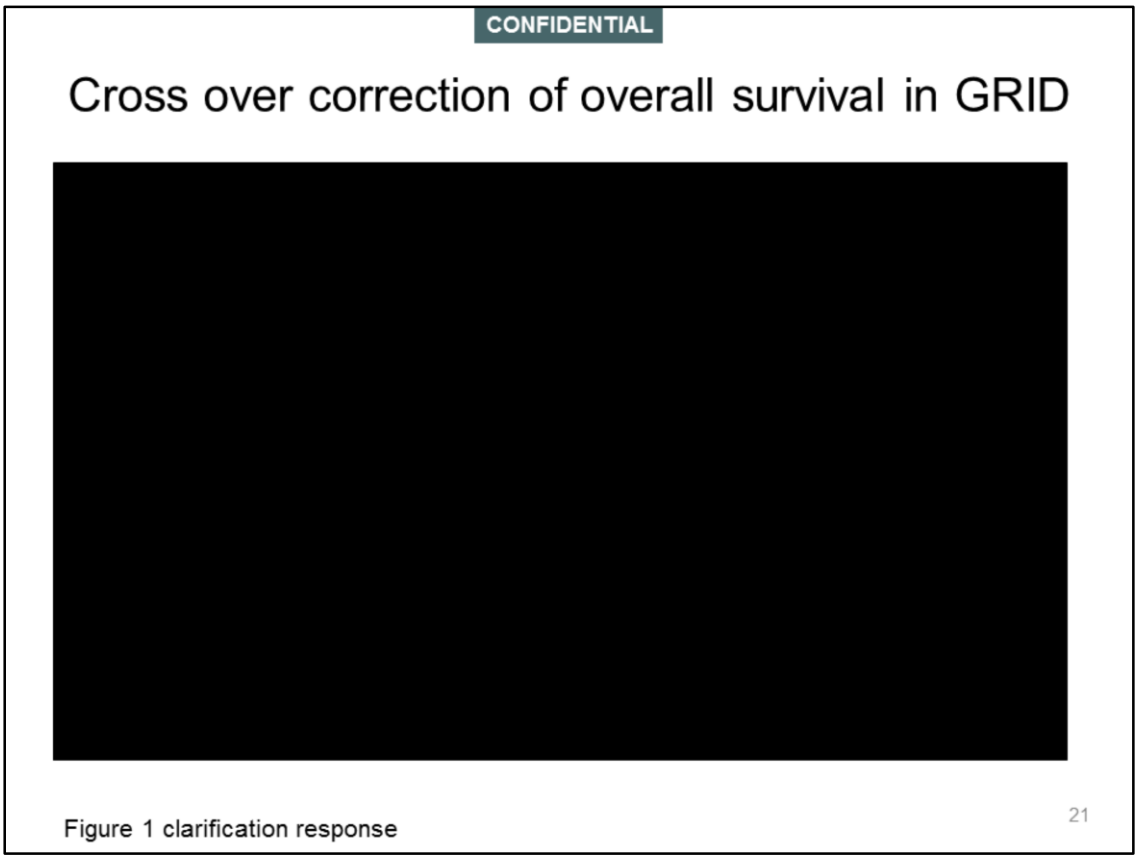
See table 34 in company's response to clarification for details of 2017 data



See figure 1 of company response to clarification

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GRID results: other outcomes

Jan 2012 data cut off

	Regorafenib + BSC (n=133)	Placebo + BSC (n=66)	Regorafenib vs. placebo (95% CI)
Time to progression (median)	165 days (5.4 months)	28 days (0.9 months)	HR 0.248 (0.170 to 0.364)
Complete response	0	0	N/A
Overall response	4.5%	1.5%	MD -2.99% (-7.70 to 1.72%)
Median duration of response	99 days (n=6)	30 days (n=1)	
Reduction in tumour size	[redacted]	[redacted]	Not reported
Secondary PFS (open-label period)	137 days (4.5 months, n=41)	151 days (5 months, n=56)	Not reported
EQ-5D (mean change from baseline to cycle 4)	-0.045 (n=84)	-0.040 (n=16)	Not reported
Abbreviations: MD, mean difference; HR, hazard ratio;			

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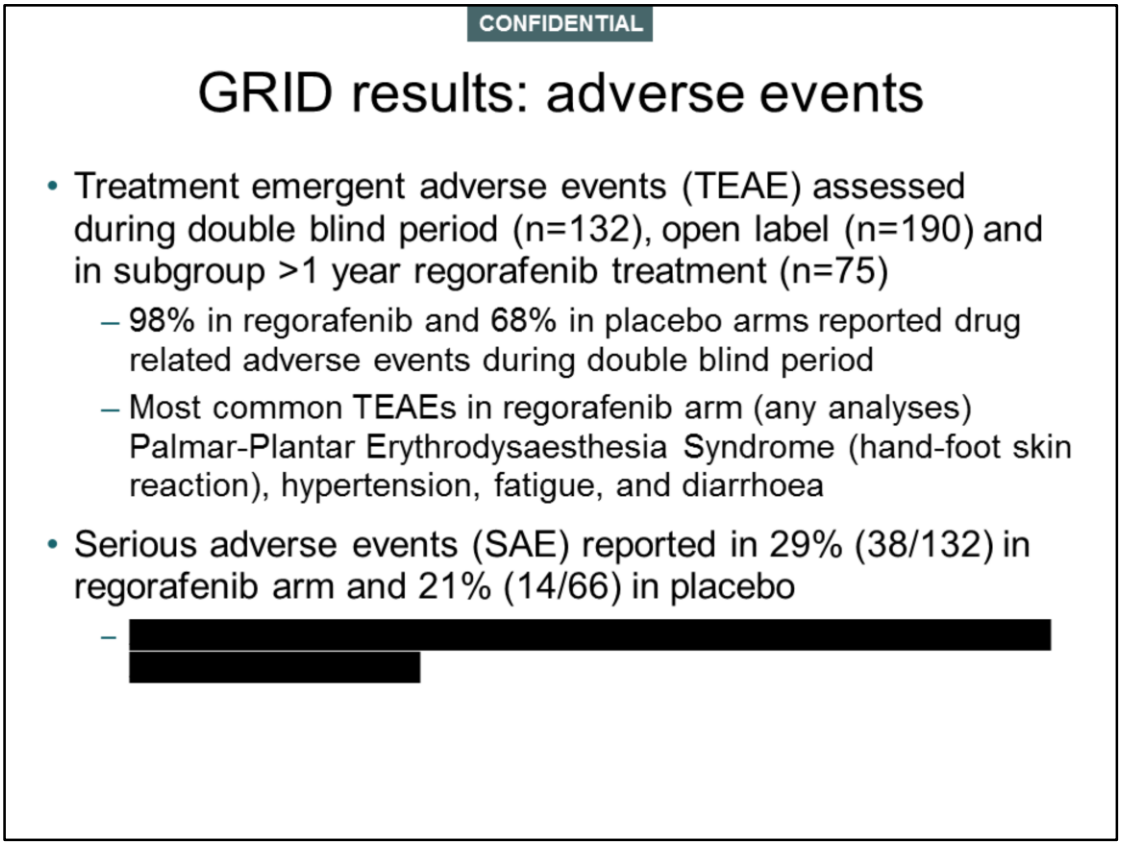
See section 4.7 (pages 92 to 102) of company submission for details of other outcomes



See section 4.12 of company submission for more details on adverse events

Other issues

- Significant benefit in regorafenib group for PFS in all pre-specified subgroups except those with duration of imatinib treatment of less than 6 months (n=22 patients)
- Company state no indirect comparison possible (no recognised or recommended standard treatment post imatinib and sunitinib)

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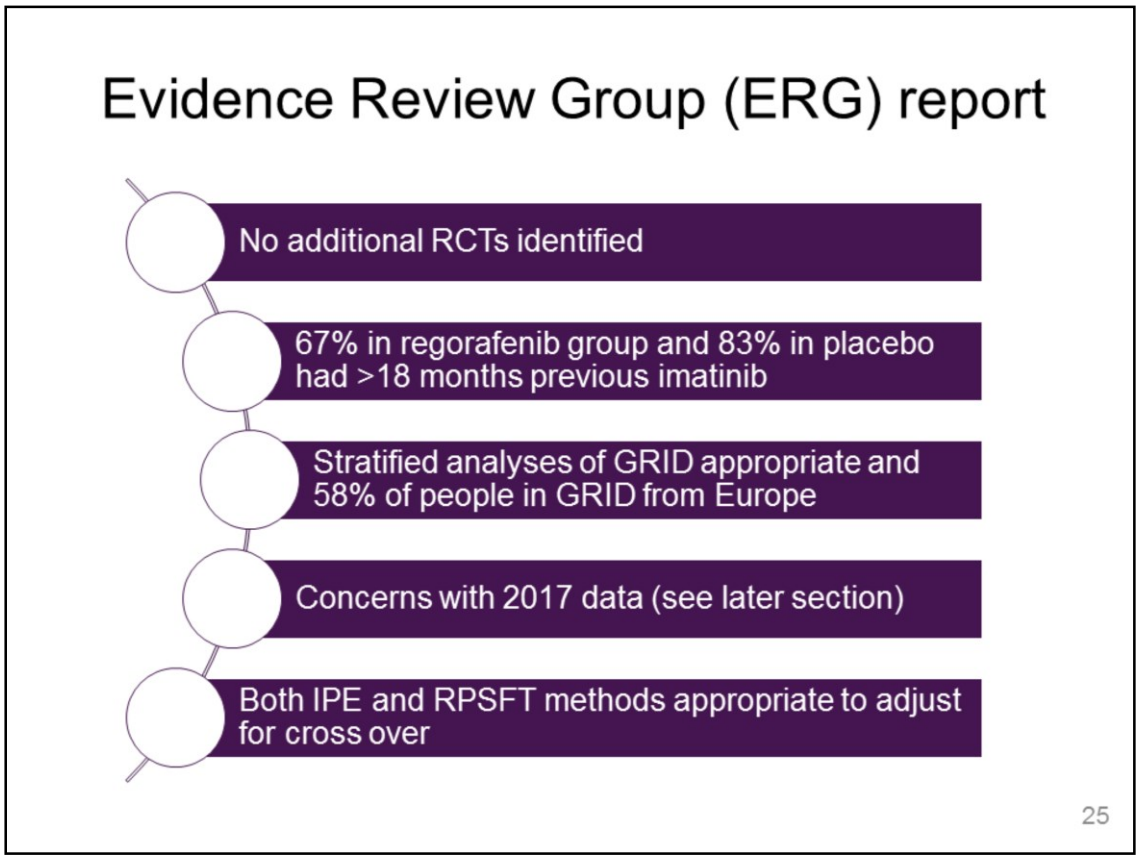
See section 4.8 (pages 102 to 108) of company submission for details on subgroup analyses and section 4.10 for details on indirect comparison



See section 1.2 (page 11) and 1.3 (page 13) of the ERG report for summary of clinical effectiveness evidence submitted by company and ERG's critique of this evidence

Key issues: clinical effectiveness

- GRID trial compared regorafenib with best supportive care
  - Does committee agree that BSC is the most appropriate comparator?
- In GRID 58% of people were from Europe, regorafenib was allowed after disease progression in both arms and only people with performance status 0-1 were included
  - Does committee agree that GRID is generalisable to clinical practice?
- Company and ERG agree that given high cross over from placebo to regorafenib, analyses for overall survival need to be adjusted
  - Does committee agree that cross over adjusted OS is appropriate?
- GRID results show improvements in PFS and OS after cross over correction
  - Does committee agree that regorafenib is clinically effective compared with BSC?

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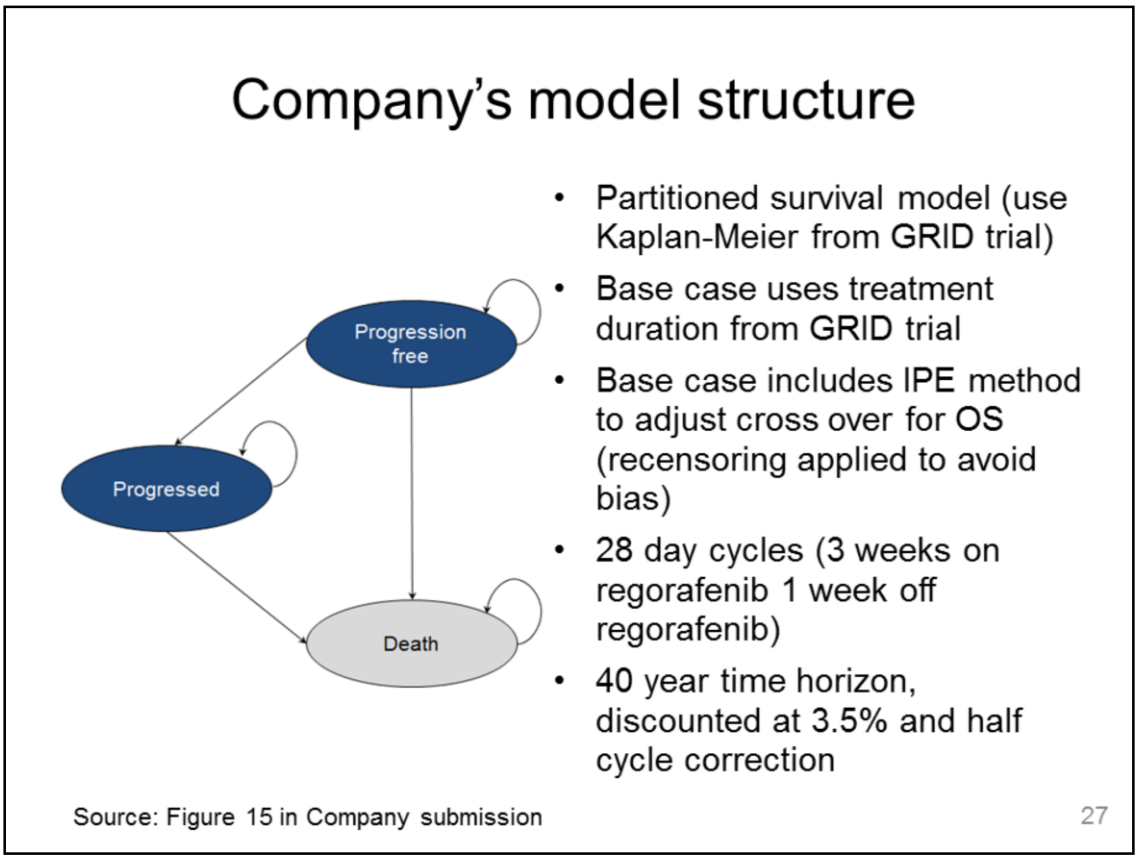
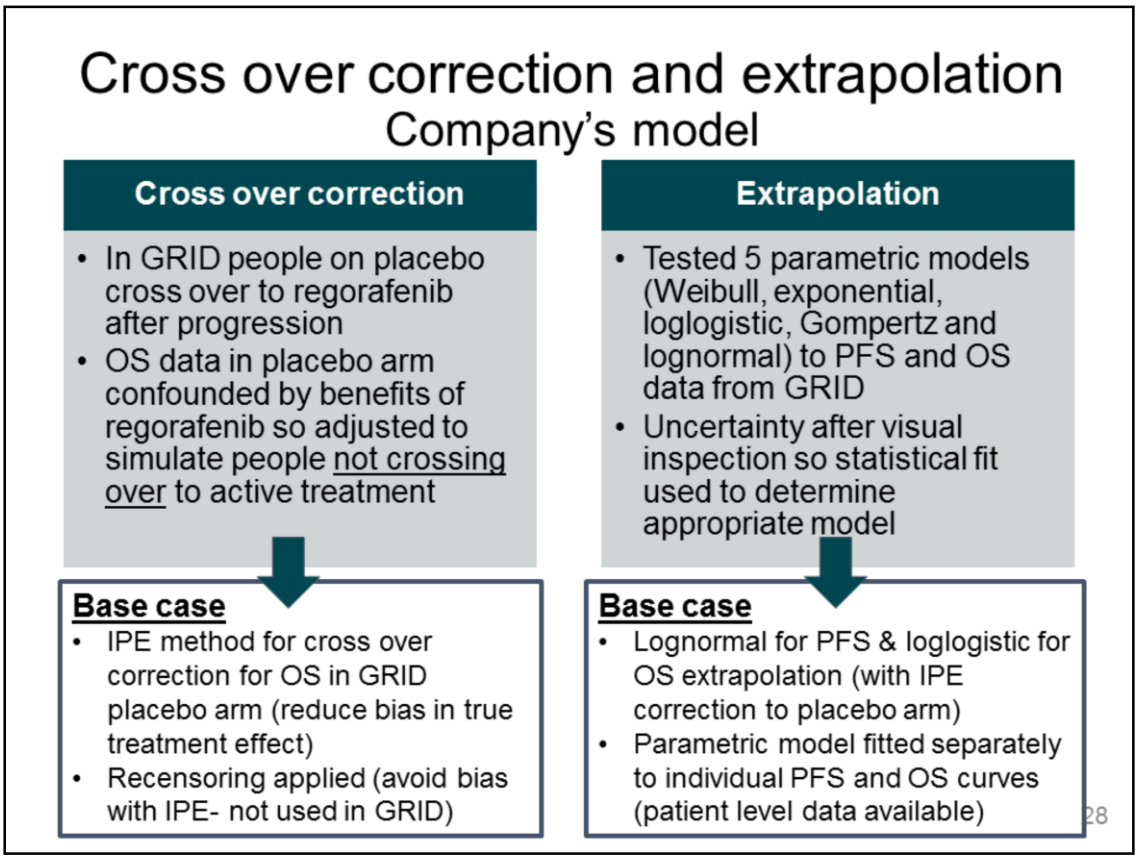
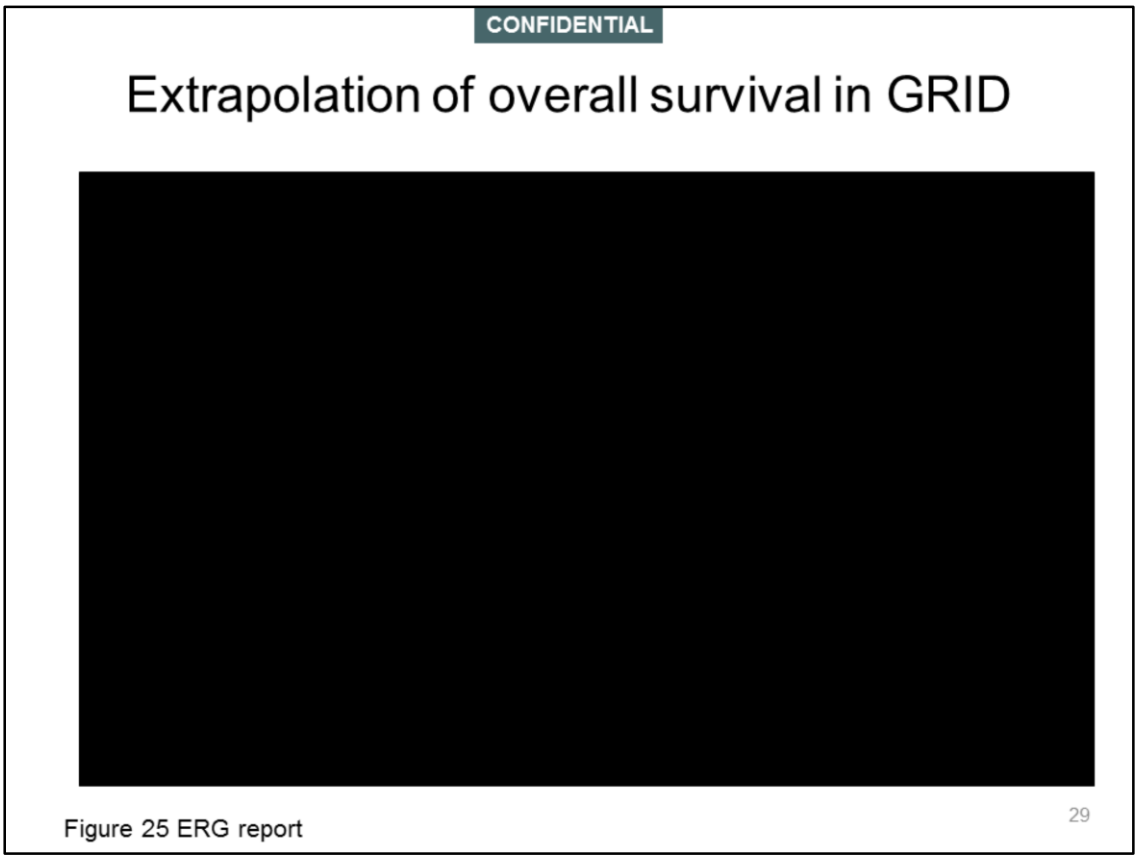


See section 5.2.2 (pages 150 to 151) of company submission for model structure

A partitioned survival model is used to determine the proportion of the cohort of people in the 3 health states at different points in time. This model type is the most suitable since it can use Kaplan-Meier survival curves from the GRID trial directly. For people receiving placebo experiencing disease progression, active treatment with regorafenib was offered (crossover option). However, this treatment continuation rule based on the investigator's opinion is not standard practice in England and Wales. This is further confirmed by the results from the 2013 physician survey, validated by two consultant oncologists in 2016, in which the average proportion of patients experiencing progression who would continue TKI treatment post-progression resulted being about 25.3%.



See section 5.3.2 (page 155 to 164) of company submission for details of cross over correction and extrapolation



See figure 25 (page 87) of ERG report

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Extrapolation of overall survival in GRID

Figure 26 ERG report

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See figure 26 (page 88) of ERG report

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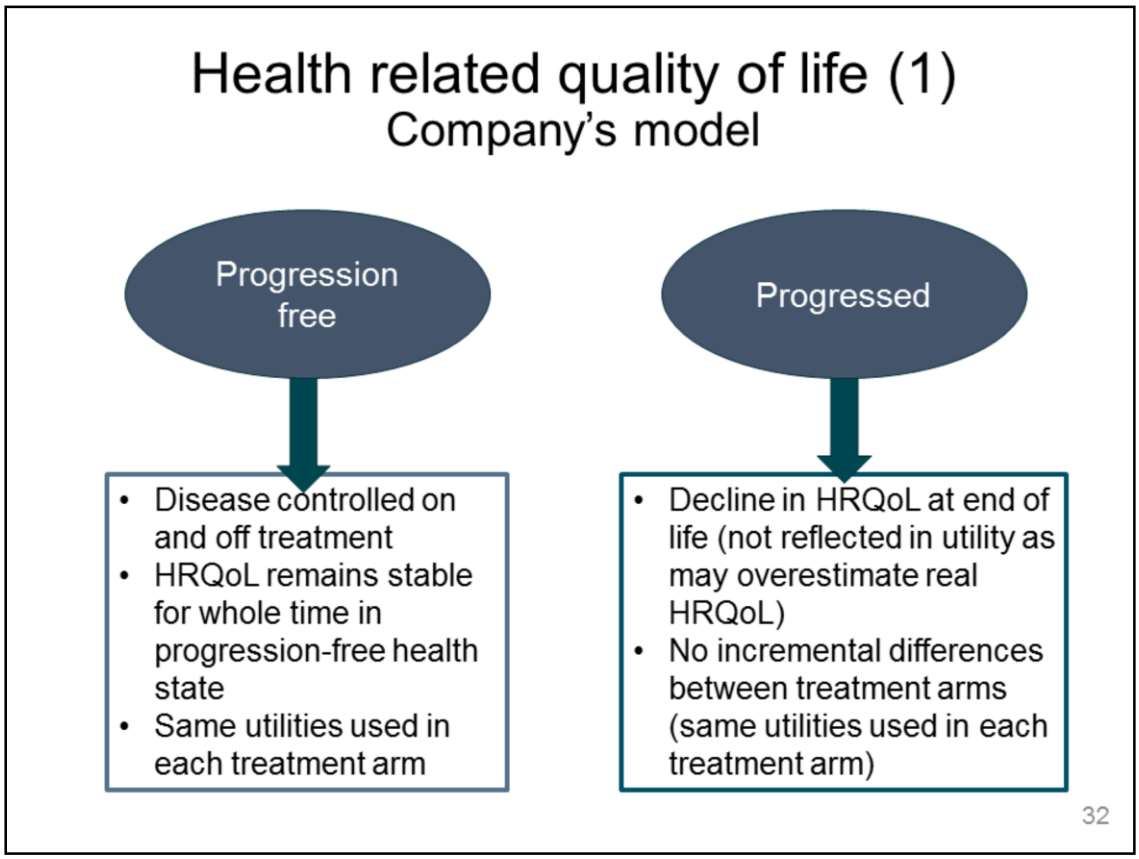
Clinical data used in base case

Outcome (base case)	Regorafenib vs. placebo
PFS (2015 data)	HR 0.27 (0.19 to 0.39)
PFS extrapolation	Lognormal
OS (IPE and 2017 data)*	[redacted]
OS extrapolation	Loglogistic
Time to treatment discontinuation (TTD)	Cost of regorafenib based on discontinuation curve and mean observed dose from GRID (no extrapolation as only 2% on treatment at end of follow up)
Abbreviations: HR, Hazard ratio; OS, overall survival; PFS, progression free survival *Hazard ratios from 2017 data may include recensoring	



See section 5.4.1 (page 168 to 171) and 5.4.7 (page 179) of company submission for details of Health-related quality-of-life data used in cost-effectiveness analysis

Health related quality of life (2)
Company's model

- GRID measured EQ-5D and European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC: scenario)
- Company carry out paired samples comparison (overall and by treatment)
- Sensitivity analysis with repeated measures (company: biased as more measurements for people in progression free state, no homogenous progressed population for estimating utility)
- **Base case uses EQ-5D data from paired samples (not split by treatment arm as no statistically significant difference between treatment arms)**

Health state	Mean utility (95% confidence interval)	
	paired samples	repeated measures
Progression-free (n=77)	**0.767 (0.718 to 0.816)***	0.743 (0.712 to 0.775)
Placebo progression-free (n=12)	0.583 (not reported)	0.750 (0.698 to 0.802)†
Regorafenib progression-free (n=27)	0.702 (not reported)	0.741 (0.706 to 0.777)†
Progressed (n=49)	**0.647 (0.571 to 0.723)***	0.703 (0.657 to 0.748)

*Values in bold used in base case. †assumed to include treatment effect and adverse events. Source: tables 36 to 39 in company submission

See table 44 (page 181) and section 5.4.1 (page 168 to 171) of company submission for utilities used in cost-effectiveness analysis

Utility values used in the cost-effectiveness analysis for people in the progression-free health state were based on baseline observations. A lower utility value for the progressed health state was adopted in the base case analysis consistently with the results from the paired-sample comparison which showed a statistically significant mean difference of -0.120 ($p = 0.001$) between baseline- and first post-progression utility.

As a consequence of the crossover period, the repeated measure analysis would contain the utility observations that occurred in the initial diagnosis of progressed disease, but also the utility observations during the active treatment phase with regorafenib. The EQ-5D paired-samples comparison data was used in the base case, without splitting by treatment, as it provided a more robust utility estimate for both the progressed and non-progressed subjects compared to the repeated measures analysis.

Similarly to the EQ-5D data, paired-samples comparison and repeated measured analysis were applied to the EORTC QLQ-C30 data in order to determine an alternative set of utility data.

Adverse events in company's model

- Most common adverse events (hand-foot skin reaction, diarrhoea and fatigue) easily manageable and negligible effect on HRQoL
- EQ-5D analyses using repeated measures (progression free split by treatment arm) assumed to represent treatment effects and adverse events. Utility in regorafenib (0.741) lower than placebo (0.750)

- **Base case:** adverse events not included (EQ-5D from paired samples)
- **Scenario with repeated measures:** lower utility values in regorafenib arm (progression free state) assumed to include adverse events

	Estimated incidence rate per cycle %		Cost per cycle (95% CI)
Adverse event	**Placebo**	**Regorafenib**	**Each treatment arm**
Hypertension	1.35	5.16	£11.86 (£9.48 to £14.23)
Hand-foot skin reaction	0	4.25	£0
Diarrhoea	0	1.07	£7.02 (£5.62 to £8.43)

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Source: Table 35 and 53 in Company submission

See section 5.3.2 (page 165) of company submission for details of adverse event rates and section 5.5.7 (page 190) for details on costs of adverse events

Treatment duration and dose intensity

- Company's new base case uses treatment duration from GRID
  - No extrapolation of discontinuation curve (only 2% on treatment at end of follow up)
  - Treatment costs independent of progression (based on discontinuation curve and mean observed dose from GRID)
  - Mean observed dose (excluding dose 0 mg) by cycle applied to calculate treatment costs per cycle

	GRID
First 3 weeks in cycle	Oral regorafenib 160 mg (4 x 40mg once daily)
4th week	No regorafenib
Dose modifications	Can be delayed or reduced according to pre-specified schedule* Allowed 2 dose reductions (160 mg to 120 mg to 80 mg) due to toxicity. Dose re-escalation allowed if resolved to <grade 3
* For (unacceptable side effects, hand-foot skin reaction, hypertension)	

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Source: Table 35 and 53 in Company submission

Company's treatment costs

- Cost of regorafenib based on discontinuation curve and mean observed dose from GRID
- No extrapolation of discontinuation curve (only 2% on treatment at end of follow up)
- Company have submitted PAS (confidential discount)

Drug	Unit cost	Drug cost per 28 day cycle	Source
Regorafenib 160 mg per day (without PAS)	£44.57/40mg tablet	£3,744.00	Bayer UK
Mean Regorafenib dose (dose as in GRID, without PAS)	£44.57/40mg tablet	£3,271.09	Bayer UK for price, Demetri, et al., 2013 (8) for mean dose

Source: Table 45 in Company submission

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See table 45 (page 182) of company submission for drug costs

Company's resource use and cost (1)

- Physician survey (2013) of 15 GIST medical oncologists (14 England and 1 Wales). Findings validated in 2016 by 2 consultant oncologists
- Physicians in 2013 randomly selected based on:
  - number of adults with metastatic/unresectable GIST personally and directly managed by each physician in past 6 months
  - number of people managed by physicians who have progressed on, are intolerant to, or otherwise unsuitable for imatinib, sunitinib or both
  - country in which the physician was based
  - profession or specialisation of the physician and her/his grade
- No specific clinical parameters assessed in 2016 except for long-term overall survival predictions

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See section 5.3.4 (page 166) of company submission for details on physicians survey

CONFIDENTIAL

Company's resource use and cost (2)

	Resource use	Progression free on TKI (£)	Progression free on BSC (£)	Progressed (£)
One time costs	Tests	55.72 (5.53)	13.82 (2.93)	N/A
	Palliative resection	Not included	Not included	[redacted] (129.38)
	Palliative radiotherapy	Not included	Not included	[redacted] (10.11)
	Total one-time costs	**55.72 (5.53)**	**13.82 (2.93)**	[redacted] **(129.77)**
Regular per cycle costs	Regular tests*	45.45 (5.46)	14.81 (4.08)	8.35 (36.00)
	Regular outpatient monitoring visits	60.49 (9.16)	46.91 (4.73)	53.68 (8.15)
	Pain management†	18.27 (2.97)	18.35 (2.97)	26.95 (3.77)
	Total per cycle costs	**124.21 (11.07)**	**80.07 (6.92)**	**88.98 (37.11)**

All values mean (standard error). Abbreviations: TKI, BSC; best supportive care
* Regular tests include: CT scan, MRI scan, full blood count and liver function test.
†Pain management includes: co-codamol, tramadol, paracetamol, morphine sulphate, dexamethasone

Source: Table 54 in Company submission

See section 5.5.1 (page 181 to 186) of company submission for resource use

All standard errors associated with cost and resource use inputs have been calculated assuming independence of variables. Although independence is unlikely, the result is a larger standard error, hence a wider confidence interval for costs and therefore overall more conservative.

See section 5.5.8 (table 53) of company submission for other costs

Summary of company's model

	Regorafenib	Best supportive care (BSC)
Health state	• All people start progression free (in line with trial) • No cost of active treatment if discontinue treatment prior to progression (progression free utility and routine costs) • OS curve determines transition to death (from progressed)	
Clinical data	2017 data used for OS	
Cross over adjustment	N/A	IPE method used to adjust BSC arm (high cross over to open label regorafenib) with recensoring
Extrapolation	PFS: lognormal OS: Log-logistic curve	PFS: lognormal OS: Log-logistic curve plus IPE correction
Discontinuation	Apply time to discontinuation of regorafenib data directly (treatment costs independent of progression)	
Utilities	Same utilities used for both arms	
Resource use	Based on 2013 physician survey (re-evaluated by clinical experts in 2016). Scenario analyses to explore assumptions	

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See table 61 (page 195) of company submission for summary of model assumptions

Company's base-case results
Regorafenib with PAS

Base case	Total QALYs	Total costs	Inc. QALYs	Inc. costs	ICER
Placebo + BSC	0.969	£10,671			
Regorafenib (2015 OS data)	1.717	£36,457	0.748	£25,786	£34,476
Regorafenib (2017 OS data)	1.733	£36,478	0.971	£26,082	£26,852
New base case: Regorafenib (2017 and GRID treatment duration)	**1.733**	**£47,249**	**0.971**	**£36,854**	**£37,941**

- Probabilistic ICERs for new base case £38,494 per QALY gained. 82% chance regorafenib cost effective at willingness to pay of £50,000 per QALY
- Model drivers: regorafenib cost, discount rate utilities and costs, utilities for progressed state, utilities for progression free state

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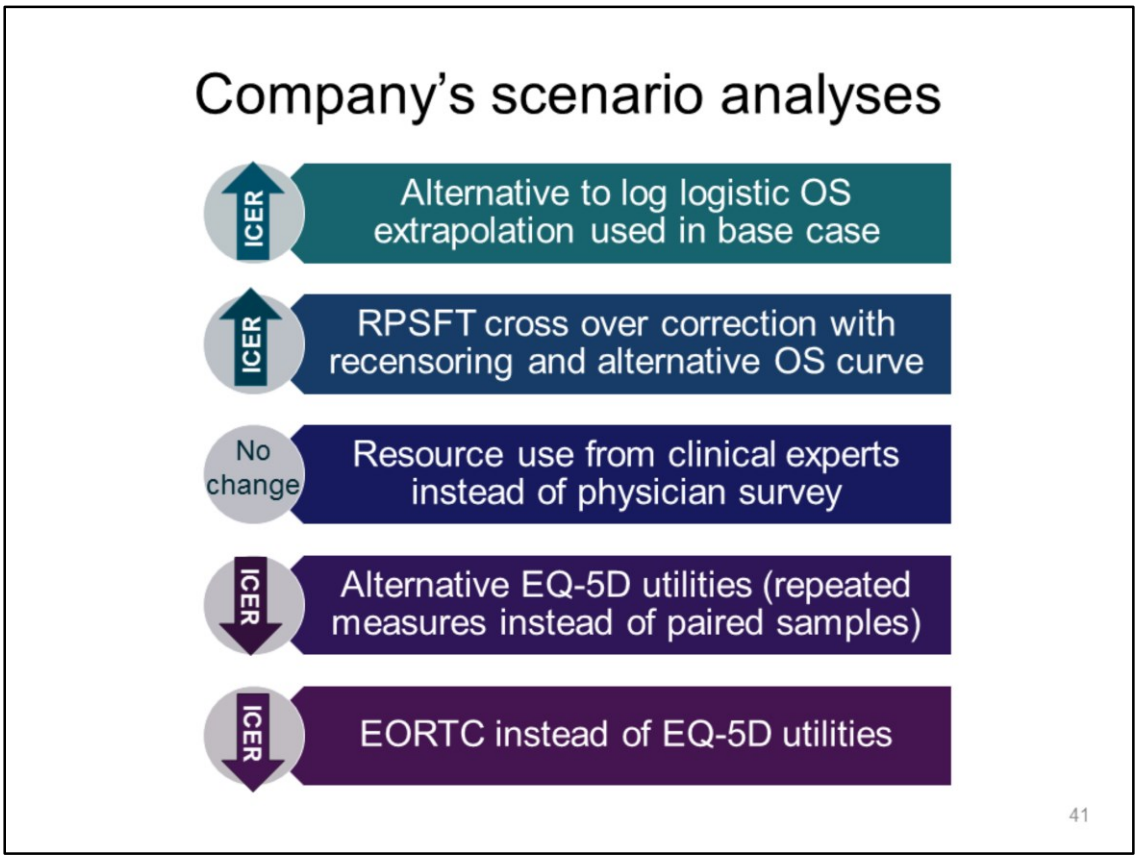
See table 63 (page 197) of company submission for base case results with PAS and 2015 data,

The model accurately represents the data from the trial, as shown in table 64 of the company submission



See section 5.8.9 (page 218) of company submission for scenario analyses

Scenario 3: Resource use assumptions were originally sourced from a 2013 physician survey of 15 physicians. The results were recently discussed with clinical experts to confirm accuracy and current day validity. The following points were raised by our clinical experts:

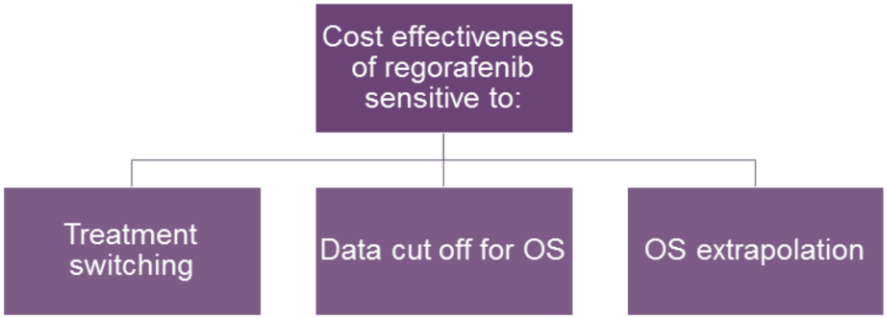
- In line with best clinical practice, all patients should receive either a CT or an MRI scan prior to starting treatment, in order to determine whether they need active treatment or BSC.
- For progression-free patients on regular TKI treatment, frequency of CT scan, blood tests and outpatient visits would be about every 12 weeks as patients would typically come into clinic every 12 weeks.
- For progression-free patients on regular BSC and for those patients who have progressed, the frequency of CT scans, MRI would be lower. For the scenario analysis, it is assumed that tests are performed every 24 weeks.
- The frequency of outpatient visits is thought to be lower:
    - Progression-free TKI patients: reduce from 6.2 to 12 weeks
    - Progression-free BSC patients: reduce from 6.9 to 8-12 weeks
- Reduce the proportion of progressed patients receiving either palliative resection or palliative radiotherapy to 5%.

Company's results from scenarios
Regorafenib with PAS

Scenario	ICER vs. BSC
Company's new base case (with PAS, 2017 OS data & treatment duration from GRID)	**£37,941**
1a. Weibull parametric curve to extrapolate OS data	£45,498
1b. Gompertz parametric model to extrapolate OS data	£47,068
2a. RPSFT cross over correction and Log-logistic OS curve	£39,493
2b. RPSFT cross over correction and Weibull OS curve	£46,996
2c. RPSFT cross over correction and Gompertz OS curve	£48,360
3. Change all resource use in line with clinical opinion	£37,806
4a. Add regorafenib cost post progression	Not relevant*
5a. EQ-5D utilities from repeated measures	£36,765
5b. EQ-5D utilities from repeated measures (PFS split treatment)	£37,514
6a. Use EORTC from GRID for utilities (repeated measures)	£34,281
6b. Use EORTC from GRID for utilities (paired samples)	£33,964
* Treatment duration derived directly from GRID discontinuation curve	

These scenario analyses are taken from the company's response to clarification in line with the new base case. See section 5.8.9 (page 218) of company submission for scenario analyses using the previous base case.

Evidence Review Group (ERG)



- High uncertainty in the cost effectiveness of regorafenib vs. BSC
  - Substantial uncertainty in cross over adjustment
  - Uncertainty in extrapolation of overall survival

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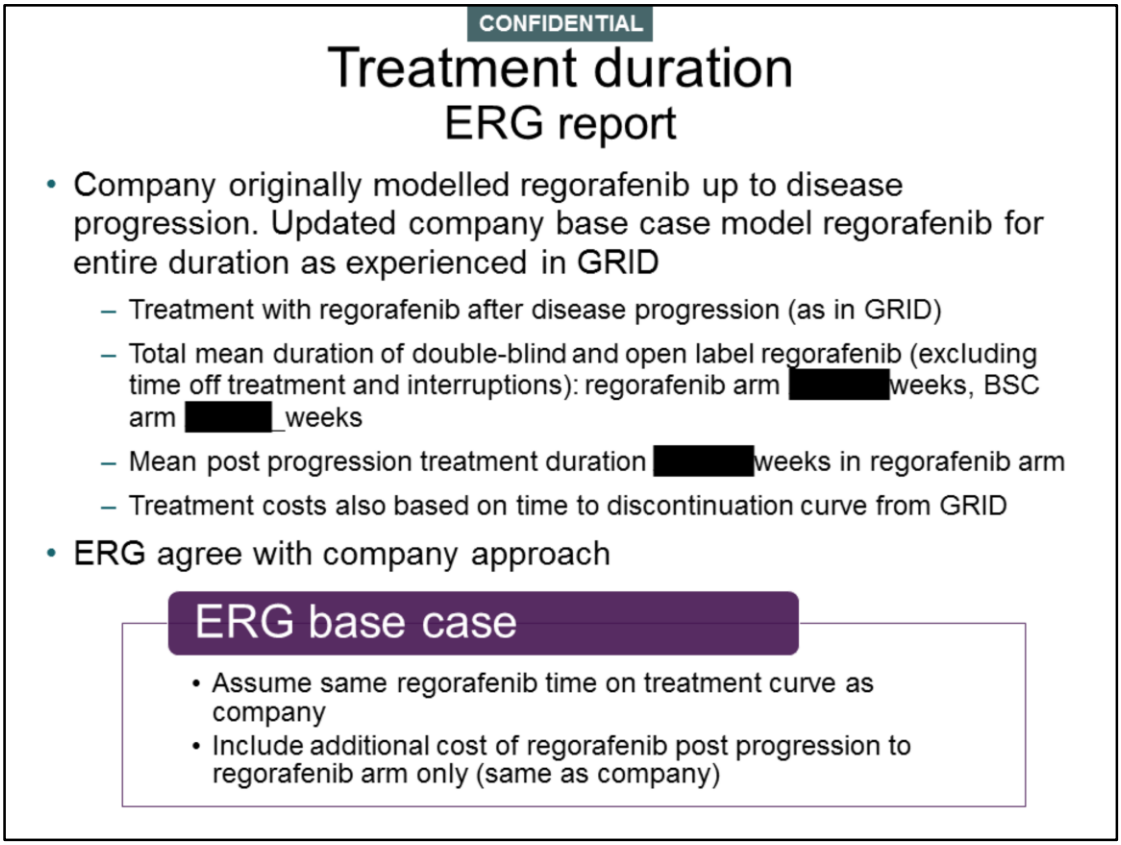

See section 5.3.8.2 (from page 102) of the ERG report for more details on treatment duration

In the company submission (page 228) the mean exposure to treatment post-progression was calculated by subtracting the mean time under actual treatment in the regorafenib arm during the double-blind phase from the mean time under actual treatment in both double-blind and open-label phases for patients randomised to the regorafenib arm

OS and treatment switching
ERG report

- Company use IPE adjustment and recensor data at earlier time-point to avoid informative censoring:
  - can lead to biased estimates of "average" treatment effect where proportional treatment effect assumption does not hold because longer term data on treatment effect may be lost (NICE TSD)
- ERG agree both IPE and RPSFT adjustments acceptable but should perform **adjustment with and without recensoring** (treatment effect generally greater when recensoring used)
- ERG unclear how relatively small increase in maturity of survival data can result in substantial reduction in estimated mean OS in placebo arm (24% lower)

Data cut	Mean OS in placebo arm	ERG base case
2015	Cross over corrected 1.64 years	Use similar recensoring and IPE adjustment (scenario for RPSFT)
2017	Cross over corrected 1.25 years	

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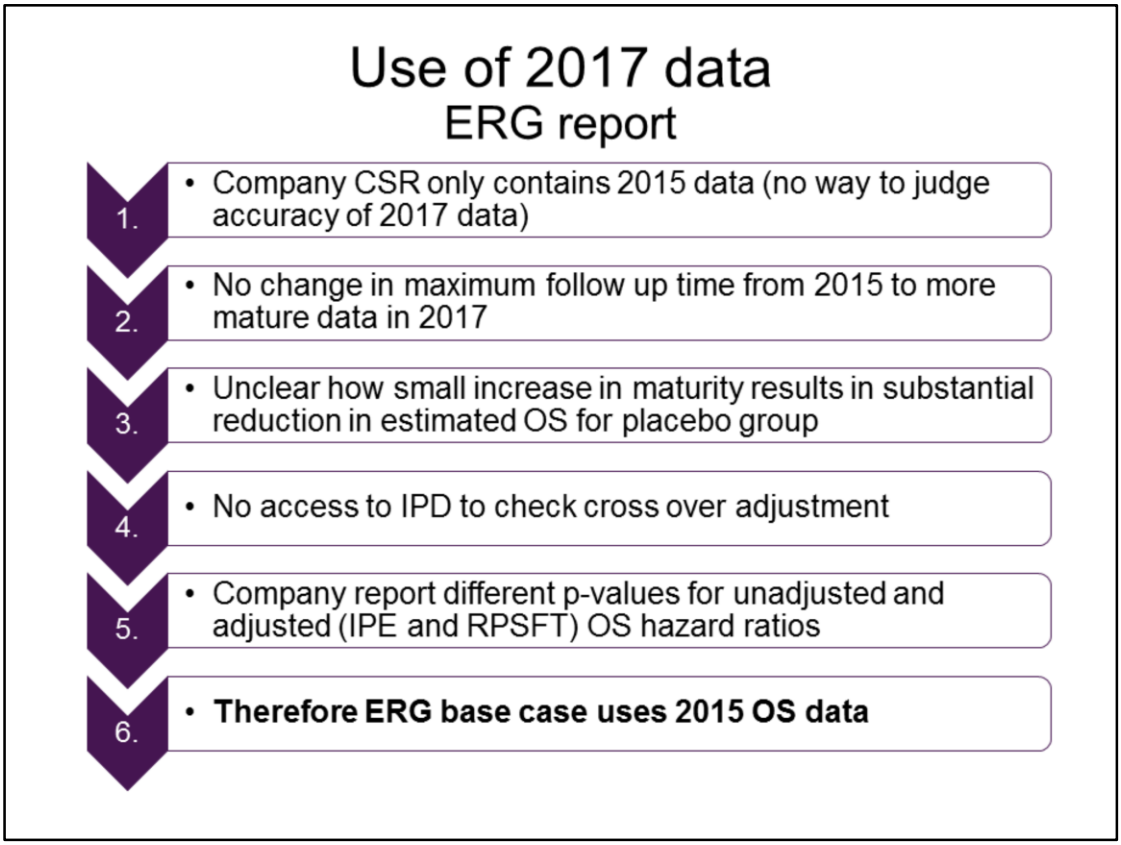
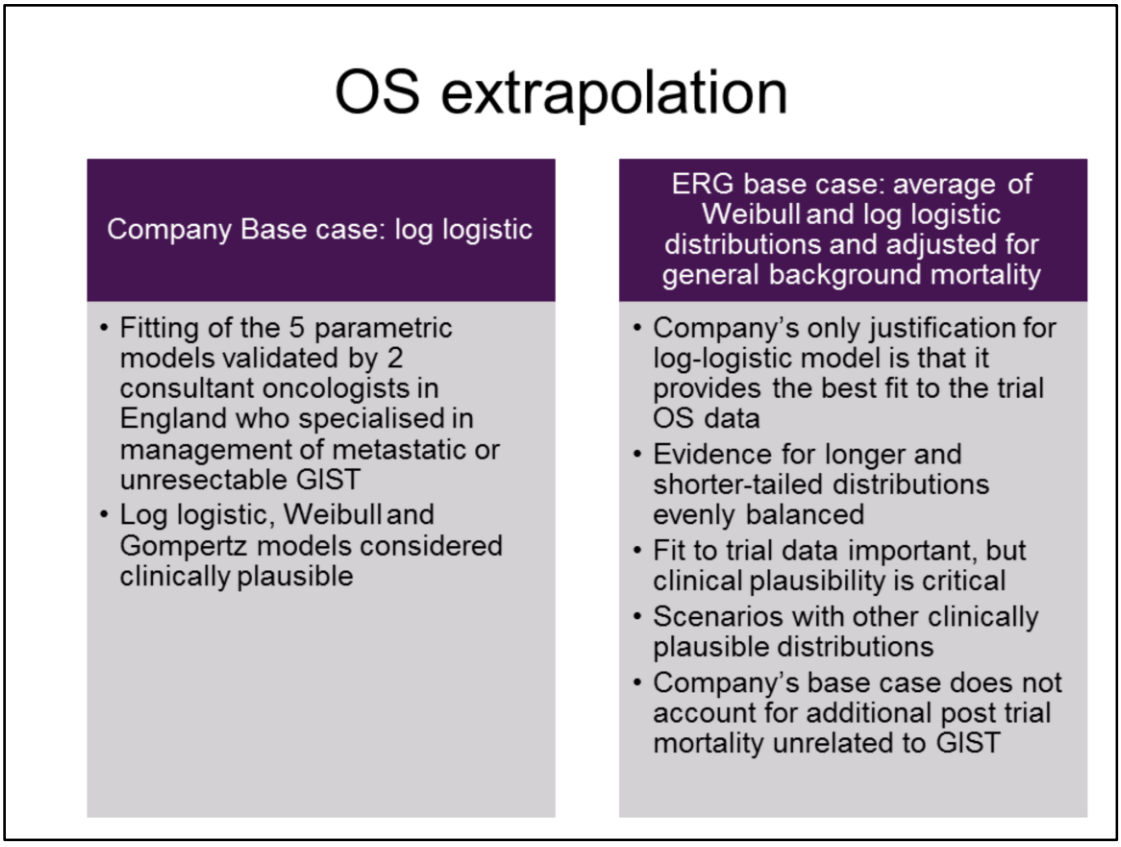


See section 5.3.6.2 (pages 82 and 83) of the ERG report for more details on the 2017 data for overall survival



See section 5.3.6.3 of ERG report (pages 87 to 95)

ERG carried out additional searches for survival curves for GIST. Reichardt et al (2015) OS data is slightly more mature than in GRID. Patients had advanced GIST and had previously failed imatinib, not but sunitinib. All 1,124 patients in this large international study took sunitinib. Median patients age was 59, virtually the same as in GRID, at 60 years. 60% of patients were male, again similar to the 64% in GRID. The ECOG distribution was similar compared with that in GRID, with patients typically with a slightly worse ECOG than in GRID. Median time to progression was substantially longer, at 8.3 months than in the regorafenib arm of GRID (4.8 months). Median OS on sunitinib, at 16.6 months, was however very similar to that of the regorafenib arm of GRID, at 17.3 months

OS is rather longer-tailed in Reichardt et al. (2015) than in the regorafenib arm of GRID (Figure 30). This might favour the choice of the log-logistic extrapolation over that of the Weibull or Gompertz. However, ERG caution against relying too much on the data from Reichardt et al. (2015), as:
(a) the uncertainty in the tail of OS in Reichardt et al. (2015) may be large, as the number of patients at risk in the tail might be low (but not reported),
(b) the patients in Reichardt et al. (2015) differed from those in GRID in that they had not previously been treated with suntinib, whereas all patients in GRID had,
(c) the patients in Reichardt et al. (2015) all took sunitinib, versus regorafenib in the regorafenib arm of GRID.

The ERG include background mortality in base case because mortality in GRID will be due almost

exclusively to causes related to GIST. However, many years later, a much larger proportion of deaths is likely to be use to causes unrelated to GIST, such as heart disease, or diabetes. Bayer's extrapolations make no allowance for this additional mortality. The ICERs increase markedly in the case of the log-logistic distribution because this is the longest-tailed distribution, and thus background mortality is more influential as the cohort ages.

Summary of ERG changes

Model parameter	Change from company base case	Rationale
Treatment duration	No change	Agree with company to model treatment duration from GRID (allows regorafenib after progression in regorafenib arm so these costs are added)
Survival data	PFS: no change **OS: 2015 data**	Can't validate company's 2017 data and inconsistencies in data reported
Cross over correction	No change (scenario analyses)	Agree both IPE and RPSFT appropriate methods (give similar estimates OS in placebo arm) and apply recensoring
Extrapolation of OS	**Distribution: average of log logistic and Weibull. ERG also add background mortality**	Company note Weibull and Gompertz models also clinically plausible. ERG: clinical plausibility is critical. Also additional general mortality likely to occur after trial
Utilities	Include **age related utility decrements**	Add aged related utility decrements - utility declines with age and not included in the company's base case

Bayer's only justification for choosing the log-logistic for their base case is that it provides the best fit to the trial OS data as measured by AIC / BIC. The ERG acknowledge that the fit to trial data is a consideration, but understand that the clinical plausibility of the extrapolations to be critical. The cost-effectiveness of Regorafenib is sensitive to choice of statistical distribution.

ERG explorations: base case results
Regorafenib with PAS

ERG base case	ICER vs. BSC
Company's base case	**£38,000**
1. OS data from 2015	£49,000
2. Add general mortality from UK population	£41,000
3. OS: average of log-logistic/Weibull	£41,000
4. Utilties decrease with age	£39,000
ERG base case (1 to 4)	**£56,000**
1 and 2	£52,000
1 and 3	£52,000
2 and 3	£43,000
1 and 2 and 3	£55,000

ERG: High uncertainty, mostly due to switching adjustment, but also extrapolation

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See section 6.1 (Table 54 on page 129) of ERG report

Model drivers: regorafenib cost, discount rate utilities and costs, utilities for progressed state, utilities for progression free state

ERG results from scenarios
Regorafenib with PAS

Scenario	ICER vs. BSC	
	Company base case*	ERG base case
Base case	**£37,941**	**£56,000**
1. ITT analysis	£149,000	£235,000
2. Model costs and QALY to progression only	£52,000	£51,000
3. OS 2017 data	No change	£44,000
4. RPSFTM cross over adjustment	£39,000	£64,000
5. OS: Weibull	£45,000	£59,000
6. OS: Gompertz	£47,000	£64,000
*Company's new base case (with PAS, 2017 data & treatment duration from GRID)		

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See section 6.1 (table 55 and table 56 on pages 131 and 132) of ERG report

Key issues: cost-effectiveness

- Company and ERG agree treatment duration should be modelled in line with GRID and include cost of regorafenib post progression (regorafenib arm only)
  - Does committee agree with this approach?
- Company prefer to use 2017 data for OS while ERG use 2015 data (not able to validate 2017 data and some inconsistencies)
  - What is the committee's preferred data cut for overall survival?
- Choice of distribution for OS extrapolation has large impact on cost effectiveness results and ERG also suggest including additional general background mortality
  - Does committee agree with average of log logistic and Weibull models?
  - Does committee agree with adding general background mortality?
- ERG add age related utility decrements as utility often declines with age
  - Does committee agree with this approach?
- Does regorafenib meet the end of life criteria?

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End of life criteria

- No 3rd line treatment option available in England currently
- Best supportive care only alternative to regorafenib
- **Short life expectancy:** median OS in placebo + BSC arm (11.9 months RPSFT correction and 11.1 months IPE correction)
- **Extension to life:** median OS difference regorafenib vs. BSC range 5.5 and 6.3 months
- **Patient population:** company estimate average 58 people per year over 5 years with metastatic GIST and failure with imatinib and sunitinib
- ERG agree regorafenib meets end of life criteria

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See section 3.4 (page 42) of company submission for end of life criteria

Innovation

- Company suggest regorafenib offers a step-change for the management of people with unresectable or metastatic GIST whose disease has progressed on, or who are intolerant to, previous treatment with imatinib and sunitinib:
  - In England, no licensed option for 3rd line treatment
  - Cross-over adjusted OS analyses showed a median OS increase varying between 5.5 and 6.3 months in favour of regorafenib when compared against BSC
- Company do not make case for substantial benefits that are not captured by QALY

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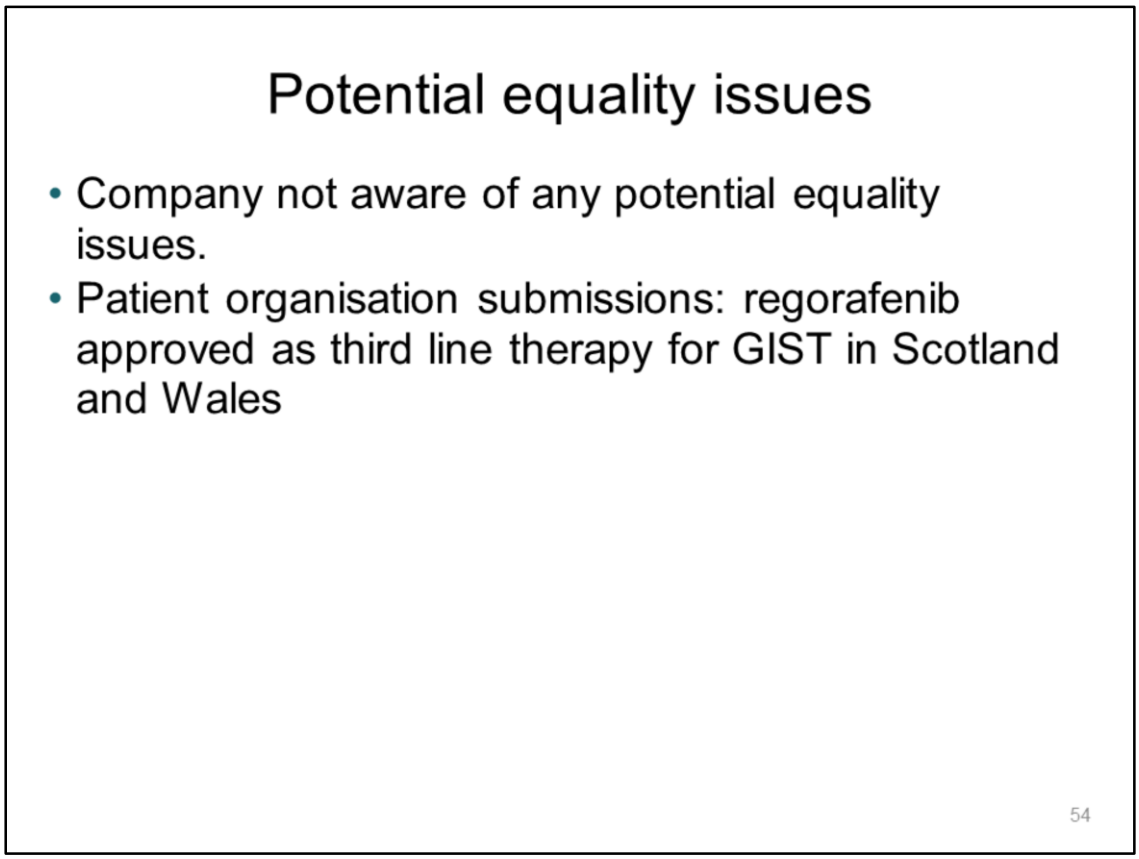
See section 2.5.1 (page 36) of company submission for innovation



See section 3.8 (page 45) of company submission for equalities issues

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Regorafenib for previously treated unresectable or metastatic gastrointestinal stromal tumours

[ID1056]

Company evidence submission

16th March 2017

File name	Version	Contains confidential information	Date
ID1056 regorafenib for previously treated unresectable GIST [ACIC]	1.0	Yes	16th March 2017

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 250 pages, excluding appendices and the pages covered by this template.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

Contents

Tables and figures

Tables

Figures

1 Executive summary

Disease background

- Gastro-intestinal stromal tumours (GISTs) are rare connective tissue tumours of the digestive system representing less than 1% of the tumours arising in the gastro-intestinal tract (1). Incidence of GIST has been reported to vary from 11 to 20 cases per million per year, with slightly higher rates observed in males (2-4).

- For people with GIST, the prognosis depends mainly on whether the tumour is resectable. Size, location, and stage of the tumour at initial diagnosis are also important factors for its prognosis (1).

- Metastatic GIST represents the terminal stage of the disease for which patients may experience general systemic symptoms such as fever, nausea, abdominal discomfort and weight loss as well as psychological distress and functional impairments (5). In addition to symptoms' negative effect on the quality of life of patients, fear of cancer recurrence or progression can also be experienced by patients.

Regorafenib

- Regorafenib is an oral tumour deactivation agent that potently blocks multiple protein kinases, including kinases involved in tumour angiogenesis, oncogenesis, and the tumour microenvironment. In particular, regorafenib inhibits mutated KIT, a major oncogenic driver in gastrointestinal stromal tumours, and thereby blocks tumour cell proliferation.

- Marketing authorisation for regorafenib was initially received on June 27th, 2013 for the treatment of metastatic colorectal cancers (CRC) who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy. A positive opinion on the extension of indication for regorafenib in the treatment of adult patients with unresectable or metastatic GIST who progressed on or are intolerant to prior treatment with

imatinib and sunitinib was released by the Committee for Medicinal Products for Human Use (CHMP) on June 26th, 2014.

- In England, regorafenib as a treatment for adult patients with unresectable or metastatic GIST who progressed on, or are intolerant to, prior treatment with imatinib and sunitinib has been funded through the Cancer Drug Fund (CDF) since 2013. This is the first NICE technology appraisal for regorafenib in this indication. Assessments by the Scottish Medicines Consortium (SMC) and All Wales Medicines Strategy Group (AWMSG) for the same indication were completed in April 2015 and July 2015, respectively (6;7).

Clinical effectiveness

Efficacy demonstrated in GRID (8)

- The GRID trial was a randomised, double-blind, placebo-controlled, multi-centre, cross-over phase 3 study to evaluate the efficacy and safety of regorafenib in patients with histologically proven metastatic and/or unresectable GIST with objective disease progression or intolerance to imatinib, as well as disease progression while on sunitinib.

- A total of 199 patients with GIST were randomised to receive either regorafenib + BSC (133 patients) or placebo + BSC (66 patients). Patients randomised to the regorafenib arm were to be treated with regorafenib 160 mg once daily for 3 weeks of every 4 week (28 day) cycle (i.e., 3 weeks on/1 week off). Patients randomised to the placebo arm were to be treated with 4 matching placebo tablets for 3 weeks of every 4 week (28 day) cycle (i.e., 3 weeks on/1 week off).

- Patient characteristics were representative of patients who would be eligible to receive treatment with regorafenib in clinical practice in England and Wales; hence GRID trial data are directly relevant to the decision problem.

- The primary objective of the GRID study was to compare the two treatment arms in terms of Progression-Free Survival (PFS), per blinded central radiology review, according to modified Response Evaluation Criteria in Solid

Tumors. The secondary objectives were to compare the regorafenib and placebo treatment arms in terms of overall survival (OS), time to progression (TTP), disease control rate (DCR), tumour response rate (RR), duration of response (DOR), and safety of regorafenib.

- Patients' health related quality of life and health utility values were measured using the European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ C30) version 3.0 and the European quality of life group (EuroQol) five dimensions questionnaire (EQ 5D), respectively.

- Results for the primary analysis of GRID show a significantly longer median PFS time in the regorafenib group than in the placebo group (147 days [4.8 months] vs 28 days [0.9 months]), with the risk of progression or death in the regorafenib arm lower than in the placebo arm (Hazard ratio [HR] 0.27, 95% CI 0.19-0.39; p<0.000001); thus the primary end point was met.

- Final analysis of the OS data from GRID was performed when approximately 160 events had been observed. As per trial design, patients receiving placebo who experienced disease progression (per blinded central radiology review) could have been offered open-label regorafenib (cross-over option). GRID data from the 08 June 2015 cut-off date showed that about 88% of placebo patients crossed over to the regorafenib arm. This implies the OS benefits in the placebo arm being confounded by the treatment effect of regorafenib.

- As a consequence of the crossover, the overall survival data in the placebo arm was corrected by using two different methods for crossover adjustment – the Iterative Parameter Estimation (IPE) method and Rank-Preserving Structural Failure Time (RPSFT) method. For this analysis no statistical approach recommended by NICE Decision Support Unit (9) for the crossover correction was considered. The analysis showed the median OS to be longer in the regorafenib group (529 days) than in the placebo group (338 days IPE [p = 0.00095]; 361 days RPSFT [p = 0.00286]). The estimated corrected hazard ratio of regorafenib to placebo using the RPSFT and IPE correction

methods were 0.616 (95% CI 0.435 - 0.871) and 0.586 (95% CI 0.417 - 0.824), respectively.

- Among the other secondary efficacy variables in the GRID study, the disease control rate (DCR) was significantly higher in the regorafenib group (52.6%) vs. the placebo group (9.1%) (one-sided p<0.000001). This result confirms the effect of kinase inhibitors in TKI-resistant disease, whereby disease stabilisation is promoted via increased necrosis inside the tumour without shrinking its actual size.

Safety profile of regorafenib in GRID

- The majority of patients in GRID experienced at least one treatment-emergent adverse event (TEAE) during the double-blind period of the study (regorafenib, n=132 [100%]; placebo, n=61 [92%]). Common adverse events included hand-foot skin reaction (HFSR), hypertension, diarrhoea, mucositis and fatigue. AEs were consistent with the known safety profile of regorafenib observed in metastatic colorectal cancer (mCRC) (10) and the drug class inducing inhibition of the VEGFR and other tyrosine kinase-mediated pathways.

- Overall, treatment with regorafenib was not associated with a substantial reduction in patient reported quality of life compared to placebo and most AEs were generally manageable by dose modification without the need to discontinue treatment.

End of life criteria

Treatment with regorafenib for patients with unresectable or metastatic GIST whose disease has progressed on, or who are intolerant to, previous treatment with imatinib and sunitinib meets the end of life criteria because of the following reasons:

1. The median OS for patients treated with BSC varies between 11.1 and 11.9 months when using the IPE and RPSFT crossover corrections, respectively (11)

2. There is sufficient evidence to indicate that the treatment offers an extension to life of at least 5.5 months compared to BSC (11)

The comparator

- Other than best supportive care (BSC), there are no lines of therapy currently recommended by NICE for the treatment of patients with unresectable or metastatic GIST who progressed on, or are intolerant to, prior treatment with imatinib and sunitinib.

- In line with the scope, the main comparator for regorafenib is BSC, defined as any method to preserve the comfort and dignity of the patient, excluding disease-specific antineoplastic therapy, radiation therapy, or surgical intervention (8).

- For patients with unresectable and/or metastatic GIST who progressed on, or are intolerant to, prior treatment with imatinib and sunitinib pain management treatments are the best supportive care currently available in clinical practice in England. According to two surveys, conducted in 2013 and 2016 and involving physicians from England and Wales, pain management treatments were confirmed to comprise co-codamol, tramadol, paracetamol, morphine sulphate and dexamethasone.

Economic effectiveness

- A commonly used oncology model structure considering three main health states – i.e., progression-free, progressed and death – was developed. The proportion of the cohort of patients in each of the three health states at different point in time is determined based on a partitioned survival model. This model type is the most suitable since it can use Kaplan-Meier survival curves from the GRID trial directly.

- In order to evaluate the clinical outcomes over a longer time horizon than that observed in the trial, parametric fittings of the Kaplan-Meier data for PFS and OS were conducted in line with the approach to the survival analysis recommended by NICE Decision Support Unit (12).

- State transitions in the model and evaluation of the clinical outcomes over a longer time horizon than that observed in the trial were based on the parametric fittings of the Kaplan-Meier data for PFS and OS extrapolated beyond the trial time horizon.

- The best fitting parametric models for the PFS and OS curves were selected after visual inspection and analysis of the lowest Akaike's Information Criterion and Bayesian Information Criterion resulting from the survival analysis. The log-normal function was selected as the best fitting curve for PFS and the log-logistic function as the best fitting curve for OS.

- Crossover adjustments based on the IPE and RPSFT methods for the OS data from the GRID placebo arm were conducted based on the methods recommended by NICE Decision Support Unit (9). Adjustment of the OS data based on the Inverse Probability of Censoring Weights (IPCW) was also considered but not used due to the high proportion of placebo patients crossing over to regorafenib (88%), a factor which is responsible for introducing high levels of bias in treatment effect estimates (9).

- The IPE method was selected as the base case crossover adjustment method since the study by Morden et al. (2011) showed that this method works particularly well in terms of reducing bias in the estimates of the true treatment effect (13) .

- Healthcare resource consumption was sourced from a survey conducted in 2013 and involving randomly selected physicians from England and Wales who manage adult metastatic/unresectable GIST patients. Findings from the survey were further validated and confirmed in 2016 by two consultant oncologists from England.

- Costs associated with the consumption of medical resources in England and Wales were retrieved from the most up-to-date sources available at the time of the submission. Utilities associated with the progression-free and progressed health states were retrieved from Poole at el. (2015), the publication of reference for the HRQL findings from GRID.

- The base-case analysis produced an ICER of £[redacted] per QALY gained when using the list price adjusted by the mean dose reduction (e.g. £3,271) and an ICER of £34,476 per QALY gained when using the PAS price ([redacted]% of the list price adjusted for mean dose reduction resulting equal to £[redacted]). Both base-case and scenario analyses demonstrated regorafenib to be a cost-effective treatment for patients with metastatic/unresectable GIST after treatment failures with imatinib and sunitinib.

Conclusions

- Results of the GRID study demonstrate clinical benefits for regorafenib over best supportive care / placebo in the treatment of metastatic and/or unresectable GIST after progression on imatinib and sunitinib

- Adverse events associated with regorafenib during the GRID study were as expected for this drug class, and generally manageable with dose modifications, without the need to discontinue treatment.

- Regorafenib was found to be a cost-effective treatment for patients with metastatic/unresectable GIST after treatment failures with imatinib and sunitinib. The base case analysis results produced an ICER of £[redacted] per QALY gained with the list price. Using the PAS price for regorafenib, the incremental cost per QALY gained was reduced to £34,476.

1.1 Statement of decision problem

The decision problem for regorafenib for previously treated unresectable or metastatic gastrointestinal stromal tumours is presented in Table 1.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) whose disease has progressed on, or who are intolerant to, previous treatment with imatinib and sunitinib	Patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) whose disease has progressed on, or who are intolerant to, previous treatment with imatinib and sunitinib	
Intervention	Regorafenib	Regorafenib	
Comparator (s)	Best supportive care (BSC)	Best supportive care (BSC)	
Outcomes	• Overall survival • Progression-free survival • Adverse events of treatment • Health-related quality of life	• Overall survival • Progression-free survival • Adverse events of treatment • Health-related quality of life	
Economic analysis	Cost-effectiveness analysis expressed in terms of incremental cost per quality-adjusted life year over a lifetime horizon	Cost-effectiveness analysis expressed in terms of incremental cost per quality-adjusted life year over a lifetime horizon	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Subgroups to be considered	-	No subgroups to be considered	
Special considerations including issues related to equity or equality	-	No issues related to equity or equality	

1.2 *Description of the technology being appraised*

Table 2. Technology being appraised

UK approved name and brand name	Regorafenib (Stivarga®)
Marketing authorisation/CE mark status	Positive CHMP opinion for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib indication was received on 26th June 2014. Market authorisation approval for this indication was then received on 28th July 2014
Indications and any restriction(s) as described in the summary of product characteristics	• Metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy • Unresectable or metastatic gastrointestinal stromal tumours (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib
Method of administration and dosage	• Treatment for oral use • The recommended dose of regorafenib is 160 mg (4 tablets of 40 mg) taken once daily for 3 weeks followed by 1 week off therapy. This 4-week period is considered a treatment cycle • Dose modifications are to be applied in 40 mg (one tablet) steps. The lowest recommended daily dose is 80 mg. The maximum daily dose is 160 mg

1.3 Summary of the clinical effectiveness analysis

Evidence for the efficacy and safety of regorafenib in patients with unresectable or metastatic GIST who have progressed on or are intolerant to prior treatment with imatinib and sunitinib, is based on the results of one pivotal phase 3 randomised controlled trial (the GRID study) (8).

Efficacy demonstrated in GRID (8)

This study was a randomised, double-blind, placebo-controlled, multi-centre, cross-over phase 3 study to evaluate the efficacy and safety of regorafenib in patients with histologically proven metastatic and/or unresectable GIST with objective disease progression or intolerance to imatinib, as well as disease progression while on sunitinib.

The study population was representative of patients with metastatic and/or unresectable GIST with objective disease progression or intolerance to imatinib, as well as disease progression while on sunitinib.

A total of 199 patients with GIST were randomised to receive either regorafenib + BSC (133 patients) or placebo + BSC (66 patients). Patients randomised were to be treated with regorafenib received 160 mg po once daily for 3 weeks of every 4 week (28 day) cycle (i.e., 3 weeks on/1 week off). Each 160 mg dose consisted of four 40 mg tablets. Patients randomised to the placebo arm were to be treated with 4 matching placebo tablets for 3 weeks of every 4 week (28 day) cycle (ie, 3 weeks on/1 week off).

In this poor prognosis patient population (see section 4.7.3), the GRID study demonstrated that compared with placebo, regorafenib (160 mg p.o., o.d. [oral, once daily]) for 3 weeks of every 4-week cycle) provides:

- a clinically relevant and significant prolongation of progression-free survival (PFS)
- disease control
- and overall survival benefits (after correction for crossover)

Results for the primary analysis of GRID show a significantly longer median PFS time in the regorafenib group than in the placebo group (147 days [4.8 months] vs 28 days [0.9 months]), with the risk of progression or death in the regorafenib arm lower than in the placebo arm (Hazard ratio [HR] 0.27, 95% CI 0.19-0.39; p<0.000001); thus the primary end point was met.

Sensitivity analyses produced consistent and supportive results for prolongation of PFS in the regorafenib group compared to the placebo group. Regorafenib was also effective across all subgroups of patients, including geographic region, prior line of treatment, age, sex, baseline BMI, duration of imatinib treatment, ECOG performance status, and mutational status.

Despite the potential confounding effect of the crossover design of GRID, analysis of overall survival using two different methods to correct for crossover – the Iterative Parameter Estimation (IPE) method and Rank-Preserving Structural Failure Time (RPSFT) method - showed median OS to be longer in the regorafenib group (529 days) than in the placebo group (338 days IPE [p = 0.00095]; 361 days RPSFT [p = 0.00286]). The estimated corrected hazard ratio of regorafenib to placebo using the RPSFT and IPE correction methods were 0.616 (95% CI 0.435 - 0.871) and 0.586 (95% CI 0.417 - 0.824), respectively.

Analyses of other secondary efficacy variables in the GRID study were also consistent with the primary efficacy results in demonstrating the efficacy of regorafenib over placebo. Median time to progression (TTP) was significantly longer in the regorafenib arm than in the placebo arm (5.4 months [165 days] versus 0.9 months [28 days], HR 0.248, 95% CI 0.170–0.364; p<0.000001). Tumour Response Rate, defined as the proportion of patients with the best overall tumour response of partial response (PR) or complete response (CR) according to modified RECIST criteria (version 1.1) that is achieved during treatment or within 30 days after termination of study medication, showed a higher trend in the regorafenib group (4.5%) compared to the placebo group (1.5%). The difference between treatment groups was not statistically significant; however, disease control rate (DCR) was significantly higher in the regorafenib group (52.6%) vs. the placebo group (9.1%) (one-sided p<0.000001) – an observed effect of kinase inhibitors in TKI-resistant

disease, whereby disease stabilisation is promoted via increased necrosis inside the tumour without shrinking its actual size.

Safety profile of regorafenib in GRID

In GRID, the majority of patients experienced at least one treatment-emergent adverse event (TEAE) during the double-blind period of the study (regorafenib, n=132 [100%]; placebo, n=61 [92%]). A high rate of TEAEs in both groups is expected for this pre-treated advanced/metastatic GIST patient population. Common adverse events included hand-foot skin reaction (HFSR), hypertension, diarrhoea, mucositis and fatigue. AEs were consistent with the known safety profile of regorafenib observed in metastatic CRC (10) and the drug class inducing inhibition of the VEGFR and other tyrosine kinase-mediated pathways.

Overall, treatment with regorafenib was not associated with a substantial reduction in patient reported quality of life compared to placebo and most AEs were generally manageable by dose modification without the need to discontinue treatment. AEs that led to permanent discontinuation of treatment were low (16.8%; n= 190). The most serious adverse drug reactions in patients receiving regorafenib were haemorrhage, severe liver injury, and gastrointestinal perforation.

Long-term treatment with regorafenib (> 1 year; n=75) was comparable with the safety profile of the overall patient population, with no unexpected safety findings. The majority of AEs occur within the first few months of treatment with significantly decreased event rates in subsequent months (14).

Strengths and limitations to the evidence base

The evidence for the use of regorafenib in unresectable or metastatic GIST which has progressed or is intolerant to prior treatment with imatinib and sunitinib, is derived from a well-designed multicentre trial (GRID study). A further strength is that the efficacy and safety of regorafenib was corroborated across all subgroup and sensitivity analyses conducted, indicating the robustness of the results and its applicability to a broad spectrum of patients, as would be seen in clinical practice. Patient characteristics in GRID are representative of patients who would be eligible to receive treatment with regorafenib in clinical practice in England and Wales;

hence the data are directly relevant to the decision problem. Regorafenib demonstrated consistent PFS benefits, independent of the number of previous treatments, patient characteristics, and mutation status. Furthermore, GRID employed the dosing regimen now licensed and used in clinical practice in England and Wales; and the comparator (placebo / best supportive care) corresponds to the lack of effective treatment options available for patients in England prior to the licensing of regorafenib. In advanced disease where life expectancy is reduced and there is no cure, relief of physical symptoms and maintenance of function become primary objectives of medical intervention. Outcome measures in the GRID study were based around assessment of treatment effects on delaying disease progression, improvements in survival, amelioration of symptoms, and health-related quality of life, all of which are directly relevant to patients with metastatic or unresectable tumours, who have limited treatment options and a poor prognosis.

The main limitation of the GRID study was the crossover design which confounded the assessment of the secondary endpoint, overall survival. The availability of promising results in studies with regorafenib in metastatic or unresectable GIST previously treated with both imatinib and sunitinib at the time of initiation of GRID, meant that the conduct of a placebo-controlled phase 3 study without the option for patients randomised to placebo to cross-over to open label regorafenib would have been unethical. This confounding effect can be clearly seen in the analysis of overall survival. Using standard Kaplan-Maier analysis median OS was 529 days (or 17.4 months) in both treatment groups (HR = 0.909), whereas use of RPSFT and IPE, two different methods used to correct for the effect of crossover from the placebo to the regorafenib arm, show longer median OS in the regorafenib group (529 days or 17.4 months) than in the placebo group (338 days or 11.1 months IPE [p = 0.00095]; 361 days or 11.9 months RPSFT [p = 0.00286]). The estimated corrected hazard ratio of regorafenib to placebo using the RPSFT and IPE correction methods were 0.616 and 0.586, respectively. In this crossover correction, no recommendations from NICE Decision Support Unit (9) were adopted.

It is considered that, despite these limitations, the available evidence base provides a robust assessment of the benefits of regorafenib anticipated in routine clinical practice in England and Wales.

End of life criteria

In current clinical practice in England, no active treatment is available for patients with unresectable or metastatic GIST whose disease has progressed on, or who are intolerant to, previous treatment with imatinib and sunitinib. Best supportive care is therefore the only treatment option available other than regorafenib.

Treatment with regorafenib for patients with unresectable or metastatic GIST whose disease has progressed on, or who are intolerant to, previous treatment with imatinib and sunitinib meets the end of life criteria because of the following reasons:

1. The median OS for patients treated with BSC varies between 11.1 and 11.9 months when using the IPE and RPSFT crossover corrections, respectively (11)

2. There is sufficient evidence to indicate that the treatment offers an extension to life of at least 5.5 months compared to BSC (11)

A retrospective study considering the evidence from 10 European institutions showed a median OS of 2.4 months (range 1.8–2.9) for adult patients with documented metastatic GIST who had been treated with BSC as third-line therapy after progression on first-line imatinib and second-line sunitinib.

Conclusions

Results of the GRID study demonstrate clinical benefits for regorafenib over best supportive care / placebo in the treatment of metastatic and/or unresectable GIST after progression on imatinib and sunitinib. Across all patient groups, regorafenib provided consistent PFS benefits, independent of the number of previous treatments, patient characteristics, and mutation status. Using different methods to correct for the effect of a crossover design, there is also evidence for an improvement of overall survival. Analyses of other secondary efficacy variables such as median TTP and disease control rate were also consistent with the primary efficacy results in demonstrating the efficacy of regorafenib over placebo. The adverse events associated with regorafenib during the GRID study were as expected for this drug

class, and generally manageable with dose modifications, without the need to discontinue treatment.

1.4 Summary of the cost-effectiveness analysis

A commonly used oncology model structure considering three main health states – i.e., progression-free, progressed and death – was developed. The proportion of the cohort of patients in each of the three health states at different point in time is determined based on a partitioned survival model. This model type is the most suitable since it can use Kaplan-Meier survival curves from the GRID trial directly.

Parametric fittings of the Kaplan-Meier data for PFS and OS extrapolated beyond the trial time horizon were used to inform state transitions in the model and evaluate clinical outcomes over a longer time horizon than that observed in the trial. The best fitting parametric models for the PFS and OS curves were selected based on the lowest Akaike's Information Criterion and Bayesian Information Criterion resulting from the survival analysis. The log-normal function was selected as the best fitting curve for PFS and the log-logistic function as the best fitting curve for OS.

To adjust for the patients in the placebo arm who crossed over onto open-label regorafenib treatment after progression and simulate placebo patients not crossing over to active treatment, OS data for the GRID placebo arm was adjusted using two different methods (9): the IPE and the RPSFT methods. Adjustment of the OS data based on the Inverse Probability of Censoring Weights (IPCW) was also considered but not used due to the high proportion of placebo patients crossing over to regorafenib (88%), a factor which is responsible for introducing high levels of bias in treatment effect estimates (9). The recommendations from NICE Decision Support Unit (9) were adopted for the crossover adjustment of the OS data.

The IPE method was selected as the base case crossover adjustment method since the study by Morden et al. (2011) showed that this method works particularly well in terms of reducing bias in the estimates of the true treatment effect.

As shown in Table 3, base-case analysis produced an ICER of £[redacted] per QALY gained when using the list price and an ICER of £34,476 per QALY gained when using the PAS price ([redacted]% of the list price adjusted for dose reduction). Both

base-case and scenario analyses demonstrated regorafenib to be a cost-effective treatment for patients with metastatic/unresectable GIST after treatment failures with imatinib and sunitinib.

Table 3. Incremental cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (LYs)	ICER (£) incremental (QALYs)
Cost-effectiveness results when using regorafenib list price								
Placebo + BSC	10,671	1.474	0.969					
Regorafenib	[redacted]	2.521	1.717					
				[redacted]	1.047	0.748	[redacted]	[redacted]
Cost-effectiveness results when using regorafenib PAS price								
Placebo + BSC	10,671	1.474	0.969					
Regorafenib	36,457	2.521	1.717					
				25,786	1.047	0.748	24,623	34,476
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years								

Some limitations to the model exist. Firstly, it is not possible to accurately observe the impact of regorafenib on OS in the trial due to the high percentage of crossover (88%) from the placebo arm, which introduces bias into the effectiveness estimates. Furthermore, the inability to separately identify any benefit of post-progression treatment in the regorafenib arm was a further limitation for the effectiveness estimates. It is unclear whether continued treatment with regorafenib post-progression confers any benefit. Continuation of active treatment post disease progression is not included in the licensed indication for regorafenib.

Regorafenib was found to be a cost-effective treatment for adult patients with unresectable or metastatic gastrointestinal stromal tumours who progressed on or are intolerant to prior treatment with imatinib and sunitinib.

2 The technology

When completing the template, refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

In addition ensure that all information provided in the regulatory submission is available on request.

2.1 *Description of the technology*

2.1.1 Give the brand name, UK approved name, the therapeutic class and a brief overview of the mechanism of action. For devices, provide details of any different versions of the same device.

The UK approved name for regorafenib, a small-molecule multikinase inhibitor, is Stivarga®.

Regorafenib is an oral tumour deactivation agent that potently blocks multiple protein kinases, including kinases involved in tumour angiogenesis (VEGFR1, -2, -3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF, BRAFV600E), and the tumour microenvironment (PDGFR, FGFR). In particular, regorafenib inhibits mutated KIT, a major oncogenic driver in gastrointestinal stromal tumours, and thereby blocks tumour cell proliferation.

2.2 *Marketing authorisation/CE marking and health technology assessment*

2.2.1 Indicate whether the technology has a UK marketing authorisation/CE marking for the indications detailed in this submission. If so, give the date on which this was received. If not, state the current UK regulatory status, with relevant dates (for example, date of application and/or expected date of approval from the Committee for Human Medicinal Products).

Initial marketing authorisation for regorafenib (Stivarga®) was received on June 27th, 2013 for the treatment of metastatic colorectal cancers who have been previously

treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy.

On June 26th, 2014 the CHMP released its positive opinion on the extension of indication for regorafenib in the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib.

Treatment with regorafenib (Stivarga®) for patients with unresectable or metastatic GIST whose disease has progressed on, or who are intolerant to, previous treatment with imatinib and sunitinib has been funded through the Cancer Drug Fund (CDF) since 2013. This is the first NICE technology appraisal for regorafenib in this indication.

2.2.2 Give the (anticipated) indication(s) in the UK. For devices, provide the date of (anticipated) CE marking, including the indication for use. If a submission is based on the company's proposed or anticipated marketing authorisation, the company must advise NICE immediately of any variation between the anticipated and the final marketing authorisation approved by the regulatory authorities.

Regorafenib is currently indicated for the treatment of the following two indications:

- Metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy
- Unresectable or metastatic gastrointestinal stromal tumours (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib

It is anticipated that regorafenib will receive a marketing authorisation for the treatment of hepatocellular carcinoma (HCC).

2.2.3 Summarise any (anticipated) restrictions or contraindications that are likely to be included in the (draft) summary of product characteristics (SmPC).

Contraindications include hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SmPC (see Appendix 1).

2.2.4 Include the (draft) SmPC for pharmaceuticals or information for use (IFU) for devices in an appendix.

The summary of product characteristics (SmPC) for regorafenib is provided in Appendix 1.

2.2.5 Provide the (draft) assessment report produced by the regulatory authorities (that is, the European public assessment report for pharmaceuticals) and a (draft) technical manual for devices in an appendix.

The European public assessment report is provided in Appendix 1.

2.2.6 Summarise the main issues discussed by the regulatory authorities (preferably by referring to the [draft] assessment report [for example, the European public assessment report]). State any special conditions attached to the marketing authorisation (for example, if it is a conditional marketing authorisation).

Main issues discussed by regulatory authorities were related to biomolecular and safety analyses limited by the small sample size or relatively short duration of the safety follow-up of patients enrolled in the pivotal 14874 study (10).

Pharmacovigilance activities and interventions detailed in the agreed Risk-Management Plan (RMP) presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP are being performed by Bayer.

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

Regorafenib for previously treated unresectable or metastatic gastrointestinal stromal tumours who progressed on or are intolerant to prior treatment with imatinib and sunitinib has been available in the UK since 2013.

2.2.8 State whether the technology has regulatory approval outside the UK. If so, please provide details.

Regorafenib has regulatory approval outside the UK. The technology received U.S. Food and Drug Administration (FDA) approval on September 27th, 2012 for the treatment of patients with colorectal cancer that has progressed after treatment and spread to other parts of the body (15). On February 25th, 2013 FDA approved regorafenib for the treatment of patients with advanced gastrointestinal stromal tumours (GIST) that cannot be surgically removed and no longer respond to other FDA-approved treatments for this disease (16).

2.2.9 State whether the technology is subject to any other health technology assessment in the UK. If so, give the timescale for completion.

Regorafenib is not subject to any other health technology assessment in the UK. Assessments by the Scottish Medicines Consortium (SMC) and All Wales Medicines Strategy Group (AWMSG) were completed in April 2015 and July 2015, respectively (6;7).

2.3 *Administration and costs of the technology*

2.3.1 For pharmaceuticals, complete the table 'Costs of the technology being appraised' in the company evidence submission template, including details of the treatment regimen and method of administration. Indicate whether the acquisition cost is list price or includes a patient access scheme, and the anticipated care setting. Specify the sources of information and data used to complete the table, for example SmPC or trial data. For more information see section 5.5 of the NICE guide to the methods of technology appraisal.

Table 4. Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	Film-coated tablet	SmPC (17)
Acquisition cost (excluding VAT) *	List price: £3,744 per pack	Bayer PLC
Method of administration	Oral use	SmPC (17)
Doses	160 mg per day (4 tablets of 40mg)	SmPC (17)
Dosing frequency	Once daily for 3 weeks followed by 1 week off therapy	SmPC (17)
Average length of a course of treatment	28 days (21 days on treatment and 7 days off treatment)	SmPC (17)
Average cost of a course of treatment	Cost based on list price: £3,271 Cost based on PAS price: £[redacted]	Costs calculated based on list or PAS price when considering dose reduction
Anticipated average interval between courses of treatments	One week off therapy between two consecutive treatment courses	SmPC (17)
Anticipated number of repeat courses of treatments	Mean number of treatment courses: 5.05	Calculated dividing the average overall time under treatment in weeks (20.221 weeks) by the duration of a single treatment course (4 weeks) (18)
Dose adjustments	The lowest recommended daily dose is 80mg. The maximum daily dose is 160mg	SmPC (17)
Anticipated care setting	All care settings	

* Indicate whether this acquisition cost is list price or includes an approved patient access scheme. When the marketing authorisation or anticipated marketing authorisation recommends the intervention in combination with other treatments, the acquisition cost of each intervention should be presented.

2.3.2 Provide details of any patient access scheme that has been referred to NICE for inclusion in the technology appraisal by ministers and formally agreed by the company with the Department of Health before the date of evidence submission to NICE for the technology. For more

information see section 5 of the NICE guide to the processes of technology appraisal.

A patient access scheme (PAS) was submitted to the Department of Health on December 2016 for the inclusion in this technology appraisal. Bayer is offering a PAS in the form of a confidential discount. The discount offered is [redacted]% and reduces the cost of a course of treatment of regorafenib from £3,744 to £[redacted] when no dose reduction is considered.

2.3.3 For devices, provide the list price and average selling price in a table similar to the table presented in the template, 'Costs of the technology being appraised'. 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.

2.4 *Changes in service provision and management*

2.4.1 State whether additional tests or investigations are needed (for example, diagnostic tests to identify the population for whom the technology is indicated in the marketing authorisation) or whether there are particular administration requirements for the technology. For more information see section 5.9 of the NICE guide to the methods of technology appraisal.

No additional tests or investigations are needed to identify the population for whom regorafenib is indicated in its marketing authorisation. There are no particular administration requirements for the technology.

2.4.2 Identify the main resource use to the NHS associated with the technology being appraised. Describe the location or setting of care (that is, primary and/or secondary care, commissioned by NHS England specialised services and/or clinical commissioning groups),

staff costs, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Regorafenib is an oral multikinase inhibitor requiring no specific settings of care for its administration and allowing patients to be treated at home. According to a resource use survey conducted in 2013 and involving 15 physicians from England and Wales, full blood count and liver function tests as well as CT and MRI scans are usually carried out for GIST patients. The findings from that survey were revalidated in 2016 by two consultant oncologists based on the current clinical practice in England. Based on the evidence collected through the two physician surveys, no further tests or monitoring visits are required for the administration of regorafenib. The average annual monitoring and tests frequency per patient with progression-free GIST treated with regorafenib is reported in Table 5.

Table 5. Average monitoring and tests frequency for progression-free patients during treatment with regorafenib

Monitoring and tests	Average annual monitoring and test frequency for progression-free patients during treatment with regorafenib (weeks)	Source
CT scan	12.07	2013 physician survey§ (19)
MRI scan	19.91	
Full blood count	6.43	
Liver function test	6.43	

§Validated by two consultant oncologists in 2016 based on the current English clinical practice

Unit and total annual costs associated with monitoring and tests per patient with progression-free GIST treated with regorafenib are reported in Table 6.

Table 6. Unit and total annual costs for monitoring and tests per patient treated with regorafenib

Tests	Unit costs	Total annual costs	Source
CT scan	£40§	£172	NHS reference costs 2015-16 (IMAG); code RD26Z - Computerised Tomography Scan of three areas, with contrast; https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016; assumed one CT scan every 3-months as reported in the ERG report for sunitinib [TA179] (20)

Tests	Unit costs	Total annual costs	Source
MRI scan	£147	£384	Cost per scan (weighted average of all MRI - adult; IMAG - codes: RD01A, RD02A, RD03Z, RD04Z, RD05Z, RD06Z, RD07Z) - NHS reference costs 2015-16 (20)
Full blood count	£3	£24	NHS reference costs 2015-16 (DAPS); code DAPS05 - Haematology; https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016; (20)
Liver function test	£1	£10	NHS reference costs 2015-16 (DAPS); code DAPS04 - Clinical Biochemistry; https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016; (20)

§Calculated on a three-month basis

For each test, the total annual cost was determined as the unit cost multiplied by the corresponding average annual frequency.

Regular outpatient monitoring visits are also required for patients with GIST treated with regorafenib. Results from the resource use survey involving 15 physicians from England and Wales showed these visits to take place every 6.15 weeks on average (19). Unit and total annual costs associated with the outpatient monitoring visits per patient are reported in Table 7.

Table 7. Unit and total annual cost of outpatient monitoring visits per patient with GIST treated with regorafenib

	Unit costs	Total annual costs	Source
Regular outpatient monitoring visits	£93	£786	PSSRU Unit costs of Health & Social Care 2015, pg. 177 - Table 10.8b (21)

The total annual outpatient visit cost was determined as the unit cost of an outpatient visit multiplied by its average annual frequency.

No staff or administration costs, other than those associated with the administration of best supportive care, are attributable to the treatment with regorafenib.

2.4.3 Specify if the technology requires additional infrastructure in the NHS to be put in place.

Regorafenib requires no additional infrastructure to be put in place in the NHS.

2.4.4 State if and to what extent the technology will affect patient monitoring compared with established clinical practice in England.

Regorafenib does not affect the types of patient monitoring tests compared with the established clinical practice in England and Wales. However, as reported in section 5.5.1, the average frequency of monitoring tests with regorafenib is slightly higher compared to BSC.

2.4.5 State whether there are any concomitant therapies specified in the marketing authorisation or used in the key clinical trials (for example, for managing adverse reactions) administered with the technology.

GIST patients randomised to receive regorafenib in the GRID trial also received best supportive care. Arterial hypertension, hand-foot skin reaction (HFSR), and diarrhoea were the three grade 3 and 4 adverse events reported in at least 3% of patients enrolled in the GRID trial. Arterial hypertension was treated in accordance with local standard medical practice, while HFSR was treated with keratolytic creams and moisturizing creams for symptomatic relief.

2.5 *Innovation*

2.5.1 If you consider the technology to be innovative with potential to make a substantial impact on health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation:

- state whether and how the technology is a ‘step-change’ in the management of the condition
- provide a rationale to support innovation, identifying and presenting the data you have used.

Bayer considers regorafenib as an innovative treatment offering a step-change for the management of patients with unresectable or metastatic GIST whose disease

has progressed on, or who are intolerant to, previous treatment with imatinib and sunitinib. This is based on the two following reasons:

- In England, no licenced treatment is currently recommended for patients with unresectable or metastatic GIST whose disease has progressed on, or who are intolerant to, previous treatment with imatinib and sunitinib (22)
- Cross-over adjusted OS analyses showed a median OS increase varying between 5.5 and 6.3 months in favour of regorafenib when compared against BSC (11)

3 Health condition and position of the technology in the treatment pathway

When completing the template, refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

3.1 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.

Gastro-intestinal stromal tumours (GISTs) are rare connective tissue tumours that show a differentiation profile similar to the interstitial cells of Cajal involved in the regulation of the digestive system. These neoplasms represent less than 1% of the tumours arising in the gastro-intestinal tract (1). The incidence of GIST has been reported to vary from 11 to 20 cases per million per year, with slightly higher rates observed in males (2-4).

Pathologically, most of GISTs are caused due to oncogenic mutations in either KIT or PDGFRA (23). The majority of the cases (75% to 80%) have KIT mutations that typically affect the juxtamembrane domain encoded by exon 11, while 5% to 8% GISTs have PDGFRA mutation and 12% to 15% have KIT and PDGFRA wild-type mutations (23). The presence of the cell-surface antigen CD117 is considered to be the gold standard criterion for diagnosis of GIST (24). This technique allows the separation of GISTs from rarer GI-associated muscle-derived myosarcomas (immunopositive for actin and desmin) and schwannomas. Rare KIT-negative GIST, which resembles KIT-positive forms in all respects other than immunoreactivity for KIT (around 5% of GISTs) are thought to contain mutations in the PDGFRA gene (25).

For people with GIST, the prognosis depends mainly on whether the tumour is resectable. Size, location, and stage of tumour at initial diagnosis are also important factors for the prognosis of the tumour (26).

Surgery represents the cornerstone treatment of localised GISTs (26). Complete removal of GIST is potentially curative, especially when it is small in size and the risk

classification is low. However, the risk of relapse after surgery can be substantial, as defined by available risk classifications, and treatment with imatinib as an adjuvant treatment option in adult patients is recommended for up to 3 years (27). Treatment with imatinib 400 mg daily is also the recommended standard treatment in locally advanced inoperable and metastatic patients. Once metastatic or unresectable patients with GIST develop confirmed progression or intolerance on imatinib, the next recommended treatment option is sunitinib (28). As reported in the ESMO clinical practice guidelines, after confirmed progression on sunitinib, treatment with regorafenib is the standard third-line targeted therapy for patients progressing on or failing to respond to imatinib and sunitinib (26).

Pain management treatments are used for unresectable and/or metastatic GISTs who progressed on or failed to respond to imatinib and sunitinib. According to a survey conducted in 2013 and involving physicians from England and Wales, pain management treatments were confirmed to comprise co-codamol, tramadol, paracetamol, morphine sulphate and dexamethasone.

3.2 Describe the effects of the disease or condition on patients, carers and society.

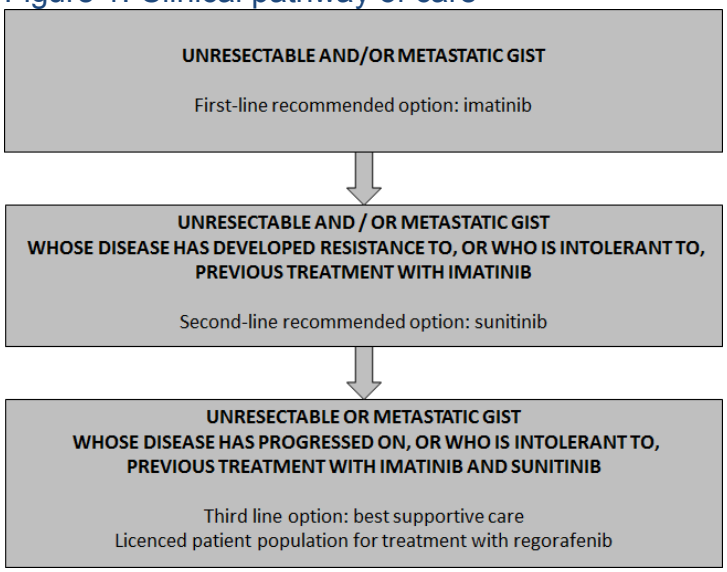
Metastatic GIST is a terminal disease for which patients may experience general systemic symptoms such as fever, nausea, abdominal discomfort and weight loss as well as psychological distress and functional impairments (5). In addition to symptoms' negative effect on the quality of life of patients, fear of cancer recurrence or progression can also be experienced by patients. This fear is not only associated with the medical condition caused by the disease, but also with psychosocial concerns, such as relying on others to perform daily activities, worries about future life, disability, or death (29). Because of the terminal stage of the disease, QALY gained by patients should be valued more highly than those gained at any other time in life.

3.3 Present the clinical pathway of care that shows the context of the proposed use of the technology. This information may be presented in a diagram. Explain how the new technology may change the existing

pathway. If a relevant NICE clinical guideline has been published, the response to this point should be consistent with the guideline and any differences should be explained.

The clinical pathway of care for patients with GIST sits within the NICE pathway for stomach cancer. Figure 1 provides the pathway of care under current NICE guidance, including the positioning of regorafenib as a therapy in the treatment of patients with unresectable or metastatic GIST whose disease has progressed on, or who are intolerant to, previous treatment with imatinib and sunitinib.

Figure 1. Clinical pathway of care



Where surgery is not considered appropriate, drug therapy for metastatic GIST in the form of sequential treatment with pharmacological agents such as imatinib and sunitinib, is recommended.

NICE TA guidance 196 recommends imatinib therapy at 400 mg/day as the first-line management treatment for people with KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic gastro-intestinal stromal tumours (30). Continuation with imatinib therapy is recommended only if a response to initial treatment is achieved within 12 weeks and until the tumour ceases to respond (30). For unresectable and/or metastatic GISTs progressing upon treatment with 400 mg/day imatinib, no high-dose regimen with imatinib - e.g. 600 or 800 mg/day - is recommended (30) .

For GISTs resistant or intolerant to imatinib, NICE TA guidance 179 recommends sunitinib as the second-line treatment option for unresectable and/or metastatic GISTs (28). This treatment is administered orally at the dosage of 50 mg once daily for 4 consecutive weeks, followed by a 2-week rest period (that is, a complete treatment cycle of 6 weeks) until confirmed disease progression. The dose may be adjusted in steps of 12.5 mg according to tolerability (within the dose range 25–75 mg) (28).

In England, there are no other lines of therapy recommended by NICE for the treatment of patients with unresectable or metastatic GIST whose disease has progressed upon treatment with sunitinib.

Positioning of regorafenib in the current pathway

The proposed indication for regorafenib is 'for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours who progressed on or are intolerant to prior treatment with imatinib and sunitinib', as noted previously in section 2.2.2. Bayer considers that regorafenib is an innovative treatment offering clinicians and patients a step-change in the management of unresectable or metastatic GISTs who progressed on or are intolerant to prior treatment with imatinib and sunitinib, for the reasons set-out further in section 2.5.1.

Regorafenib can therefore be standard for the third-line targeted therapy of unresectable or metastatic GISTs whose disease has progressed on, or who are intolerant to, previous treatment with imatinib and sunitinib.

3.4 Provide information about the life expectancy of people with the disease or condition in England and the source of the data. Please provide information on the number of people with the particular therapeutic indication for which the technology is being appraised. If the marketing authorisation also includes other therapeutic indications for the technology, provide information about the numbers of people with these diseases or conditions in England and provide the source of the data. This is to assess whether the technology may be suitable for consideration as

a ‘life-extending treatment at the end of life’ as described in section 6.2.10 of the NICE guide to the methods of technology appraisal.

In current clinical practice in England, no active treatment is recommended for patients with unresectable or metastatic GIST whose disease has progressed on, or who are intolerant to, previous treatment with imatinib and sunitinib. Best supportive care is therefore the only treatment option available, alternative to regorafenib.
In a retrospective study considering the clinical evidence from 10 European institutions a median OS of 2.4 months (range 1.8–2.9) was found for adult patients with documented metastatic GIST who had been treated with BSC as third-line treatment after progression on first-line imatinib and second-line sunitinib (31) .

In the GRID trial, the median OS for regorafenib arm was 17.4 month compared with 11.9 and 11.1 months for the placebo + BSC arm when RPSFT and IPE crossover corrections were applied, respectively (see section 4.13.2) (14). The difference in median OS between regorafenib and placebo + BSC was therefore found to range between 5.5 and 6.3 months.

We estimate that approximately 60 new patients per year with unresectable or metastatic GIST in England are eligible for further TKI treatment after their disease has progressed on, or who are intolerant to, previous treatment with imatinib and sunitinib. This estimate was calculated based on data retrieved from Office for National Statistics (32), NICE TA179 (28), and Demetri et al. (2006) (33). More details on calculations and assumptions used to estimate this value are reported in section 6.2.

3.5 Provide details of any relevant NICE guidance, pathways or commissioning guides related to the condition for which the technology is being used. Specify whether any subgroups were explicitly addressed.

There are three relevant NICE TA recommendations relating to the treatment of adult patients with unresectable or metastatic GIST who progressed on or are intolerant to prior treatment with imatinib and sunitinib.

NICE Technology Appraisal 86, imatinib for the treatment of unresectable and/or metastatic gastro-intestinal stromal tumours, was published in October 2004 and partially updated in November 2010, with recommendations as follows (1):

1.1 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 gastro-intestinal stromal tumours (GISTs).

1.2 Continuation with imatinib therapy is recommended only if a response to initial treatment is achieved within 12 weeks

1.3 Responders should be assessed at intervals of approximately 12 weeks thereafter. Continuation of treatment is recommended at 400 mg/day until the tumour ceases to respond

1.4 An increase in the dose of imatinib is not recommended for people receiving imatinib who develop progressive disease after initially responding

1.5 This recommendation has been updated and replaced by NICE technology appraisal guidance 209

1.6 The use of imatinib should be supervised by cancer specialists with experience in the management of people with unresectable and/or metastatic GISTs

NICE Technology Appraisal 209, imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours, was published in November 2010 to update recommendation 1.5 of TA86. All other recommendations in TA86 are still valid. Recommendations in NICE technology appraisal 209 guidance are as follows and should be read in conjunction with NICE Technology Appraisal 86 (1;34):

1.1 Imatinib at 600 or 800 mg/day is not recommended for people with unresectable and/or metastatic gastrointestinal stromal tumours whose disease has progressed after treatment with 400 mg/day imatinib

1.2 People who are currently receiving 600 or 800 mg/day imatinib for unresectable and/or metastatic gastrointestinal stromal tumours should have the option to continue therapy until they and their clinicians consider it appropriate to stop

NICE Technology Appraisal 179, sunitinib for the treatment of gastrointestinal stromal tumours, was published in September 2009 with recommendations as follows (28):

1.1 Sunitinib is recommended, within its licensed indication, as a treatment option for people with unresectable and/or metastatic malignant gastrointestinal stromal tumours if:

- imatinib treatment has failed because of resistance or intolerance, and
- the drug cost of sunitinib (excluding any related costs) for the first treatment cycle will be met by the manufacturer

1.2 The use of sunitinib should be supervised by cancer specialists with experience in treating people with unresectable and/or metastatic malignant gastrointestinal stromal tumours after failure of imatinib treatment because of resistance or intolerance

3.6 Provide details of other clinical guidelines (for example, UK guidance from the royal societies or European guidance) and national policies.

The most recent European clinical practice guidelines for diagnosis, treatment and follow-up of GISTs were published by ESMO in 2014 (26).

Within these guidelines, treatment of advanced inoperable and metastatic patients with 400 mg/day imatinib is recommended as the standard treatment (26).

Standard second-line treatment with sunitinib is recommended following confirmed progression or intolerance on imatinib (after attempts to manage side-effects also through expert advice, also exploiting dose reductions and possibly plasma level assessment) (33).

The most recent UK clinical guidelines were published by the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland in August 2009 (35). Key treatment recommendations for unresectable and/or metastatic GISTs are in line with those reported in ESMO clinical guidelines 2014 (26).

3.7 Describe any issues relating to current clinical practice, including any variations or uncertainty about established practice.

In England, there is currently no active treatment option recommended for patients with unresectable or metastatic GISTs who progressed on or are intolerant to prior treatment with imatinib and sunitinib.

3.8 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 about equality issues see NICE's equality scheme.

Provide an assessment of whether the use of this technology is likely to raise any equality issues. Please document if there are any potential issues that:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for whom the technology is or will be licensed
- could lead to recommendations that have a different impact on people protected by the equality legislation compared with the wider population, for example 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.

Please provide any evidence that would enable the Committee to identify and consider the impact of equality issues. State how the analysis has addressed these issues.

We are not aware of any equity or equality issues.

4 Clinical effectiveness

Section 4 provides detailed guidance on the level of information that should be included in the evidence submission template about the clinical effectiveness of the appraised technology.

Evidence on outcomes should be obtained from a systematic review, defined as systematically locating, including, appraising and synthesising the evidence to obtain a reliable and valid overview of the data.

When completing the template, also refer to the NICE guide to the methods of technology appraisal (section 5.2) and the NICE guide to the processes of technology appraisal (section 3.2).

For further information on how to implement the approaches described in the NICE methods guide, see the technical support documents produced by the NICE Decision Support Unit[1] about evidence synthesis:

- Introduction to evidence synthesis for decision making (technical support document 1).
- A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials (technical support document 2).
- Heterogeneity: subgroups, meta-regression, bias and bias-adjustment (technical support document 3).
- Inconsistency in networks of evidence based on randomised controlled trials (technical support document 4).
- Evidence synthesis in the baseline natural history model (technical support document 5).
- Embedding evidence synthesis in probabilistic cost-effectiveness analysis: software choices (technical support document 6).

[1] Although the Decision Support Unit is funded by NICE, technical support documents are not formal NICE guidance or policy.

- Evidence synthesis of treatment efficacy in decision making: A reviewer's checklist (technical support document 7).

4.1 *Identification and selection of relevant studies*

To identify and select relevant studies, it is expected that a systematic literature search will be carried out in line with the NICE guide to the methods of technology appraisal sections 5.2.2 and 5.2.4.

In exceptional circumstances, however, such as when all published or unpublished clinical data are within the company's possession, custody or control – a systematic literature search may not be necessary. If a systematic literature search is not included in the submission, the company must confirm that no other additional relevant studies have been done outside its organisation. NICE requires the medical director of the company to sign a statement confirming that all clinical trial data necessary to address the remit and scope of the technology appraisal as issued by the Department of Health and NICE, within the company's or any of its associated companies' possession, custody, or control in the UK or elsewhere in the world, have been disclosed to NICE. NICE also requires companies to consent to it being provided directly by European Economic Area regulatory authorities all clinical trial data necessary to address the remit and scope of the technology appraisal as issued by the Department of Health and NICE. This includes all data that have been submitted to the regulatory authorities by the company or any of its associated companies and that were relevant to the granting of a marketing authorisation, and for NICE to use those data in carrying out the technology appraisal. NICE will only ask regulatory authorities directly after having first approached the company for the information and the company is unable or unwilling to provide the information in a timely manner. See section 3.1 of the NICE guide to the processes of technology appraisal.

Provide the information specified in sections 4.1.1–4.1.6.

4.1.1 Advise whether a search strategy was developed to identify relevant studies for the technology. If a search strategy was developed and a

literature search carried out, provide details under the subheadings listed in this section. Key aspects of study selection can be found in Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).

A systematic literature review was conducted to identify published evidence for the clinical efficacy and safety of regorafenib in patients with metastatic and/or unresectable gastrointestinal stromal tumours (GIST) who have progressed after therapy with at least imatinib and sunitinib. This formed part of a broader review of the literature to inform on the clinical management, economic burden, clinical guidelines and quality of life associated with GIST.

The clinical evidence literature review was conducted from 2000 to 19 March 2012 and then updated three times:

- An update from 19 March 2012 up to July 2013
- An update from 19 July 2013 to 11 May 2016
- A further update from 11 May 2016 to 12 December 2016

Search strategy

4.1.2 Describe the search strategies used to retrieve relevant clinical data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided so that the results may be reproduced. This includes a full list of all information sources and the full electronic search strategies for all databases, including any limits applied. The search strategies should be provided in an appendix.

The latest clinical search was undertaken on 12 December 2016 using the following databases:

- Medline (from 11 May 2016 to 12 December 2016)
- Embase (from 11 May 2016 to 12 December 2016)

- Medline in process (from May 2016 to 12 December 2016)
- Cochrane Central Register of Controlled Trials (CENTRAL) (from 11 May 2016 to 12 December 2016)

Results were added to the previous searches. The overall time-frame of clinical effectiveness literature review was thus: 01 January 2000 to 12 December 2016.

In addition, proceedings from three major conferences were searched for relevant abstracts/posters with results of recent and updated trials:

- American Society of Clinical Oncology (ASCO) (ASCO-GI specific and ASCO Annual meeting) (2009-2011; 2012-2013; 2014-2016)
- European Society for Medical Oncology (ESMO) (ESMO-GI specific and Annual conference) (2009-2011; 2012-2013; 2014-2016)

The search is outlined below in section 4.1.3. Full details of the literature search strategy including search terms employed are provided in Appendix 2.

Study selection

4.1.3 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process in a table. Justification should be provided to ensure that the rationale for study selection is transparent. A suggested table format is provided below.

Bibliographic details and abstracts of all citations detected by the literature search were downloaded into a database. Citations were first screened by two independent reviewers based on the abstract supplied with each citation using the eligibility criteria described in Table 8. Discrepancies between the two reviewers at the first pass stage were reconciled by a third independent reviewer. Citation duplicates and studies that did not match the eligibility criteria were excluded at this first pass stage. Full-text copies of all references that could potentially meet the eligibility criteria were ordered and reviewed against the study selection criteria.

Studies were included if they met at least one of the PICOS criteria presented in Table 8.

Table 8. Eligibility criteria used in the search strategy

Clinical evidence	Inclusion	Exclusion
Patient population / disease	Adult patients with metastatic, advanced, or unresectable GIST. Including 3rd line or later patients.	Studies in children or adolescents Studies conducted in animals or in vitro. Patients with GIST that can be treated by surgery. Patients diagnosed with the following: gastrointestinal leiomyosarcoma that appeared to behave as GIST; soft-tissue sarcoma that appeared to behave as GIST; oesophageal leiomyosarcoma; gastric leiomyoma; gastric leiomyoblastoma; small intestinal leiomyoma and leiomyosarcoma; colonic and rectal leiomyoma and eiomyosarcoma; gastrointestinal autonomic nerve tumour; eiomyoma and leiomyosarcoma of omentum and mesentery; retroperitoneal leiomyosarcoma Mixture of treatment diagnoses (with no metastatic, advanced, or unresectable GIST specific subgroup data available)
Interventions / Comparators	Regorafenib studies vs. placebo or BSC	Any other intervention
Outcome measures	Efficacy outomes e.g. progression-free survival (PFS), overall survival (OS), Time to progression (TTP), disease control rate (DCR), response rate (ORR), duration of response (DOR). Safety outcomes e.g. adverse events Health-related Quality of life (HRQoL)	-

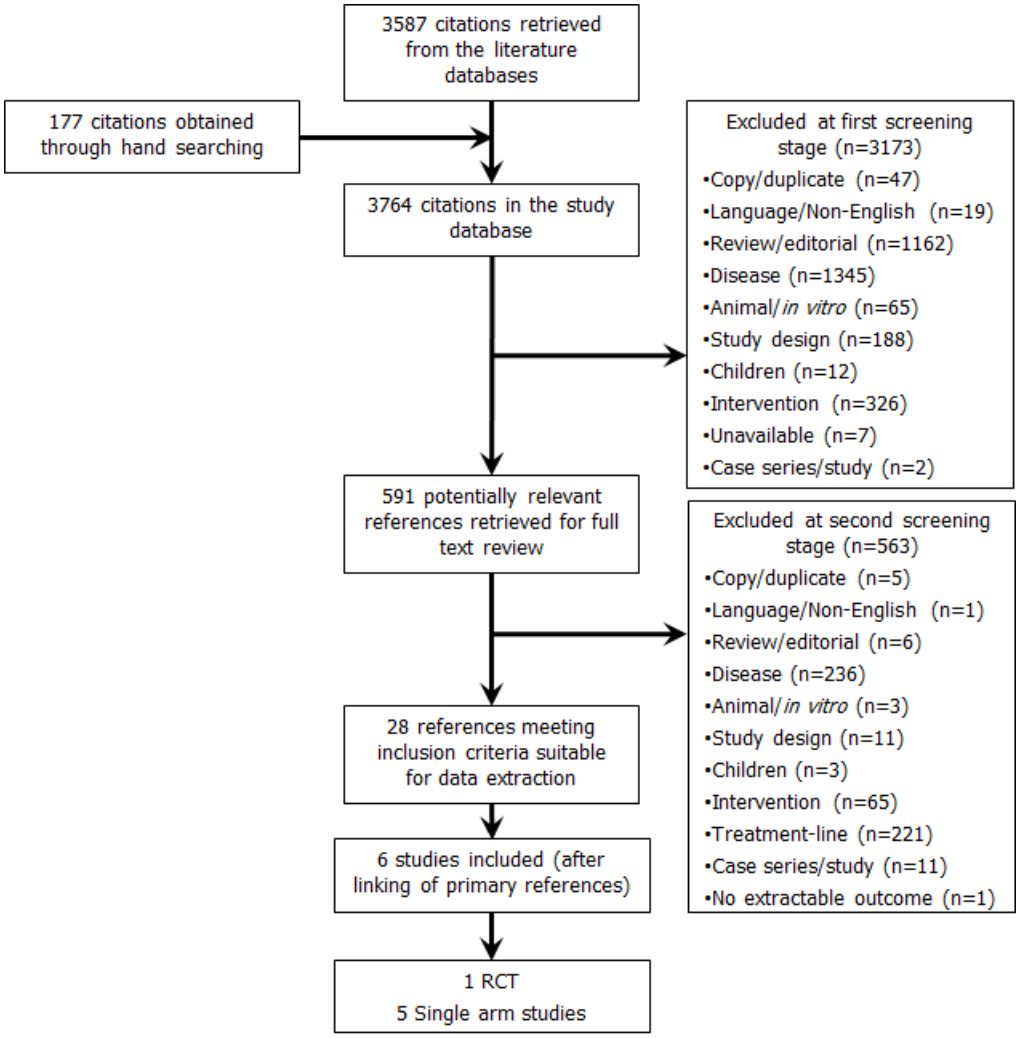
Clinical evidence	Inclusion	Exclusion
Study design	Randomised control trials (of any blinding status); non-randomised, controlled studies; uncontrolled single-arm trials; Cohort studies	Case control or cross-sectional studies Case series/reports
Restrictions	Language: English	Non-English studies

GIST: Gastrointestinal Stromal Tumour

4.1.4 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 PRISMA flow diagram. The total number of studies in the statement should equal the total number of studies listed in section 4.2.

A flow diagram of the numbers of records included and excluded at each stage is provided in Figure 2.

Figure 2. PRISMA Flow diagram of the included clinical studies



Overall, the search (including the original search, the 2013 update, the 2016 May update and the 2016 December update) yielded 3,764 references and 47 were removed as duplicates. Initial screening of titles/abstracts yielded 591 potentially relevant references of studies in the third-line treatment of metastatic and/or unresectable gastrointestinal stromal tumours, which were evaluated as full-text reports (where available). Of relevance to the decision problem in this submission, 28 publications concerned the use of regorafenib. These publications related to 6 studies: one randomised controlled trial (RCT), and 5 single-arm studies. The single-arm studies included limited information and patient numbers. This section further focuses on the identified RCT, the optimum design for assessing the benefits of treatments in oncology.

4.1.5 When data from a single study have been drawn from more than 1 source (for example, a poster and a published report) or when trials are linked (for example, an open-label extension to a randomised controlled trial [RCT]), this should be clearly stated.

The RCT (GRID study) was a phase III, double-blind, placebo-controlled multicentre study which took place across 57 study centres in 17 countries.

Study characteristics and pre-defined data were extracted into a Microsoft Access® extraction grid. References reporting clinical data from the same primary data source were identified and termed as 'linked studies' (linked to primary data source), and this was recorded in the extraction grid. In this manner the linkage of information allowed to avoid the duplication of reported data.

4.1.6 Provide a complete reference list for excluded studies in an appendix.

A complete reference list for the excluded studies is reported in Appendix 2.

4.2 *List of relevant randomised controlled trials*

NICE prefers RCTs that directly compare the technology with 1 or more relevant comparators. The company must confirm that all relevant evidence globally within its possession, custody or control has been submitted in the evidence submission for the technology. Please refer to the NICE guide to the methods of technology appraisal sections 3.3.2–3.3.7, 5.2.1 and 5.2.3 for details on the types of evidence to be considered.

Provide the information specified in sections 4.2.1–4.2.2.

4.2.1 In a table, present the list of relevant RCTs comparing the intervention with other therapies (including placebo) in the relevant patient group. Highlight which studies compare the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, state this. A suggested table format is presented below.

One double-blind RCT was identified in the literature (8), comparing regorafenib with placebo in patients with metastatic and/or unresectable gastrointestinal stromal tumours who have progressed after therapy with at least imatinib and sunitinib. A list of relevant RCTs is reported in Table 9.

Table 9. List of relevant RCTs

Trial number (acronym)	Population	Intervention	Comparator	Primary study reference
NCT01271712 (GRID)	Metastatic and/or unresectable gastrointestinal stromal tumours (GIST) who have progressed after therapy with at least imatinib and sunitinib	Regorafenib (+BSC) 160mg od N=133	Placebo (+ BSC) N=66	Demetri 2013 (8)

BSC=best supportive care; mg=milligrams; od=once daily.

4.2.2 When the RCTs listed above have been excluded from further discussion, justification should be provided to ensure that the rationale for doing so is transparent. For example, when RCTs have been identified, but there is no access to the level of data required, this should be stated.

The RCT listed in Table 9 is directly relevant to the decision problem.

4.3 *Summary of methodology of the relevant randomised controlled trials*

It is expected that all key aspects of methodology will be in the public domain; if a company wishes to submit aspects of the methodology in confidence, prior agreement must be obtained from NICE.

Provide the information specified in sections 4.3.1 and 4.3.2.

4.3.1 Items 3 to 6b of the CONSORT checklist should be provided for all RCTs listed:

- **Trial design** – brief description of trial design, including details of randomisation if applicable.
- **Eligibility criteria** – a comprehensive description of the eligibility criteria used to select the trial participants, including any definitions and any assessments used in recruitment.
- **Settings and locations where the data were collected** – describe the locations where the trial was carried out, including the country and, if applicable, the care setting (for example, primary care [GP or practice nurse], secondary care [inpatient, outpatient, day case]).
- **Trial drugs and concomitant medications** – provide details of trial drugs and comparator(s), with dosing information and titration schedules if appropriate. Provide an overview of concomitant medications permitted and disallowed during the trial.
- **Primary, secondary and tertiary outcomes** – all outcome measures listed in the trial protocol, whether primary, secondary or tertiary, should be identified and completely defined. The rationale for excluding data on any of the outcomes listed in the study protocol should be provided. When outcomes are assessed at several time points after randomisation, indicate the pre-specified time point of primary interest. For many non-pharmacological interventions it is helpful to specify who assessed outcomes (for example, if special skills are required to do so) and how many assessors there were. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant 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 adherence. 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).

Proof of the efficacy of regorafenib in the treatment of patients with GIST, who have been previously treated with 2 tyrosine kinase inhibitors (TKIs) comprises one phase III study:

- GRID: Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial (Study 14874) (8;10;14;18;36).

Overview

The primary objective of the GRID study was to compare regorafenib and placebo treatment in terms of progression-free survival (PFS) in patients with metastatic and/or unresectable GIST who have progressed after therapy with at least imatinib and sunitinib.

Secondary objectives included evaluation of overall survival (OS), time to progression (TTP), disease control rate (DCR), tumour response rate (RR), duration of response (DOR), and safety of regorafenib. Health-related quality of life, pharmacokinetics, secondary PFS during open label treatment, and biomarker analysis were exploratory objectives within the study.

The GRID study was completed in August 2011 and results were published in 2013 (8). The EMA recommended use of regorafenib for the 'treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib' on 26th June 2014 and a CHMP variation assessment report (EPAR report scientific discussion) was published (10). Other data included in this submission (i.e. unpublished) has been drawn from the Clinical Study Report (CSR)(18) , an addendum to the CSR (14), study protocol (36) and European submission dossier for the licensing of regorafenib in GIST (37).

NB. All patients also received best supportive care (BSC) – in the text the 'regorafenib + BSC' arm is generally written as 'regorafenib' and the 'placebo + BSC' is generally written as 'placebo'.

Trial design (8;10;36)

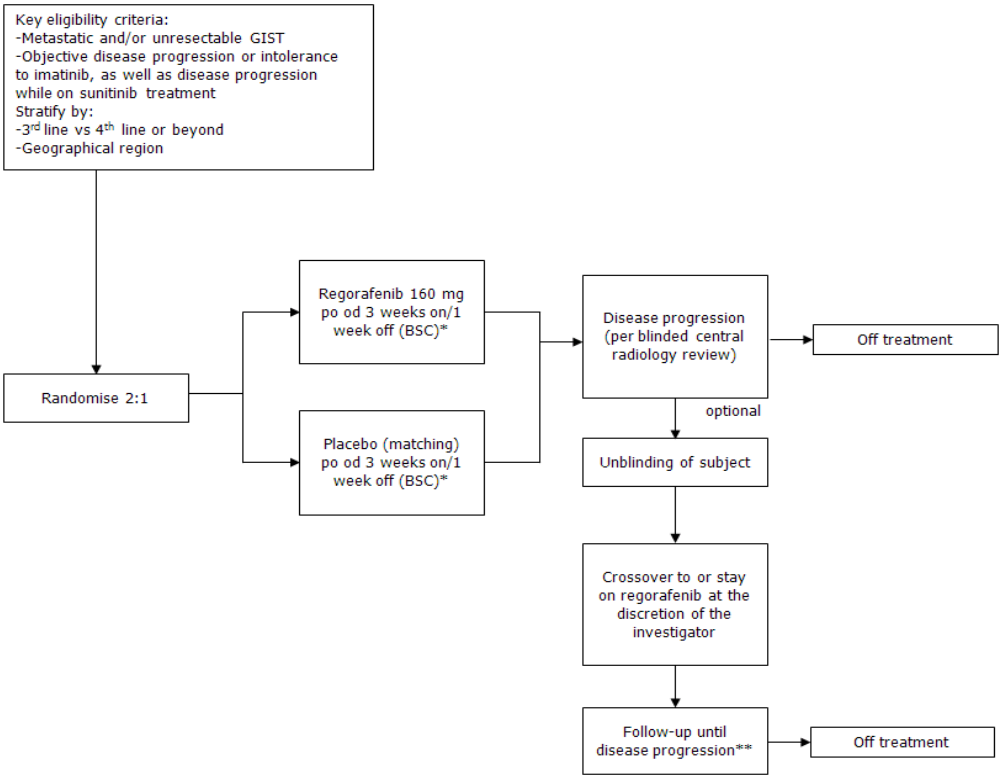
GRID was a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial which took place across 57 study centres in 17 countries from:

- Europe (Austria, Belgium, Finland, France, Germany, Italy, Netherlands, Poland, Spain, United Kingdom (UK)),
- North America (United States (US); Canada),
- Israel
- and Asia (China; Japan; Singapore, South Korea).

Study enrolment started in January 2004 and was completed in August 2011, during which time a total of 240 patients were screened. Of these, 199 patients were randomised on a 2:1 basis to receive regorafenib (n=133) or matching placebo (n=66). At randomisation, patients were stratified by treatment line (3^{rd} vs. 4^{th} line therapy or beyond) and geographical region (Asia vs. rest of the world).

Patients continued masked study treatment until disease progression, unacceptable toxicity or withdrawal of patient from the study. Upon progression, patients receiving placebo were offered open-label regorafenib (cross-over option). Patients receiving regorafenib who experienced disease progression and for whom, in the investigator's opinion, treatment with regorafenib was providing clinical benefit, were offered the opportunity to continue open-label regorafenib.

Figure 3. GRID study design



BSC: Best Supportive Care; GIST: Gastrointestinal Stromal Tumour; po: per os
** Patients could continue treatment with regorafenib even after 1st progression (for regorafenib patients) or 2nd progression (for cross over patients)

Upon discontinuation of study treatment all patients were followed for survival until death was documented, except for those who specifically withdrew consent to follow-up or did not sign the consent form for long term follow-up. Assessment of survival status was performed every 3 months.

Method of randomisation

Randomisation was performed via an interactive voice response system (IVRS). Investigators received the randomisation number for each participant through the IVRS and study drug supply was also managed via IVRS. Computer-generated randomisation lists were prepared by Bayer (pre-allocated block design, block size 12). Randomisation was stratified by treatment line (3rd vs. 4th line therapy or beyond) and geographical region (Asia vs. rest of the world).

Masking

Patients, investigators, and the study sponsor were masked to treatment assignment through the use of the unique drug pack numbers pre-printed onto each bottle, which was assigned to the patient by the IVRS.

Regorafenib and placebo were identical in appearance in order to preserve blinding.

Assessment of the primary endpoint (PFS) was carried out by central radiology reviewers who were masked to assignment and data from patients.

Eligibility criteria

Table 10 reports the eligibility criteria for the GRID study.

Table 10. Eligibility criteria

Inclusion criteria	Exclusion criteria
• Male or female patients ≥ 18 years of age having provided signed informed consent. • Histologically confirmed metastatic and/or unresectable GIST who experienced disease progression or intolerance to imatinib, as well as disease progression while on sunitinib. • Patients could have received other systemic therapies, including investigational agents, except any vascular endothelial growth factor receptor (VEGFR) inhibitors other than sunitinib. • At least one measurable lesion with CT or MRI (according to modified Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1)). A lesion in a previously irradiated area was eligible as long as there was objective evidence of progression of the lesion prior to study enrolment. • Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1. • Adequate haematological, hepatic, cardiac, and renal function, defined as follows: - Total bilirubin ≤ 1.5 x the upper limit of normal (ULN). - Alanine transaminase (ALT) and aspartate aminotransferase (AST) ≤ 3.0 x ULN (≤ 5 x ULN for patients with liver involvement of their GIST). - Lipase ≤ 1.5 x the ULN	• Prior treatment with regorafenib, or any VEGFR inhibitor except sunitinib. • Use of any approved tyrosine kinase inhibitors or investigational agents within 1 week or a minimum 5 half-lives of the agent, whichever is shorter, prior to receiving study drug. • Previous assignment to treatment during this study. Patients permanently withdrawn from study participation will not be allowed to re-enter the study. • Previous or concurrent cancer that is distinct in primary site or histology from GIST within 5 years prior to randomisation EXCEPT for curatively treated cervical cancer in situ, non-melanoma skin cancer, and superficial bladder tumours (Ta [Non-invasive tumour], Tis [Carcinoma in situ], and T1 [Tumour invades lamina propria]). • Major surgical procedure, open biopsy, or significant traumatic injury within 28 days before start of study medication. • Pregnant or breast-feeding patients. • Women of childbearing potential and men must agree to use adequate contraception (barrier method of birth control) from informed consent until at least 3 months after the last study drug administration. • Congestive heart failure ≥ New York Heart Association (NYHA) class 2. • Unstable angina (angina symptoms at rest), new-onset angina (begun within the last 3

Inclusion criteria	Exclusion criteria
- Serum creatinine ≤ 1.5 x the ULN. - Glomerular filtration rate (GFR) ≥ 30 ml/min/1.73 m^2 according to the Modified Diet in Renal Disease (MDRD) abbreviated formula. - International normalised ratio and partial thromboplastin time (INR and PTT) ≤ 1.5 x ULN. Patients being treated with an anti-coagulant, such as warfarin or heparin, were allowed to participate provided that no prior evidence of an underlying abnormality in these parameters existed. Close monitoring of at least weekly evaluations was performed until INR and PTT was stable based on a pre-dose measurement as defined by the local standard of care. - Platelet count ≥ 100000/mm^3, haemoglobin (Hb) ≥ 9 g/dl, absolute neutrophil count (ANC) ≥ 1500/mm^3. - Alkaline phosphatase limit ≤ 2.5 x ULN (≤ 5 x ULN for patients whose cancer involved their liver). • Resolution of all toxic effects of previous therapy to grade 1 or lower (excluding alopecia, anaemia, and hypothyroidism).	months). Myocardial infarction less than 6 months before start of study drug. • Cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted). • Uncontrolled hypertension (systolic blood pressure > 140 mmHg or diastolic pressure > 90 mmHg despite optimal medical management). • Pheochromocytoma. • Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischaemic attacks), deep vein thrombosis, or pulmonary embolism within the 6 months before start of study drug. • Ongoing infection > grade 2 National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. • Known history of human immunodeficiency virus (HIV) infection. • Known history of chronic hepatitis B or C. • Seizure disorder requiring medication. • Symptomatic metastatic brain or meningeal tumours unless the patient is > 6 months from definitive therapy, has a negative imaging study within 4 weeks of study entry, and is clinically stable with respect to the tumour at the time of study entry. Also, the patient must not be undergoing acute steroid therapy or taper (chronic steroid therapy was acceptable provided that the dose is stable for one month prior to and following screening radiographic studies). • History of organ allograft. • Evidence or history of bleeding diathesis. Any haemorrhage or bleeding event ≥ NCI-CTCAE version 4.0 grade 3 within 4 weeks of start of study drug. • Non-healing wound, ulcer, or bone fracture. • Renal failure requiring haemo- or peritoneal dialysis. • Dehydration NCI-CTCAE version 4.0 grade ≥ 1. • Substance abuse or medical, psychological, or social conditions that may interfere with the patient's participation in the study or evaluation of the study results. • Known hypersensitivity to the study drug, study drug class, or excipients in the formulation. • Any illness or medical conditions that are unstable or could jeopardize the safety of the patient and his/her compliance in the study.

Inclusion criteria	Exclusion criteria
	• Interstitial lung disease with ongoing signs and symptoms at the time of informed consent. • Patients unable to swallow oral medications. • Persistent proteinuria of NCI-CTCAE version 4.0 grade 3 or higher (> 3.5 g/24 hrs, measured by urine protein: creatinine ratio on a random urine sample). • Any malabsorption condition. • Close affiliation with the investigational site, e.g., a close relative of the investigator or dependent person (e.g., employee of or student at the investigational site).

Trial drugs and concomitant medications

For the first 3 weeks of each 4-week cycle patients were randomised to receive daily dose of:

- Oral regorafenib 160 mg (4 x 40mg tablets, once daily) plus BSC
- Matching placebo plus BSC

Regorafenib 40mg tablets (and matching placebo) were supplied as coated, immediate-release, non-divisible, grey-orange-red, oval tablets in high-density polyethylene (HDPE) bottles with a white child-resistant closure and induction seal. Study drug had to be stored in its original bottle at a temperature not above 25 °C (77 °F).

BSC was defined as any method to preserve the comfort and dignity of the patient, and included any concomitant medications or treatments: antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy necessary to provide BSC, except other investigational anti-tumour agents or anti-neoplastic chemo/hormonal/immune/radio-therapy.

Patients were treated until disease progression according to modified RECIST 1.1 (per blinded central radiology review), clinical progression, unacceptable toxicity, and/or consent withdrawal.

Dose modification

Throughout both the masked and open-label phases, study drug could be delayed or reduced according to a pre-specified schedule (Table 11); in the case of unacceptable toxic effects (Table 8), hand-foot skin reaction (HFSR) (Table 13) and hypertension (Table 14). Up to two regorafenib dose-reductions due to toxicity were allowed (from 160 mg to 120 mg to 80 mg). After implementation of a dose reduction, dose re-escalation was permitted provided that toxicities were resolved to grade <3 (or <2 in case of hand-foot syndrome [HFS]).

Table 11. Regorafenib dose levels (36)

Dose level	**Dose**	
Dose level 0 (standard dose)	160mg po od	4 tablets of regorafenib, 40mg/tablet, or 4 matching placebo tablet
Dose level -1	120mg po od	3 tablets of regorafenib, 40mg/tablet, or 3 matching placebo tablet
Dose level -2	80mg po od	2 tablets of regorafenib, 40mg/tablet, or 2 matching placebo tablet

Table 12. Dose modification / delay for toxicities related to study drug (except hand-foot skin reaction and hypertension)[a] (36)

NCI-CTCAE v4.0	**Dose Interruption**	**Dose Modification**	**Dose for Subsequent Cycles**
Grade 0-2	Treat on time	No change	No change
Grade 3[b]	Delay until < grade 2[b]	Reduce 1 dose level	If toxicity remains <grade 2, dose re-escalation can be considered at the discretion of the treating investigator. If dose is re-escalated and toxicity (≥ grade 3) recurs, institute permanent dose reduction
Grade 4	Delay until < grade 2[b]	Reduce by 1 dose level. Permanent discontinuation can be considered at treating investigator's discretion.	

[a] excludes alopecia, non-refractory nausea/vomiting, non-refractory hypersensitivity and asymptomatic laboratory abnormalities
[b] If no recovery after a 4-week delay, treatment will be permanently discontinued

Table 13. Dose modification for hand-foot skin reaction (36)

Skin Toxicity Grade	Occurrence	Suggested Dose Modification
Grade 1: Numbness, dysaesthesia, paraesthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the patient's normal activities	Any	Maintain dose level and immediately institute supportive measures for symptomatic relief
Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort which affects the patient's normal activities	1st occurrence	Consider decreasing dose by one dose level and immediately institute supportive measures. If there is no improvement, interrupt therapy for a minimum of 7 days, until toxicity resolves to grade 0-1[b].
	No improvement within 7 days or 2nd occurrence	Interrupt therapy until toxicity resolves to grade 0-1. When resume treatment, treat at reduced dose level[b].
	3rd occurrence	Interrupt therapy until toxicity resolves to grade 0-1. When resume treatment, decrease dose by one additional dose level[a,b]
	4th occurrence	Discontinue therapy.
Grade 3: Moist desquamation, ulceration, blistering or severe pain of the hands or feet or severe discomfort that causes the patient to be unable to work or perform activities of daily living	1st occurrence	Institute support measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to grade 0-1. When resume treatment, decrease dose by one dose level[b].
	2nd occurrence	Institute support measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to grade 0-1. When resume treatment, decrease dose by one additional dose level[a,b].
	3rd occurrence	Discontinue treatment permanently.

[a] Patients requiring > 2 dose reductions should discontinue protocol therapy
[b] If toxicity returns to grade 0-1 after dose reduction, dose re-escalation is permitted at the discretion of the investigator

Table 14. Management of treatment-emergent hypertension (36)

Event Grade (NCI-CTCAE v4.0)	Characteristic	Management
Grade 1		[redacted]
Grade 2	Asymptomatic Grade 2	
	Symptomatic Grade 2	
Grade 3		
Grade 4		Discontinue therapy

[a] If blood pressure remains controlled for at least one full cycle, dose re-escalation is permitted at the investigator's discretion.
[b] Patients requiring a delay of >4 weeks should discontinue protocol therapy
[c] Patients requiring >2 dose reductions should discontinue protocol therapy

Treatment compliance

Designated study personnel were responsible for dispensing the study drug to patients. Drug accountability was performed at every patient visit, with bottles returned to the investigator with any unused medication. Information was recorded in the drug dispensing log.

During the double-blind period, patients who were assigned to receive regorafenib had a median and mean overall treatment duration of 22.9 weeks and 20.2 weeks respectively (vs. patients assigned to placebo: median 7.0 weeks, mean 9.1 weeks).

The median and mean daily dose for regorafenib-treated patients during the double-blind treatment period was 146.8 mg and 139.8 mg, respectively. For patients in the

placebo arm the median and mean daily dose was 160 mg and 159.5 mg, respectively.

Concomitant medications (36)

All medication necessary for the patient's welfare, and not expected to interfere with the evaluation of the study drug, could be given at the discretion of the principal investigator. These included standard therapies for concurrent medical conditions, prophylactic anti-emetics, bisphosphonates and treatment with non-conventional therapies (e.g. herbs or acupuncture) and vitamin/mineral supplements.

[redacted]

Patients taking narrow therapeutic index medications (e.g., warfarin, quinidine, cyclosporine, and digoxin) were monitored proactively. Warfarin is metabolised by the cytochrome enzyme CYP2C9 and its levels may be especially affected by regorafenib.

Patients taking warfarin, heparin or similar were allowed to participate provided that no prior evidence of underlying abnormality in coagulation parameters existed. Weekly evaluations were performed until INR and PTT were stable based on a pre-dose measurement as defined by the local standard of care.

Concomitant medication metabolised by the cytochrome enzymes CYP2C8, CYP2B6, or CYP2C9 or the phase II glucuronosyl transferases UGT1A1 and 1A9 were to be avoided, where possible. Likewise, since there was a possibility of increased regorafenib toxicity, chronic co-administration of CYP3A4 inhibitors with regorafenib should be avoided; and as there was a possibility of decreased regorafenib efficacy upon chronic co-administration of CYP3A4 inducers with regorafenib, chronic co-administration of CYP3A4 inducers with regorafenib was also to be avoided where possible.

Primary, secondary and tertiary outcomes (8;10;36)

Table 15 summarises GRID study endpoints, and how each were measured. Progression-free survival (PFS) was chosen as the primary endpoint since improvement in PFS is a valuable endpoint to establish clinical benefit. Also, overall survival as a primary endpoint would have likely failed to detect a treatment effect in the GRID trial due to its cross-over design.

The secondary variable, OS is also a well-recognised endpoint for clinical activity in patients with advanced stage solid tumours and serious or life threatening diseases. The safety assessments used in this study included those considered standard of care for patients with metastatic and/or unresectable gastrointestinal stromal tumours and were appropriate for patient safety and for assessing toxicity.

All efficacy variables related to tumour response and disease progression were evaluated by central radiology evaluation based on Response Evaluation Criteria In Solid Tumours (RECIST) (v1.1), with the following modifications: no lymph nodes and no bone lesions were chosen as target lesions, and PET scan was not considered acceptable for radiological evaluation. Moreover, a progressively growing new tumour nodule within a pre-existing tumour mass must be expanding on at least two sequential imaging studies or must be at least 2 cm in size and a new active lesion (e.g. enhancing with contrast or other criteria to rule out artefact) in order to be considered as evidence of progression.

Radiological evaluation included a computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis and met the standard of care for the imaging of lesions in the respective organ system(s).

Measurable tumour lesions were defined as those that could be accurately measured in at least one dimension [redacted]. Tumour lesions situated in a previously irradiated area were not considered measurable unless there had been demonstrated progression in the lesion.

Target lesions - All measurable lesions, excluding lymph nodes or bone lesions, up to a maximum of 2 lesions per organ and 5 lesions in total (lesions with the longest diameter), representative of all involved organs were identified as target lesions and recorded and measured at baseline. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions was calculated and reported as the baseline sum diameters. This was used as the reference to further characterise any objective tumour regression. If there were > 5 measurable lesions, those not selected as target lesions were considered together with non-measurable disease as non-target lesions.

Non-target lesions – Included all non-measurable lesions (or sites of disease) plus any measurable lesions over and above the 5 listed as target lesions. Measurements were not required but these lesions were noted at baseline and followed as “present”, “absent”, or in rare cases “unequivocal progression”.

Table 15. GRID trial – primary and secondary endpoints and measures (8;10;36)

Endpoint	Timing of assessments	Definition of Measure
Primary Endpoint		
Progression-free survival (PFS)	Tumour assessments were made at baseline, then every 4 weeks for the first 3 months, every 6 weeks for the months 4 to 6, and every 8 weeks thereafter until the end of study drug administration. An investigator assessment was also made at each evaluation. Only investigator assessments were made during the open-label period.	The date of randomisation to the date of first observed radiological progression according to blinded central radiology review, or death due to any cause, if death occurred before progression. The actual date of radiological assessment was used as the date of progression. Patients without tumour progression or death at the time of analysis were censored at their last date of radiological tumour assessment. PFS was assessed by central radiology reviewers who were masked to assignment and data from patients. Two readers reviewed the images. Adjudication by another radiology reviewer was used when only one reader assessed a progression or when the date of progression was discordant between the two independent readers.
Secondary Endpoints		
Overall Survival (OS)	Assessment of survival status was performed every 3 months.	The date of randomisation until the date of death due to any cause. If a patient was alive at the date of database cut-off, then it was censored at the database cut-off date. All patients were followed for survival until death was documented, except for those who specifically withdraw consent to follow-up.
Time to progression (TTP)	See primary endpoint for tumour assessment timing.	The date of randomisation until the date of radiological progression. Patients without tumour progression at the time of analysis were censored at their last date of radiological tumour assessment. The date of progression was the date of first observation of progression.
Tumour response rate (OR)		The proportion of patients with the best overall tumour response of partial response (PR) or complete response (CR) according to RECIST version 1.1 criteria that is achieved during treatment or within 30 days after termination of study medication.
Disease control rate (DCR)		The rate of complete response or partial response plus stable disease lasting for at least 12 weeks.
Duration of response (DOR)		The number of days from the date of first documented objective response of PR or CR, whichever is noted earlier, to first disease progression or death before progression. Patients without progression or death before progression at the time of analysis were censored at the date of their last tumour assessment.

Endpoint	Timing of assessments	Definition of Measure
Safety and tolerability: adverse events, physical examinations, vital signs, ECOG performance status, and laboratory assessments	Days 1 and 15 of each treatment cycle for the first six cycles. Cardiac function was assessed with 12-lead electrocardiogram (ECG) at screening, day 1 of the first two treatment cycles (and subsequent cycles at the discretion of the investigator), and at treatment end.	Investigators rated severity of adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) [NCI CTCAE V4.0]. NCI-CTCAE version 4.0 is harmonised with the Medical Dictionary for Regulatory Activities (MedDRA) Terminology v12.0) at the AE term level and is widely used within the oncology research community as the standard for documentation and analysis of AEs occurring in cancer research, for defining protocol parameters such as maximum tolerated dose, dose modification, and for comparison of safety profiles between interventions.
Exploratory endpoints		
Health-related quality of life (HRQoL)	At baseline (Day 1 of Cycle 1), on day 1 of cycles 2-4, and day 1 of every other cycle thereafter and within 14 days at the end of treatment.	Health-related quality of life questionnaires (EORTC QLQ-C30 and EuroQoL EQ-5D) were routinely completed by patients. EORTC QLQ-C30 was developed to assess the quality of life of cancer patients. It has been translated and validated into 81 languages and is used in more than 3,000 studies worldwide. The EORTC QLQ-C30 includes five functional scales (physical, role, emotional, social, and cognitive functioning), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status scale, and a number of single items assessing additional symptoms (dyspnoea, sleep disturbances, constipation, and diarrhoea), and perceived financial impact. Higher scores (range 0-100) represent a higher level of functioning and better HRQoL. A change of ≥10 points on the EORTC QLQ-C30 scale is considered clinically meaningful (38;39) . EuroQoL EQ-5D is a standardised instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. The EQ-5D contains a descriptive system which measures five health dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each dimension contains three levels of response to reflect the degree of problems patients have experienced: no problem (level 1), some problems (level 2), and extreme problems (level 3). These five health dimensions are summarised into a single score, the EQ-5D index score. A change of 0.07 to 0.12 points on the EQ-5D index and a change of 7 to 12 points on the VAS are considered as clinically meaningful (39).
Pharmacokinetics of regorafenib	Day 15 of cycles 1 and 2	Performed in patients from selected sites ONLY.

Endpoint	Timing of assessments	Definition of Measure
Biomarker evaluation of regorafenib	At screening, on day 1 and day 15 of cycle 1, day 15 of subsequent cycles, and at the end of treatment)	Including tumour genotype for mutational status of target oncogene. ONLY in patients who gave genetic consent.
Secondary PFS during open label treatment	Only investigator assessments were made during the open-label period.	The time from first progression until second progression or death, whatever came first, during or after open-label treatment with regorafenib per investigator assessment

4.3.2 Provide a comparative summary of the methodology of the RCTs in a table. A suggested table format is presented below.

The GRID study is the only Phase III trial available for regorafenib in the treatment of GIST who progressed on or are intolerant to prior treatment with imatinib and sunitinib. A summary of trial methodology is displayed in Table 16.

Table 16. Summary of trial methodology

Trial number (acronym)	Study 14874 (GRID)
Location	• Asia: China; Japan; Singapore; South Korea; • Rest of the World: Austria; Belgium; Canada; Netherlands; Poland; Spain; United Kingdom; United States Finland; France; Germany; Israel; Italy;
Trial design	Randomized, double-blind, placebo-controlled, multi-centre, cross-over Phase 3 study to evaluate the efficacy and safety of regorafenib in patients with metastatic and/or unresectable GIST whose disease had progressed despite prior treatments with at least imatinib and sunitinib. Patients must have shown objective disease progression or intolerance to imatinib, as well as disease progression while on sunitinib treatment. See section 4.3.1 for more details

Eligibility criteria for participants	The following criteria were used to evaluate patients for inclusion in the study: 1. Male or female patients ≥ 18 years of age. 2. Patients with histologically confirmed metastatic and/or unresectable GIST. 3. At least imatinib and sunitinib as prior treatment regimens, with objective disease progression or intolerance to imatinib, as well as disease progression while on sunitinib therapy. Additionally, disease progression or intolerance to other systemic therapies, as well as investigational new agents, is allowed, except prior treatment with any other vascular endothelial growth factor receptor (VEGFR) inhibitor. 4. Patients were to have at least one measurable lesion according to modified RECIST, version 1.1. A lesion in a previously irradiated area is eligible to be considered as measurable disease as long as there was objective evidence of progression of the lesion prior to study enrolment. 5. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1. 6. Adequate bone marrow, liver, and renal function as assessed by the following laboratory requirements conducted within 7 days of starting study treatment: – Total bilirubin ≤ 1.5 x the upper limit of normal (ULN). Documented Gilbert syndrome was allowed if total bilirubin is mildly elevated (< 6 mg/dL). – Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3.0 x ULN (≤ 5 x ULN for patients with liver involvement of their GIST). – Lipase ≤ 1.5 x the ULN – Serum creatinine ≤ 1.5 x the ULN. – Glomerular filtration rate (GFR) ≥ 30 ml/min/1.73 m2 according to the Modified Diet in Renal Disease (MDRD) abbreviated formula. – International normalized ratio (INR) ≤ 1.5 x ULN and partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN. – Patients who are being treated with an anti-coagulant, such as warfarin or heparin, were allowed to participate provided that no prior evidence of an underlying abnormality in these parameters exists. Close monitoring of at least weekly evaluations will be performed until INR and PTT are stable based on a pre-dose measurement as defined by the local standard of care. – Platelet count ≥ 100000/cubic millimetres $(mm)^3$, haemoglobin (Hb) ≥ 9.0 g/dl, absolute neutrophil count (ANC) ≥ 1500/mm^3. Transfusion of patients to meet the inclusion criteria was not allowed.

Trial number (acronym)	Study 14874 (GRID)
	– Alkaline phosphatase limit ≤ 2.5 x ULN (≤ 5 x ULN for patients whose cancer involved their liver). 7. Recovery to NCI-CTCAE v4.0 grade 0 or 1 level or recovery to baseline preceding the prior treatment from any previous drug/procedure-related toxicity (except alopecia, anaemia, and hypothyroidism).
Settings and locations where the data were collected	The study was conducted at 57 study centres in 17 countries.
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])** **Permitted and disallowed concomitant medication**	The following investigational products were used in the study: • Regorafenib, 40 mg tablets • Placebo tablets matching in appearance Patients randomized to regorafenib were 133 and received 160 mg po od for 3 weeks of every 4 week (28 day) cycle (intermittent dosing: 3 weeks on/1 week off treatment). Each 160 mg dose consisted of four 40 mg tablets Patients randomized to the placebo arm were 66 and were treated with 4 matching placebo tablets for 3 weeks of every 4 week cycle (i.e., 3 weeks on/1 week off). Missed or vomited tablets could not be compensated for by treatment at a later date/time with the dose missed or a second dose (if vomited).
Primary outcomes (including scoring methods and timings of assessments)	See Table 15
Secondary/tertiary outcomes (including scoring methods and timings of assessments)	See Table 15
Pre-planned subgroups	• Progression-free survival was evaluated in subgroups of geographic region, prior line of treatment, age, sex, baseline BMI, duration of imatinib treatment, ECOG performance status, and mutational status • Overall survival was evaluated in subgroups of geographic region, prior line of treatment, age, sex, baseline BMI, duration of imatinib treatment, ECOG performance status, and mutational status.

4.4 *Statistical analysis and definition of study groups in the relevant randomised controlled trials*

4.4.1 During completion of this section consider items 7a (sample size), 7b (interim analyses and stopping guidelines), 12a (statistical methods used to compare groups for primary and secondary outcomes) and 12b (methods for additional analyses, such as subgroup analyses and adjusted analyses) of the CONSORT checklist.

Primary efficacy analysis was performed at data cut-off 26 January 2012, when the predetermined criteria of 144 PFS events were reached.

The overall survival analysis was performed as of the cut-off date of 08 June 2015, when approximately 160 deaths had occurred.

The primary population for efficacy analysis was the intention-to-treat (ITT) population. The population for safety analysis consisted of all patients who received at least one dose of study medication.

As reported in Table 17, study analysis sets included:

- Intention-to-treat (ITT)
- Safety analysis set (SAF)
- Patient Reported Outcome analysis set (PROAS)

Table 17. Definition of all data analysis sets

Analysis set	Definition	Number of valid patients in treatment group	
		Regorafenib + BSC	Placebo + BSC
Intention-to-treat (ITT)	All randomised patients	N=133 (100%)	N=66 (100%)
Safety analysis set (SAF)	All randomised patients who received at least one dose of study medication	N=132* (99.2%)	N=66 (100%)
Patient Reported Outcome analysis set (PROAS)	All FAS patients with evaluable PRO assessments at baseline and at least one post-baseline assessment.	N=123 (92.5%)	N=62 (93.9%)

*One patient in the regorafenib group was not treated with study drug

4.4.2 For each trial listed, provide details of the trial population included in the primary analysis of the primary outcome and methods used to take account of missing data (for example, a description of the intention-to-treat analysis carried out, including censoring methods, or whether a per-protocol analysis was carried out).

The primary population for the efficacy analysis was the full analysis set (FAS) population, which was defined as all randomized patients and comprised 199 patients, including 66 patients randomized to placebo + BSC and 133 patients randomized to regorafenib + BSC.

Methods used to take account of missing data are discussed in section 4.4.3.

4.4.3 For each trial, provide details of the statistical tests used in the primary analysis. Also provide details of the primary hypothesis or hypotheses under consideration, the power of the trial and a description of sample size calculation, including rationale and assumptions in a table. If the outcomes were adjusted for covariates, provide the rationale. A suggested table format is presented below.

The null hypothesis that both treatment arms have the same PFS distribution was tested against the alternative hypothesis that the distribution of PFS times in the regorafenib arm is different from the control arm according to the Lehmann alternative.

Statistical analysis - primary outcomes

The PFS of the two treatment groups (regorafenib vs. placebo) was compared using a stratified log rank test with a one-sided alpha of 0.01 stratified by the same stratification factors as used for randomisation (i.e. prior therapies and geographical region). The Kaplan-Meier method was used to calculate estimates of median times

to PFS, and hazard ratios (HRs) and 95% confidence intervals (CIs) derived from a Cox proportional hazard model.

Analysis was performed when the predetermined criteria of 144 PFS events were reached (data cut-off of 26 January 2012): 81 events among the 133 patients (61%) in the regorafenib group and 63 events among the 66 patients (95%) in the placebo group.

Sensitivity analysis

These included, a PFS comparison considering only the first 122 PFS events as initially planned in the protocol, PFS unstratified analyses and PFS analyses based on local investigators assessment.

Sample size, power calculation

Sample size was based on the primary efficacy endpoint PFS. With 199 patients randomised, assuming a target treatment effect of 100% improvement in PFS, a randomisation ratio of 2:1 (regorafenib to placebo), a one-sided alpha of 0.01, and a power of 0.94, 144 events were needed for the final PFS analysis. Other assumptions included exponential distribution of the PFS event times, median time of PFS in the control group of [redacted] months, and a [redacted]% drop-out rate of patients evaluable for PFS.

Missing data, patient withdrawals (8;18)

Missing or not evaluable tumour assessments (including a scheduled assessment that was not done, and an incomplete assessment that did not result in an unambiguous tumour response according to modified RECIST v1.1) were not used in the calculation of derived efficacy variables unless a new lesion occurred, or the lesions that were evaluated already showed progressive disease (PD). No imputation was performed for missing lesion assessment and tumour response. For example, if a patient missed a scan visit and PD was documented at the next

available scan visit, the actual visit date of the first documented PD was used. If a date was incomplete, such as only the year and month were available, day 15 of the month was used for the calculation.

Patient withdrawals

Table 18 summarises the reasons for discontinuation of treatment during the double-blind and open-label phases of the GRID study (as of data cut-off for the primary efficacy analysis). Table 19 summarises patient disposition as at the overall survival analysis of 08 June 2015.

At the time of the primary efficacy analysis, 38 patients (29%) in the regorafenib group and seven (11%) patients in the placebo group discontinued study treatment, during the double-blind period. The most common reason for termination of study treatment was radiologically confirmed disease progression.

Table 18. Primary reason for discontinuation during the GRID study – as at 26 January 2012 cut-off (ITT) (8)

	Regorafenib + BSC N=133 n (%)	**Placebo + BSC N=66 n (%)**	**Total N=199 n (%)**
Study drug never administered	1 (0.8%)	0 (0%)	1 (0.5%)
Started double-blind treatment	**132 (99.2%)**	**66 (100.0%)**	**199 (99.5%)**
Discontinued double-blind treatment but no open-label	**38 (28.6%)**	**7 (10.6%)**	**45 (22.6%)**
Adverse event not associated with clinical disease progression	3 (2.3%)	0	3 (1.5%)
Adverse event associated with clinical disease progression	5 (3.8%)	4 (6.1%)	9 (4.5%)
Progressive disease – radiological progression	20 (15.0%)	2 (3.0%)	22 (11.1%)
Progressive disease – clinical progression	1 (0.8%)	1 (1.5%)	2 (1.0%)
Non-compliance with study medication	2 (1.5%)	0	2 (1.0%)
Consent withdrawn	4 (3.0%)	0	4 (2.0%)
Lack of efficacy	1 (0.8%)	0	1 (0.5%)
Death	2 (1.5%)	0	2 (1.0%)
Double-blind treatment ongoing as of data cut-off	**53 (39.8%)**	**3 (4.5%)**	**56 (28.1%)**
Started open-label treatment period	**41 (30.8%)**	**56 (84.8%)**	**97 (48.7%)**
Discontinued open-label treatment	**17 (12.8%)**	**23 (34.8%)**	**40 (20.1%)**
Adverse event not associated with clinical disease progression	0	3 (4.5%)	3 (1.5%)
Adverse event associated with clinical disease progression	2 (1.5%)	1 (1.5%)	3 (1.5%)
Progressive disease – radiological progression	12 (9.0%)	11 (16.7%)	23 (11.6%)
Progressive disease – clinical progression	0	2 (3.0%)	2 (1.0%)
Physician decision	2 (1.5%)	0	2 (1.0%)
Consent withdrawn	0	5 (7.6%)	5 (2.5%)
Death	1 (0.8%)	1 (1.5%)	2 (1.0%)
Ongoing with open-label treatment with regorafenib	**24 (18.0%)**	**33 (50.0%)**	**57 (28.6%)**

Table 19. Primary reason for discontinuation during the GRID study – as at 08 June 2015 cut-off (ITT) (14) no data on last placebo patient w/d from double-blind phase

	Regorafenib+ BSC N=133 n (%)	**Placebo+ BSC N=66 n (%)**	**Total N=199 n (%)**
Study drug never administered	1 (0.8%)	0 (0%)	1 (0.5%)
Started double-blind treatment	**132 (99.2%)**	**66 (100.0%)**	**198 (99.5%)**
Discontinued double-blind treatment but no open-label	[redacted]	[redacted]	[redacted]
Adverse event not associated with clinical disease progression	3 (2.3%)	0	3 (1.5%)
Adverse event associated with clinical disease progression	[redacted]	4 (6.1%)	9 (4.5%)
Progressive disease – radiological progression	[redacted]	2 (3.0%)	22 (11.1%)

	Regorafenib+ BSC N=133 n (%)	Placebo+ BSC N=66 n (%)	Total N=199 n (%)
Progressive disease – clinical progression	1 (0.8%)	1 (1.5%)	2 (1.0%)
Non-compliance with study medication	2 (1.5%)	0	2 (1.0%)
Consent withdrawn	4 (3.0%)	0	4 (2.0%)
Lack of efficacy	1 (0.8%)	0	1 (0.5%)
Death	2 (1.5%)	0	2 (1.0%)
Double-blind treatment ongoing as of data cut-off	**0**	**0**	**0**
Started open-label treatment period	[redacted]	**58 (87.9%)**	**149 (74.9%)**
Discontinued open-label treatment	[redacted]	[redacted]	[redacted]
Adverse event not associated with clinical disease progression	[redacted]	[redacted]	[redacted]
Adverse event associated with clinical disease progression	[redacted]	[redacted]	[redacted]
Progressive disease – radiological progression	[redacted]	[redacted]	[redacted]
Progressive disease – clinical progression	[redacted]	[redacted]	[redacted]
Physician decision	[redacted]	[redacted]	[redacted]
Consent withdrawn	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Protocol deviation / Non-compliance with study drug	[redacted]	[redacted]	[redacted]
Switching to other therapy	[redacted]	[redacted]	[redacted]
Ongoing with open-label treatment with regorafenib	[redacted]	[redacted]	[redacted]

Statistical analysis – secondary, tertiary and other endpoints

TTP and OS were analysed with the same log-rank test as PFS, using the same stratification factors. Overall response rate and DCR were analysed with the Cochran-Mantel-Haenszel test. DOR was descriptively analysed only.

A pre-planned interim analysis of overall survival was done at the time of the final PFS analysis. Overall survival estimates were calculated using the Kaplan-Meier method. An updated analysis of OS, was performed as of the cut-off date of 08 June 2015, when approximately 160 deaths had occurred. For the updated analysis of OS, a secondary analysis was performed which applies the Rank Preserving Structural Failure Time (RPSFT) method and the Iterative Parameter Estimate (IPE) method to correct for the effect of cross-over of patients from the placebo treatment to regorafenib treatment on the OS endpoint. Results are described descriptively and the HR, 95% confidence interval and Kaplan-Meier curves were reported.

Health Related Quality of life / Patient Reported Outcomes (PRO) data as measured by the EORTC QLQ-C30 and EuroQoL EQ-5D were analysed using an analysis of covariance (ANCOVA) model, comparing the time-adjusted AUCs between the two treatment groups with covariates for baseline HRQoL score and stratification factors. Least-squares mean estimates, standard errors, and 95% confidence intervals (CI) were estimated for each treatment group and for the treatment group difference. Sensitivity analysis using different imputation methods for imputing missing assessments and additional exploratory analyses may be carried out using the linear mixed effect models to explore the effects of treatment, time, and other covariates on the endpoints, assuming the missing data mechanism is missing at random.

Safety parameters and remaining exploratory endpoints were analysed by treatment group with descriptive statistics only.

Subgroup analyses

The following subgroups were analysed for PFS, OS and safety parameters:

- Stratification levels: third line of treatment, fourth line of treatment and beyond
- Geographical region: Asia, rest of world (non-Asia); also North America (USA, Canada [CAN]) vs. not-North America
- Age: < 65 years, ≥ 65 years
- Sex: male, female
- ECOG performance status: 0, 1
- Body mass index (BMI) (kg/m2): <25, 25≤ BMI <30, 30≤ BMI
- Duration of treatment with imatinib (months): < 6, ≥6-<18, ≥18
- Mutationally-defined subgroups: initial KIT Exon 11 mutation, initial KIT Exon 9 mutation

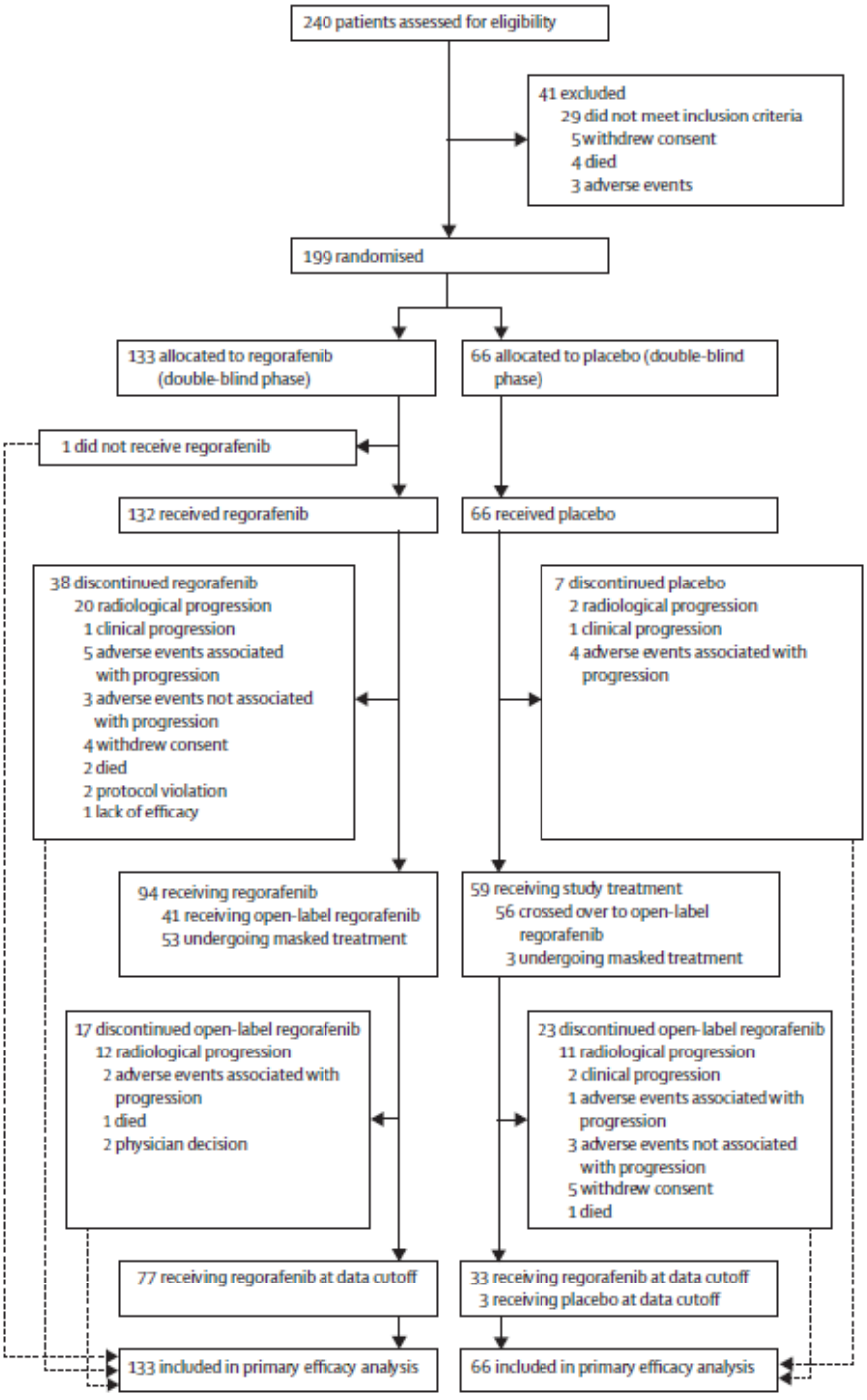
4.5 *Participant flow in the relevant randomised controlled trials*

4.5.1 Provide details of the numbers of participants who were eligible to enter the trials. Include the number of participants randomised and allocated to each treatment. Provide details of and the rationale for participants who crossed over treatment groups, were lost to follow-up or withdrew from the RCT. Provide a CONSORT diagram showing the flow of participants through each stage of each of the trials.

Disposition of study patients is reported in Figure 4.

.

Figure 4. Patient disposition (primary efficacy analysis; data cut-off 26 January 2012) (8)


240 patients assessed for eligibility
41 excluded
29 did not meet inclusion criteria
5 withdrew consent
4 died
3 adverse events
199 randomised
133 allocated to regorafenib (double-blind phase)
66 allocated to placebo (double-blind phase)
1 did not receive regorafenib
132 received regorafenib
66 received placebo
38 discontinued regorafenib
20 radiological progression
1 clinical progression
5 adverse events associated with progression
3 adverse events not associated with progression
4 withdrew consent
2 died
2 protocol violation
1 lack of efficacy
7 discontinued placebo
2 radiological progression
1 clinical progression
4 adverse events associated with progression
94 receiving regorafenib
41 receiving open-label regorafenib
53 undergoing masked treatment
59 receiving study treatment
56 crossed over to open-label regorafenib
3 undergoing masked treatment
17 discontinued open-label regorafenib
12 radiological progression
2 adverse events associated with progression
1 died
2 physician decision
23 discontinued open-label regorafenib
11 radiological progression
2 clinical progression
1 adverse events associated with progression
3 adverse events not associated with progression
5 withdrew consent
1 died
77 receiving regorafenib at data cutoff
33 receiving regorafenib at data cutoff
3 receiving placebo at data cutoff
133 included in primary efficacy analysis
66 included in primary efficacy analysis

In the GRID trial, patients who discontinue placebo could cross-over to treatment with regorafenib and being treated the same as those initially assigned to the active drug (follow-up every 6 weeks).

4.5.2 In a table describe the characteristics of the participants at baseline for each of the trials. Provide details of baseline demographics, including age, gender and relevant variables describing disease severity and duration and if appropriate previous treatments and concomitant treatment. Highlight any differences between trial groups. A suggested table format is presented below.

Baseline demographics and disease characteristics

As can be seen in Table 20, demographics and baseline disease characteristics were comparable between the regorafenib and the placebo groups. There were more males (64%) than females (36%), and patients ranged in age from 18 to 87 years (median age 60 years). The majority of patients were White (68%), followed by Asian (25%). The geographical distribution of the patients was wide: 24% of the patients were from Asia, and 76% from other regions including Europe (58%), North-America (18%), and Israel (0.2%).

Approximately 55% of patients had an ECOG performance status of 0, while 44.7% had a performance status of 1. The median time since most recent progression or relapse to randomisation was 5.84 weeks.

All patients in the placebo group and 132 (99.2%) patients in the regorafenib group had prior surgical treatment for cancer. One hundred and thirteen patients (113/199, 56.8%) had received two prior lines of treatment for metastatic and/or unresectable GIST (i.e. imatinib and sunitinib), and 43% (n=86) had received three or more previous lines of anticancer therapy for GIST. Most patients had been treated with imatinib for ≥18 months. However, a higher proportion of patients in the placebo group had received imatinib therapy for more than 18 months than in the regorafenib group. The most common location of the primary tumour site at initial diagnosis was the stomach (36.7%), followed by the jejunum (16.1%), and the ileum (11.6%).

Historical tumour samples were available for 96 patients (48.2%). Of patients with mutation biomarker data, 53.1% (51/96) had GIST with an initial pre-study baseline mutation in KIT exon 11, and 16% (15/96) had GIST harbouring an initial pre-study baseline mutation in KIT exon 9. Eight patients (8/96, 8.3%) were wild type (no KIT and no PDGFRα mutation).

Table 20. Characteristics of participants in the studies across treatment groups (GRID study, ITT)

Characteristic	Regorafenib + BSC (n=133)	Placebo + BSC (n=66)
Median Age	60 (51-67)	61 (48-66)
Age group n (%)		
<65 years	90 (67.7)	46 (69.7)
≥65 years	43 (32.3)	20 (30.3)
Sex		
Men	85 (64%)	42 (64%)
Women	48 (36%)	24 (36%)
Ethnic Group		
White	90 (68%)	45 (68%)
Black or African American	0	1 (2%)
Asian	34 (26%)	16 (24%)
Not reported or missing	9 (7%)	4 (6%)
Geographic Region		
Asia	32 (24.1%)	15 (22.7%)
Rest of world	101 (75.9%)	51 (77.3%)
Geographic Region		
North America	22 (16.5%)	14 (21.2%)
USA	15 (11.3%)	11 (16.7%)
Canada	7 (5,3%)	3 (4.5%)
Non-North America	111 (83.5%)	52 (78.8%)
ECOG performance status		
0	73 (55%)	37 (56%)
1	60 (45%)	29 (44%)
Time since initial diagnosis to randomisation		
Mean (range), weeks	296.4 (32.3-774)	310.6 (47.0-657)
Median, weeks	256.0	272.2
Time since recent progression / relapse to randomisation		
Mean (range), weeks	13.29 (0.7-145)	16.7 (0.4-421)
Median, weeks	6.34	4.27
Extent of disease at baseline		
Metastatic	90 (67.7%)	38 (57.6%)
Unresectable	5 (3.8%)	10 (15.2%)
Metastatic and unresectable	35 (26.3%)	14 (21.2%)
Missing	3 (2.3%)	4 (6.1%)
Histology		
Missing	5 (3.8%)	4 (6.1%)
Spindle cells	66 (49.6%)	30 (45.5%)
Epithelioid	12 (9.0%)	4 (6.1%)
Mixed	18 (13.5%)	10 (15.2%)
Unknown	32 (24.1%)	18 (27.3%)
Number of tumour sites		
1	16 (12.0%)	9 (13.6%)
2	31 (23.3%)	20 (30.3%)
3	39 (29.3%)	13 (19.7%)
4	21 (15.8%)	9 (13.6%)
≥5	26 (19,5%)	15 (22.7%)
Previous systemic anti-cancer therapy		
2 lines	74 (56%)	39 (59%)
>2 lines	59 (44%)	27 (41%)
Duration of previous imatinib therapy		
≤ 6 months	18 (14%)	4 (6%)

Characteristic	Regorafenib + BSC (n=133)	Placebo + BSC (n=66)
6–18 months	26 (20%)	7 (11%)
> 18 months	89 (67%)	55 (83%)
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		

4.6 *Quality assessment of the relevant randomised controlled trials*

4.6.1 The validity of the results of an individual RCT will depend on the robustness of its overall design and execution, and its relevance to the decision problem. The quality of each RCT identified in section 4.2 should be appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The quality assessment will be validated by the Evidence Review Group.

Provide the information specified in sections 4.6.2–4.6.4.

4.6.2 Describe the methods used for assessing risk of bias and generalisability of individual RCTs (including whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.

- The following are the minimum criteria for assessment of risk of bias and generalisability in parallel group RCTs, but the list is not exhaustive:
  - Was the randomisation method 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 blind to treatment allocation, 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?
- Consider how closely the RCT(s) reflects routine clinical practice in England.
- In addition to parallel group RCTs, there are other randomised designs (for example, randomised crossover trials and randomised cluster trials) in which further quality criteria may need to be considered when assessing bias. Key aspects of quality to be considered can be found in Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).

Table 21 presents a quality assessment of the GRID study, which was completed to the highest standard with adequate randomisation and blinding procedures.

The complete quality assessment of the GRID study is presented in Appendix 3.

Table 21. Quality assessment results for GRID

Trial number (acronym)	GRID study
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	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 / Yes / Yes

The patient population in this trial represents a group of patients in clinical practice in England and Wales, who typically have very few treatment options. The design of the GRID study reflects such a patient situation, in the inclusion/exclusion criteria and also in the selection of comparator i.e. placebo. The dose of regorafenib given in the study, including any modifications due to toxicity reflect the recommendations within the Summary of Product Characteristics (SmPC; see Appendix 1), which would be expected to be followed within clinical practice.

4.6.3 If there is more than 1 RCT, tabulate a summary of the responses applied to each of the quality assessment criteria. A suggested table format for the quality assessment results is presented below.

There is only 1 RCT. Quality assessment for the GRID study is presented in section 4.6.2.

4.6.4 The complete quality assessment for each RCT should be included in an appendix.

A complete quality assessment of the GRID study is included in Appendix 3.

4.7 *Clinical effectiveness results of the relevant randomised controlled trials*

4.7.1 Data from intention-to-treat analyses should be presented whenever possible and a definition of the included participants provided. If participants have been excluded from the analysis, the rationale for this should be given.

Results for the primary and secondary efficacy endpoint are reported 'as of the database cut-off date of 26 January 2012'. The overall survival analysis was performed as of the cut-off date of 08 June 2015, when approximately 160 deaths had occurred (14).

Primary efficacy endpoint

Progression-free survival (PFS)

The primary endpoint of the study, PFS, was met. According to blinded central review, median PFS for regorafenib patients was 4.8 months (interquartile range [IQR] 1.4-9.2) and for placebo patients was 0.9 months (IQR 0.9-1.8) (Hazard ratio [HR] 0.27, 95% CI 0.19-0.39; p<0.000001). The relative risk of disease progression or death was therefore reduced by 73% in the regorafenib group compared to the placebo group and the difference in PFS between treatment groups was statistically significant.

At 3 months the percentage of patients surviving without progression was 60% (95% CI 51–68) for regorafenib vs. 11% (95% CI 3–18) for placebo. At 6 months the percentage of patients surviving without progression was 38% (95% CI 29–48) for regorafenib vs. 0% (95% CI 0–0) for placebo.

At the time of analysis, after 144 events had occurred, the percentage of patients who experienced a disease progression event or death in the regorafenib group (n=81, 60.9%) was considerably lower than in the placebo group (n=63, 95.5%).

Sensitivity analyses

The results of the sensitivity analyses were supportive of and consistent with the primary analysis of PFS, showing statistically significant improvement in the regorafenib group compared with the placebo group.

Using the investigator's assessment, a significant improvement in median PFS of 7.4 months (IQR 2.7–not calculable) in the regorafenib group compared to 1.7 months (0.9–2.7) in the placebo group (HR 0.22, 95% CI 0.14–0.35; p<0.0001) was observed.

Secondary endpoints

Overall Survival (OS) - Final analysis (database cut-off 08 June 2015) (14)

A total of 162 events had occurred, 109 events (82.0%) in the regorafenib group and 53 events (80.3%) in the placebo group. Median OS time was 17.4 months in both treatment groups. The estimated OS hazard ratio of regorafenib to placebo was 0.909 (95% CI: 0.653 to 1.265). However, 58 (87.9%) patients in the placebo group crossed over to regorafenib treatment.

Given the relatively high number of patients who crossed over from placebo to open-label regorafenib, adjustments for cross-over were necessary. When the RPSFT and IPE correction models were employed to correct for the effect of cross-over from the placebo to the regorafenib arm, median OS time was longer in the regorafenib group (529 days or 17.4 months) than in the placebo group (338 days or 11.1 months IPE; 361 days or 11.9 months RPSFT) (Table 22). The estimated corrected hazard ratio of regorafenib to placebo using the RPSFT and IPE correction methods were 0.616 (95% CI 0.435, 0.871) and 0.586 (95% CI 0.417, 0.824), respectively.

Hazard ratios of OS for the ITT primary analysis and final analyses demonstrated an extension of survival times under regorafenib treatment relative to placebo. The survival prolongation at the final analysis (uncorrected and corrected) was smaller than at the primary analysis (uncorrected and corrected), which is most likely due to

the continuous cross-over of placebo patients to regorafenib treatment after progression.

Table 22. Summary of overall survival analyses for the GRID study, including uncorrected and corrected cross-over analyses (ITT) (14)

	Data cut-off 26 January 2012		Data cut-off 08 June 2015	
	Regorafenib + BSC (N=133)	***Placebo + BSC (N=66)***	**Regorafenib + BSC (N=133)**	**Placebo + BSC (N=66)**
Number of patients (%) with event	*29 (21.8%)*	*17 (25.8%)*	[redacted]	[redacted]
Number of patients (%) censored	*104 (78.2%)*	*49 (74.2%)*	[redacted]	[redacted]
Median overall survival (days), uncorrected	*A*	*A*	529	529
Median overall survival (days), corrected RPSFT[a]	*A*	*A*	529	361
Median overall survival (days), corrected IPE[b]	*A*	*A*	529	338
Range (days, without censored values): uncorrected	*(9 – 255)*	*(10 – 207)*	[redacted]	[redacted]
Range (days, without censored values): corrected RPSFT[a]	*(9 – 255)*	*(10 – 247)*	[redacted]	[redacted]
Range (days, without censored values): corrected IPE[b]	*(9 – 255)*	*(10 – 152)*	[redacted]	[redacted]
Hazard ratio: uncorrected	*0.772*		0.909	
95% CI for hazard ratio: uncorrected	*(0.423, 1.408)*		(0.653, 1.265)	
p-value (one-sided) from log rank test): uncorrected	*0.198896*		0.285777	
Hazard ratio: corrected RPSFT[a]	*0.537*		0.616	
95% CI for hazard ratio: corrected RPSFT[a]	*(0.286, 1.007)*		(0.435, 0.871)	
p-value (one-sided) from log rank test): corrected RPSFT[a]	*0.024725*		0.002862	
Hazard ratio: corrected IPE[b]	*0.565*		0.586	
95% CI for hazard ratio: corrected IPE[b]	*(0.302, 1.055)*		(0.417, 0.824)	
p-value (one-sided) from log rank test): corrected IPE[b]	*0.034931*		0.000949	

BSC=best supportive care; CI=confidence interval; IPE=iterative parameter estimation; ITT=intention-to-treat; RPSFT=rank preserving structural failure time
a Corrected for the effect of cross-over from the placebo to the regorafenib arm on the OS endpoint by RPSFT method
b Corrected for the effect of cross-over from the placebo to the regorafenib arm on the OS endpoint by IPE method
c Using the RPSFT cross-over correction method, the number (%) of patients with an event in the placebo group is 51 (77.3%)
d Using the RPSFT cross-over correction method, the number (%) of patients censored in the placebo group is 15 (22.7%)
A Value cannot be estimated due to censored data
Hazard ration is (regorafenib / placebo). Hazard ratio and its 95% CI was based on stratified Cox Regression Model

Time to progression (TTP)

The percentage of patients with disease progression was 93.9% in the placebo group and 57.1% in the regorafenib group (cut-off date of 26 January 2012). Median

TTP was 165 days (5.4 months) in the regorafenib group and 28 days (0.9 months) in the placebo group (HR 0.248, [95% CI: 0.170-0.364, p<0.000001]).

The results of an additional analysis where time to progression was evaluated according to investigators' assessment were consistent with the analysis according to central assessment (HR 0.197, p<0.000001, median TTP was 224 days vs. 52 days (7.4 vs. 1.7 months) with regorafenib and placebo, respectively.

Objective Response rate (OR), Disease Control Rate (DCR) and Duration of Response (DOR)

No cases of complete response (CR) were observed in either arm. Overall response (OR) rate was not statistically significant different between the two treatment arms: 4.5% with regorafenib (PR n= 6/133) versus 1.5% with placebo (PR n=1/66) (difference= -2.99%; 95% CI: -7.70%, 1.72%; p=0.142097).

The occurrence of stable disease as best response (occurring at any time and for any duration) was more than twice as high in regorafenib treated patients 71.4% (95 of 133 patients) compared with placebo treated patients 33.3% (22 of 66 patients).

[redacted]. The rate of stable disease was higher in regorafenib treated patients (75.9%) compared with placebo treated patients (56.1%).

Disease Control Rate (DCR: CR+PR+SD) was 52.6% (n=70/133) for the regorafenib group compared with 9.1% (n=6/66) in the placebo group (95% CI: –54.72, –32.49; p<0.0001), suggesting that regorafenib is associated with clinically meaningful tumour control in patients with advanced GIST after failure of all other approved tyrosine-kinase inhibitor therapies.

Sensitivity analysis: [redacted].

The median duration of response (central assessment) for regorafenib-treated patients was 99 days. Only one placebo treated patient reported PR and duration of response duration was 30 days.

Maximum percent reduction in the size of target lesions

As expected, more patients in the regorafenib group had reduction or stabilisation of their target lesion compared to the placebo group. [redacted].

Exploratory endpoints

Secondary PFS (SPFS)

Median secondary PFS for the placebo arm (56 patients who crossed over to regorafenib) and the regorafenib arm (41 patients who continued on regorafenib) was 151 days (5.0 months) and 137 days (4.5 months), respectively. Continued treatment with regorafenib may be clinically beneficial, as it appears to delay further disease progression.

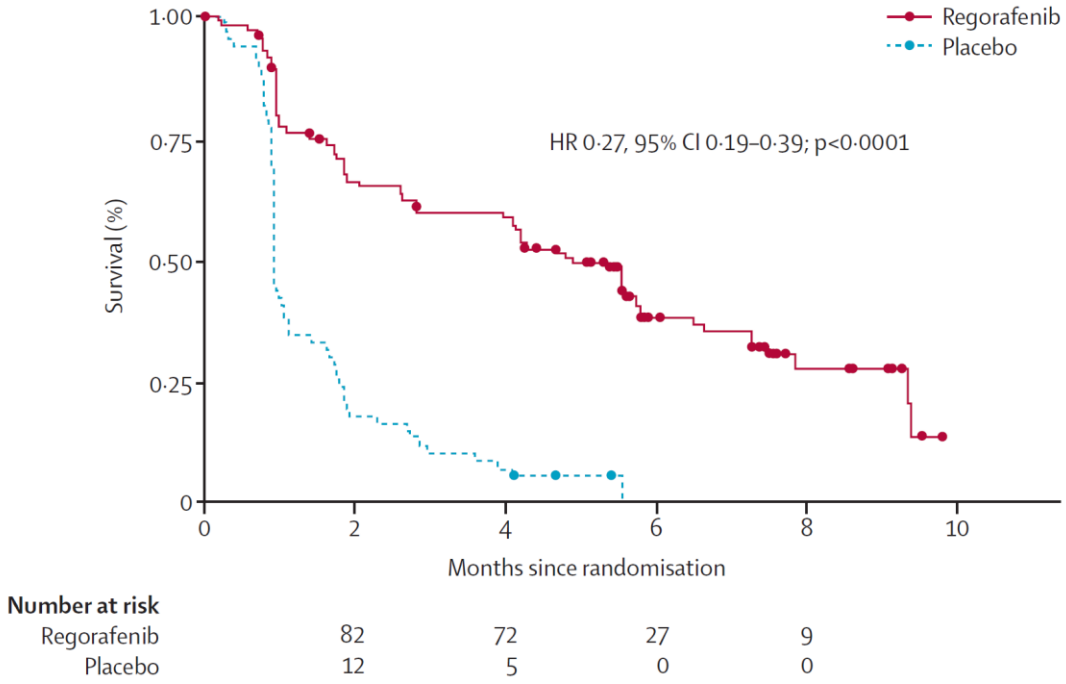
Kaplan-Maier plots are reported in section 4.7.2.

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

Progression-free survival (PFS)

Figure 5 displays the KM estimates by treatment group for PFS (144 PFS events). The estimated KM demonstrates that PFS rate was consistently higher in the regorafenib group compared to the placebo group.

Figure 5. KM estimates of the PFS rate (144 events) during the GRID trial, (central assessment, ITT) (8)



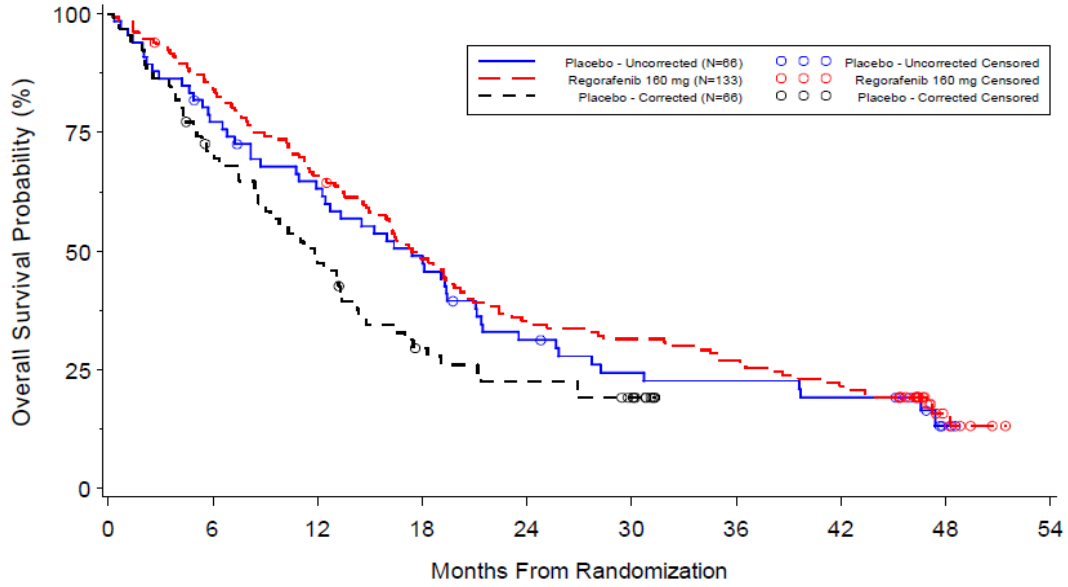
See section 4.8 for subgroup analysis of PFS.

Overall Survival (OS) - Final analysis (database cut-off 08 June 2015) (14)

The Kaplan-Meier plot for OS not adjusted for the cross-over to regorafenib is displayed in Figure 6. Kaplan-Meier plots for OS adjusted for the cross-over when using the RPFST and IPE methods are presented in Figure 7 and Figure 8, respectively.

Figure 6. Overall Survival (KM; ITT; data cut-off 08 June 2015) (14)

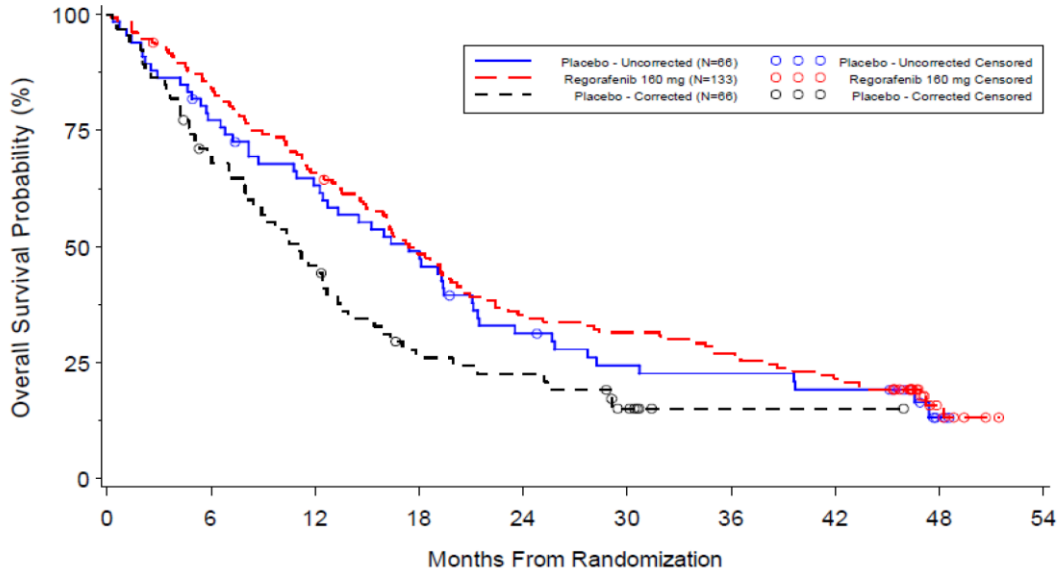
Figure 7. Overall Survival, cross-over correction by RPSFT method (ITT; data cut-off 08 June 2015) (14)



Patients at Risk

Placebo – Uncorrected	50	40	31	19	14	13	11	2
Regorafenib 160 mg	111	87	63	46	41	35	28	6
Placebo – Corrected	45	31	17	13	9	0	0	0

Figure 8. Overall Survival, cross-over correction by IPE method (ITT; data cut-off 08 June 2015) (14)



Patients at Risk

Placebo – Uncorrected	50	40	31	19	14	13	11	2
Regorafenib 160 mg	111	87	63	46	41	35	28	6
Placebo – Corrected	44	29	15	13	6	1	1	0

Secondary PFS (SPFS)

The Kaplan-Meier plot for secondary PFS is reported in Figure 9.

Figure 9. KM curves of PFS during treatment with regorafenib by double blind and open label treatment groups

See section 4.8 for subgroup analysis of OS.

4.7.3 For each outcome, provide the following information from each study:

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed both as 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.
- The number of people in each group included in each analysis and whether the analysis was intention to treat. State the results in absolute numbers when feasible.

- When interim data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of the trial. Analytical adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may help interpret the results may be included, such as adherence to medication or study protocol.
- Discuss and justify any clinically important differences in the results between the different arms of a trial and between trials.
- Specify whether unadjusted and adjusted analyses were performed, and whether the results were consistent.

Patient reported outcomes

Overall, the HRQoL of patients receiving regorafenib was not significantly different from that of patients receiving placebo.

EORTC QLQ-C30

EORTC QLQ-C30 global health status was completed by 183 (92%) patients at baseline, 167 (84%) patients at cycle 2, and 126 (63%) patients at cycle 3. Mean changes in scores from baseline for the EORTC QLQ-C30 global health status (Table 23) and the 5 functional dimensions showed a slight deterioration in patients' quality of life of similar magnitude both in the regorafenib and placebo groups. Mean changes from baseline were not clinically meaningful (i.e. ≤10 points), except for the role function subscale in the regorafenib group. The analysis of time-adjusted AUC for the EORTC QLQ-C30 showed that there was no difference in the longitudinal evolution of the least-squares mean (LS Mean) total scores between placebo and regorafenib.

Table 23. EORTC QLQ-C30 change from baseline at cycles 2, 3, 4 (double-blind treatment period)

EORTC QLQC30 measure	Regorafenib + BSC group (N=123)		Placebo + BSC group (N=62)	
	n	Mean ± SD	n	Mean ± SD
Global health status (QoL)	123		60	
Cycle 2	113	-6.19 ± 23.59	54	-3.24 ± 23.87

EORTC QLQC30 measure	Regorafenib + BSC group (N=123)		Placebo + BSC group (N=62)	
	n	Mean ± SD	n	Mean ± SD
Cycle 3	96	-7.38 ± 23.97	30	-4.17 ± 23.75
Cycle 4	85	-6.57 ± 25.40	17	2.45 ± 21.80
EOT	15	-21.11 ± 24.87	2	-37.50 ± 5.89
Physical function	123		60	
Cycle 2	113	-7.17 ± 16.96	55	-5.36 ± 15.74
Cycle 3	97	-5.96 ± 19.21	31	-5.81 ± 15.75
Cycle 4	86	-7.24 ± 18.07	17	-4.90 ± 15.37
EOT	15	-12.89 ± 19.59	2	-73.33 ± 18.86
Role function	123		59	
Cycle 2	113	-17.70 ± 33.06	54	-5.56 ± 25.49
Cycle 3	97	-17.01 ± 30.52	31	-3.76 ± 32.97
Cycle 4	86	-13.95 ± 27.16	16	4.17 ± 33.05
EOT	15	-32.22 ± 41.53	2	-33.33 ± 0
Emotional function	123		60	
Cycle 2	112	-0.32 ± 15.25	54	-0.93 ± 19.34
Cycle 3	96	1.65 ± 16.82	31	0.81 ± 16.85
Cycle 4	85	2.25 ± 15.77	17	8.17 ± 16.62
EOT	15	-11.67 ± 22.23	2	-37.50 ± 5.89
Social function	123		60	
Cycle 2	112	-6.99 ± 24.26	55	-1.21 ± 27.56
Cycle 3	96	-6.42 ± 25.86	31	-6.45 ± 32.68
Cycle 4	85	-8.04 ± 25.41	17	-1.96 ± 26.27
EOT	15	-13.33 ± 29.00	2	-58.33 ± 35.36
Cognitive function	123		60	
Cycle 2	112	-4.13 ± 17.04	55	-3.03 ± 18.45
Cycle 3	96	-1.74 ± 16.13	31	-3.76 ± 22.65
Cycle 4	85	-0.39 ± 15.85	17	-4.90 ± 26.20
EOT	15	-5.56 ± 19.59	2	-25.0 ± 11.79

BSC: Best Supportive Care; EORTC: European Organisation for Research and Treatment of Cancer; QoL: Quality of Life; QLQ-C30: Core Quality of Life Questionnaire; SD: Standard Deviation

EQ-5D

EQ-5D Questionnaire was completed by 182 (91%) patients at baseline, 163 (82%) patients at cycle 2, and 128 (64%) patients at cycle 3 (Table 24). Mean changes in scores from baseline for EQ-5D index and VAS were, overall, similar between the regorafenib and placebo groups. The differences in mean scores from baseline reflected a deterioration in health status for both groups. For both the EQ-5D and the VAS, only the changes from baseline at EOT were clinically important (based on the minimum clinically important difference). Analysis of time-adjusted AUC for the EQ-

5D index and VAS showed that regorafenib treatment maintained patients' health-related quality of life.

Table 24. EQ-5D assessment at cycles 2,3,4 of double-blind period

Utility measure	Regorafenib + BSC group (N=123)			Placebo + BSC group (N=62)		
	n	Mean (SD)	Change from baseline	n	Mean (SD)	Change from baseline
EQ-5D Index						
Baseline (Cycle 1, Day 1)	122	0.779 (0.240)	-	60	0.751 (0.195)	-
Cycle 2, Day 1	109	0.736 (0.218)	-0.050	54	0.699 (0.293)	-0.058
Cycle 3, Day 1	96	0.744 (0.218)	-0.042	32	0.705 (0.319)	-0.066
Cycle 4, Day 1	84	0.738 (0.277)	-0.045	16	0.891 (0.141)	-0.040
EQ-VAS						
Baseline (Cycle 1, Day 1)	123	69.46 (20.79)	-	61	67.36 (20.31)	-
Cycle 2, Day 1	112	66.75 (21.46)	-3.955	54	67.04 (21.21)	-0.944
Cycle 3, Day 1	97	66.90 (19.14)	-3.577	31	67.75 (25.41)	0.258
Cycle 4, Day 1	85	67.45 (21.37)	-2.612	16	76.94 (20.38)	4.313

BSC: Best Supportive Care; EOT: End of Treatment; EQ-5D: European Quality of Life - 5 Dimensions; EQ-VAS: European Quality of Life – Visual Analogue Score; FAS: Full Analysis Set; SD: Standard Deviation

To comply with a request from the health authorities, the mean changes from baseline for the EORTC QLQ-C30 and the EQ-5D were also analysed in regorafenib-treated patients with dose reduction vs. those without any dose modification (including 26 and 44 patients, respectively). No difference was found in the health-related QoL between the two groups.

EQ-5D data were used to derive health state utility values in patients with advanced gastrointestinal stromal tumours refractory to imatinib and sunitinib therapy (40). An explanation on the use of EQ-5D data to derive health state utility values is reported in detail in section 5.

Mutational analyses

Historical mutation data were available from 48% of all randomised patients in the GRID study, of which 53% had a tumour with a mutation in KIT Exon 11, 16% had a tumour with a mutation in KIT Exon 9, and 8% had no KIT and no PDGFR mutation (WT GIST).

The data show consistent treatment benefit for regorafenib versus placebo in all biomarker subgroup analyses, which is further supported by insignificant interaction p-values between subgroup and treatment.

As reported in section 4.8.4, mutational analyses indicated that both exon 9 mutant and exon 11 mutant subgroups fare better on regorafenib compared to placebo with respect to PFS:

- KIT Exon 11 (HR of 0.21; 95% CI: 0.10, 0.46)
- KIT Exon 9 (HR of 0.24; 95% CI: 0.07, 0.88)

4.8 *Subgroup analysis*

This section should be read with the NICE guide to the methods of technology appraisal, sections 5.10.1–5.10.12.

4.8.1 Provide details of any subgroup analyses carried out. Specify the rationale and whether they were pre-planned or post-hoc.

Progression-free survival

Progression-free survival was evaluated in subgroups of geographic region, prior line of treatment, age, sex, baseline BMI, duration of imatinib treatment, ECOG performance status, and mutational status.

Overall survival

Overall survival was evaluated in subgroups of geographic region, prior line of treatment, age, sex, baseline BMI, duration of imatinib treatment, and ECOG performance status. The subgroup analysis was also corrected for the effect of crossover from the placebo to the regorafenib arm on the OS endpoint using the RPSFT model and the IPE method.

Further details on subgroup analyses and their results can be found in section 4.8.4.

4.8.2 Clearly specify the characteristics of the participants in the subgroups and explain the appropriateness of the analysis to the decision problem.

Subjects in the full analysis set, defined as all randomized patients, could be represented in more than one subgroup. Baseline demographics for the subjects in the full analysis set are presented in section 4.5.2.

4.8.3 Provide details of the statistical tests used in the primary analysis of the subgroups, including any tests for interaction.

Statistical tests used in the primary analysis were based on descriptive statistics, log-rank test p-values, and hazard ratio estimates with 95% confidence.

4.8.4 Provide a summary of the results for the subgroups, with full details provided in an appendix.

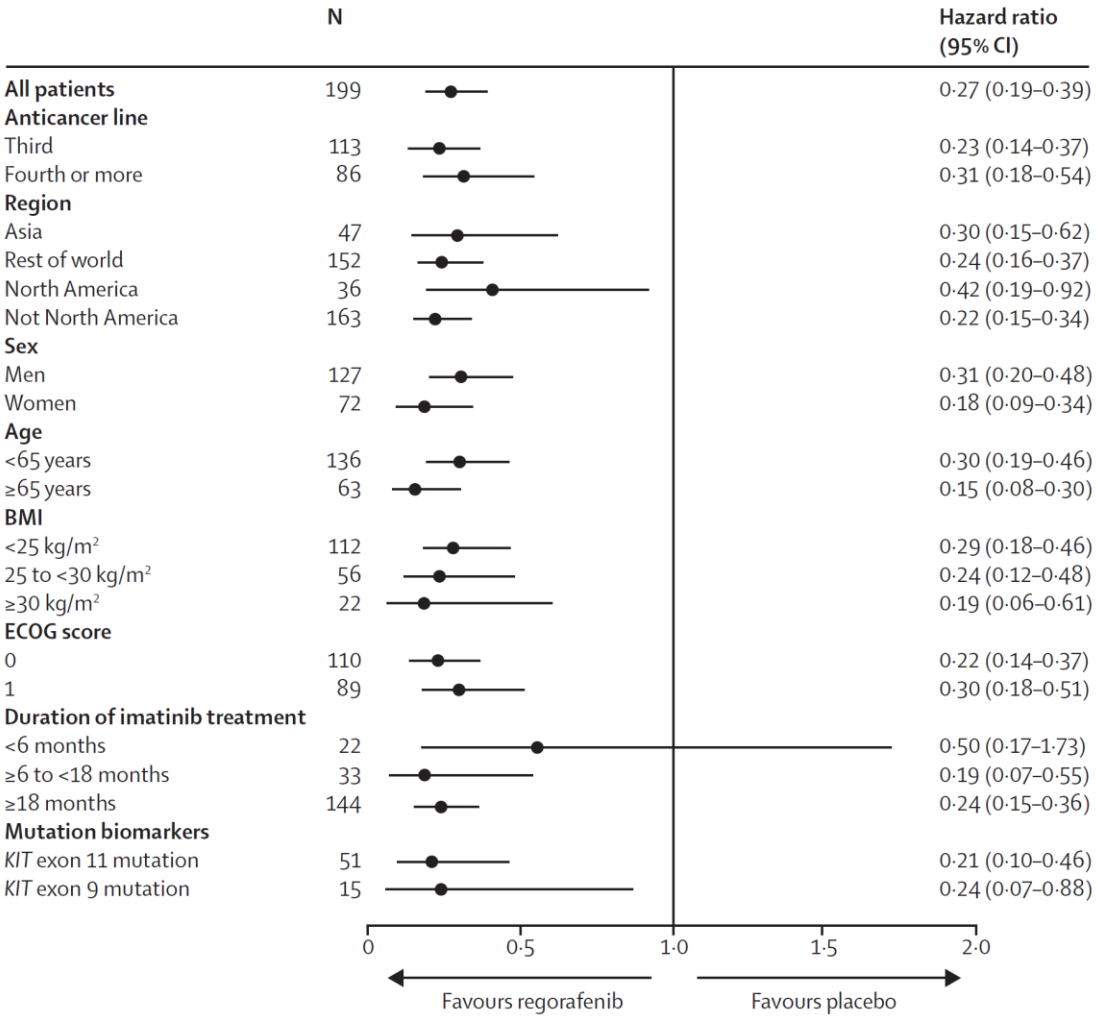
Progression-free survival

Efficacy analysis in pre-specified subgroups showed robustness in the benefit of regorafenib compared with placebo in nearly all subgroups with median PFS being substantially longer in the regorafenib group compared to the placebo group, except for the small subset of patients with duration of imatinib treatment of less than 6 months (see Figure 10). This subgroup of patients is very small, with only 22 patients. Hazard ratios in the subgroups ranged from 0.15 to 0.50 indicating a 50% to 85% relative risk reduction of disease progression or death for regorafenib-treated patients compared with placebo-treated patients in the subgroups. These results demonstrate regorafenib has a clinical benefit in a wide range of patients with metastatic and/or unresectable GIST.

Regorafenib had similar benefit for patients receiving treatment either as third-line therapy or as fourth or later line of therapy when compared with placebo. A possible explanation is that regorafenib targets several pathways contributing to GIST pathogenesis, which might block resistance mechanisms (41).

Further efficacy subgroup analyses were performed to respond to requests from health authorities including PFS analyses of patients with varying grades of hypertension, patients with varying mitotic index scores and of patients with dose modifications. There was no correlation between hypertension and PFS. Higher grades of hypertension did not lead to longer PFS. Due to low patient numbers, no conclusions can be drawn from the correlation of mitotic index and PFS. Median PFS times in patients in the regorafenib group who had dose modifications (dose reduction, dose interruption, duration of dose interruption) were also similar to those in the overall primary analysis (37).

Figure 10. Progression-free survival by subgroup (8)



BSC=best supportive care; ECOG=Eastern Cooperative Oncology Group

Overall survival (08 June 2015 data cut-off) (18)

Because of the low number of events in some of the subgroups, confidence intervals resulted being larger. For this reason, and because 58 (87.9%) of patients in the placebo + BSC group crossed over to regorafenib treatment, results must be interpreted with caution.

Consistently across all subgroups of geographic region, prior line of treatment, age, sex, baseline BMI, duration of imatinib treatment (with the exception of a small subgroup of patients who received imatinib < 6 months), and ECOG performance status, hazard ratios for subgroups in the corrected OS analyses (RPSFT and IPE) were similar to those of the corrected overall OS analysis, and showed a prolongation of median OS in the regorafenib group vs. placebo, irrespective of subgroup (see Figure 11,

Figure **12**, and Figure 13).

Figure 11. Overall survival by subgroup, uncorrected (data cut-off 08 June 2015) (14)

Figure 12. Overall survival by subgroup, RPSFT correction (data cut-off 08 June 2015) (14)

Figure 13. Overall survival by subgroup, IPE correction (data cut-off 08 June 2015) (14)

More details on the results of the subgroup analyses are reported in Appendix 4.

4.9 *Meta-analysis*

This section should be read with the NICE guide to the methods of technology appraisal, sections 5.2.8–5.2.11. For further information on how to implement the approaches described in the guide, see the series of technical support documents produced by the NICE Decision Support Unit about evidence synthesis.

Not applicable. Evidence from only one RCT was available for analysis and relevant to the decision problem (GRID study) (8).

Provide the information specified in sections 4.9.1–4.9.3.

4.9.1 If a qualitative overview is considered to be appropriate, summarise the overall results of the individual studies with reference to their critical appraisal.

Not applicable.

4.9.2 If a meta-analysis has been performed, include the following in the results:

- The characteristics and possible limitations of the data (that is, population, intervention, setting, sample sizes and the validity of the evidence) should be fully reported for each study included in the analysis and a forest plot included.
- A statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to explain the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using either a fixed effects or random effects model as appropriate.
- Provide an adequate description of the methods of statistical combination and justify their choice.

- Carry out sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

Not applicable.

4.9.3 If any of the relevant studies listed in section 4.2 are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each excluded study has on the overall meta-analysis should be explored.

Not applicable.

4.10 *Indirect and mixed treatment comparisons*

This section should be read with the NICE guide to the methods of technology appraisal, sections 5.2.12–5.2.18.

The principles of good practice for carrying out systematic reviews and meta-analyses should be carefully followed for indirect and mixed treatment comparisons. In brief, a clear description of the methods of synthesis and the rationale for how RCTs of the technology and the comparators are identified, selected and excluded is needed.

For further information on how to implement the approaches described in the NICE methods guide, see the series of technical support documents produced by the NICE Decision Support Unit about evidence synthesis.

Provide the information specified in sections 4.10.1–4.10.19.

Search strategy

4.10.1 Provide details of the search strategies used to identify trials included in the indirect comparison and network meta-analyses. As a guide, provide details of the following in an appendix:

- the eligibility criteria
- a list of all information sources
- full electronic search strategies for all databases
- a flow diagram providing details of the process for selecting studies; number of studies identified through searches, number of studies screened, number assessed for eligibility and the number included in the review with reasons for exclusion at each stage.

Evidence on the clinical benefits and adverse effects of regorafenib in patients with metastatic and/or unresectable GIST who have progressed after therapy with at least imatinib and sunitinib, was provided by the placebo-controlled study, GRID. As there is no recognised or recommended standard treatment for metastatic and/or unresectable GIST who have progressed after therapy with at least imatinib and sunitinib, an indirect comparison was not possible.

Study selection

4.10.2 Provide details of the treatments to be compared. This should include all treatments identified in the final NICE scope. If additional treatments have been included, the rationale should be provided. For example, additional treatments may be added in order to make a connected network.

Not applicable.

4.10.3 In a table, describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. Justification should be provided to ensure that the rationale for study selection is transparent. A suggested table format is provided below.

Not applicable.

4.10.4 In a table provide a summary of the trials used to carry out the indirect comparison or mixed treatment comparison. A suggested table format

is presented below. When there are more than 2 treatments in the comparator sets for synthesis, show a network diagram.

Not applicable.

4.10.5 If the table or network diagram provided in response to section 4.10.4 does not include all the trials that were identified in the search strategy, the rationale for exclusion should be provided.

Not applicable.

Methods and outcomes of included studies

4.10.6 Provide the rationale for the choice of outcome measure chosen, along with the rationale for the choice of outcome scale selected.

Not applicable.

4.10.7 Discuss the populations in the included trials, especially if they are not the same as the populations specified in the NICE scope. If they are not the same:

- provide a rationale to justify including the study
- describe the assumptions made about the impact or lack of impact this may have on the relative treatment effect
- explain whether an adjustment has been made for these differences.

Not applicable.

4.10.8 Describe whether there are apparent or potential differences in patient populations between the trials. If this is the case, explain how this has been taken into account.

Not applicable.

4.10.9 In an appendix, provide the following for each trial included in response to section 4.10.4:

- table(s) of the methods
- table(s) of the outcomes and the results
- table(s) of participants' baseline characteristics.

Not applicable.

Risk of bias

4.10.10 In an appendix, provide a complete quality assessment of each trial included in response to section 4.10.4.

Not applicable.

4.10.11 Identify any risk of bias within the trials identified, and describe any adjustments made to the analysis.

Not applicable.

Methods of analysis and presentation of results

4.10.12 Provide a clear description of the indirect or mixed treatment comparison methodology. If the company considers that an indirect treatment comparison or mixed treatment comparison is inappropriate, the rationale should be provided and alternative analyses explored (for example, naive indirect comparison or a narrative overview). Refer to the NICE guide to the methods of technology appraisal, sections 5.2.16–5.2.18.

Not applicable.

4.10.13 Supply any programming language in an appendix (for example the WinBUGS code).

Not applicable.

4.10.14 For examples of how to present the results of the analysis, see the NICE Decision Support Unit technical support documents 1-3.

Not applicable.

4.10.15 Provide the results of the analysis.

Not applicable.

4.10.16 Provide the results of the statistical assessment of heterogeneity. The degree of heterogeneity, and the reasons for it, should be explored as fully as possible.

Not applicable.

4.10.17 Justify the choice of random or fixed effects model.

Not applicable.

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

Not applicable.

4.10.19 Discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

Not applicable.

4.11 *Non-randomised and non-controlled evidence*

RCTs directly comparing the technology being appraised with relevant comparators provide the most valid evidence of relative efficacy. However, such evidence may not always be available and may not be sufficient to quantify the effect of treatment over the course of the disease. Therefore, data from non-randomised and non-controlled studies may be needed to supplement RCT data.

List of relevant non-randomised and non-controlled evidence

Provide the information specified in sections 4.11.1 and 4.11.2.

4.11.1 In a table present the list of non-randomised and non-controlled evidence (for example, experimental and observational data) considered relevant to the decision problem and justify including each study. A suggested table format is presented below.

Evidence of relative efficacy from GRID study directly comparing regorafenib plus BSC vs placebo plus BSC is sufficient to evaluate the effect of the treatment over the course of the disease. The five single-arm studies (42-46) selected after the full text review included limited information and patient numbers. No non-randomised and non-controlled evidence was needed to supplement the GRID study data.

4.11.2 If trials listed above have been excluded from further discussion, 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 data required, this should be stated.

Summary of methodology of the relevant non-randomised and non-controlled evidence

It is expected that all key aspects of methodology will be in the public domain; if a company wishes to submit aspects of the methodology in confidence, prior agreement must be obtained from NICE.

4.11.3 Provide a comparative summary of the methodology of the studies in a table.

Not needed.

Statistical analysis of the non-randomised and non-controlled evidence

4.11.4 For non-randomised and non-controlled evidence such as observational studies, the potential biases should be identified before data analysis, either by a thorough review of the subject area or

discussion with experts in the clinical discipline. Ideally these should be quantified and adjusted for.

Not needed.

Participant flow in the studies

4.11.5 In a table describe the characteristics of the participants at baseline for each of the studies. Provide details of baseline demographics, including age, gender and relevant variables describing disease severity and duration and if appropriate previous treatments and concomitant treatment. Highlight any differences between study groups. A suggested table format is presented below.

Not needed.

Quality assessment of the relevant non-randomised and non-controlled evidence

4.11.6 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 identified in section 4.11.1 should be quality appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The quality assessment will be validated by the Evidence Review Group.

Provide the information specified in sections 4.11.7–4.11.9.

4.11.7 Describe the methods used for assessing risk of bias of individual studies (including whether this was done at the study or outcome level) and how this information is to be used in any data synthesis. For the quality assessments of non-randomised and non-controlled evidence, 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 (University of

York Centre for Reviews and Dissemination). This includes information on a number of initiatives aimed at improving the quality of research reporting.

Not needed.

4.11.8 If there is more than 1 non-randomised or non-controlled study, tabulate a summary of the responses applied to each of the quality assessment criteria.

Not needed.

4.11.9 A complete quality assessment for each study should be included in an appendix.

Not needed.

Clinical effectiveness results of the relevant non-randomised and non-controlled evidence

4.11.10 Data from trial analyses should be presented whenever possible and a definition of the included participants provided. If participants have been excluded from the analysis, the rationale for this should be given.

Not needed.

4.11.11 The information may be presented graphically to supplement text and tabulated data.

Not needed.

4.11.12 For each outcome, provide the following information from each study:

- The unit of measurement.
- The size of the effect.
- A 95% confidence interval.
- The number of participants.

- When interim 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 study. 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 or study protocol.
- Include whether unadjusted and adjusted analyses were performed, and whether the results were consistent.

Not needed.

4.12 *Adverse reactions*

4.12.1 Evidence from comparative RCTs and regulatory summaries is preferred, but 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 reactions commonly associated with the comparator, or that the occurrence of adverse reactions is not statistically significantly different to those associated with other treatments.

Evidence of the safety and tolerability of regorafenib in addition to BSC, compared to placebo plus BSC, in patients with GIST who had been previously treated with imatinib and sunitinib, is provided by safety analyses and adverse event (AE) reporting from the international, multicentre, randomised placebo-controlled, double-blind phase 3 GRID study (8;10;14;18) .

The design, methodology, descriptions of all endpoints, and efficacy results from the GRID study are detailed earlier in section 4. Safety and tolerability were assessed by analysis of adverse events, physical examinations, vital signs, ECOG performance status, and laboratory assessments, on days 1 and 15 of each treatment cycle for the first six cycles. Cardiac function was assessed with 12-lead electrocardiogram (ECG) at screening, day 1 of the first two treatment cycles (and subsequent cycles at

the discretion of the investigator), and at treatment end. Investigators rated severity of adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) [NCI CTCAE V4.0].

The primary safety analyses in the GRID study included treatment-emergent adverse events (TEAEs) that occurred during the double-blind period (up until the primary efficacy analysis cut-off date 26 January 2012). The safety analysis set (SAF) comprised 198 patients who had received at least one dose of study medication (regorafenib, n=132; placebo, n=66).

Secondary analyses included:

1. TEAEs for all regorafenib-treated patients, which includes 132 patients randomised to regorafenib during double-blind phase, and 58 patients initially randomised to placebo who crossed over to regorafenib in the open-label portion of the study (a total of 190 patients) (up until cut-off date 08 June 2015) and

2. TEAEs for the subgroup of patients with > 1 year of regorafenib treatment (n=75)

During the double-blind treatment period, among patients included in the safety analyses (data cut-off 26 January 2012), the median and mean actual time under study treatment were 15.96 weeks (range 0.1-38.3) and 15.03 weeks (SD = 8.628), respectively. The median and mean actual time under study treatment during the double blind and open label period were 18.66 weeks (range 0.1-38.3) and 17.54 weeks (SD = 9.13). The median and mean daily dose were 146.8 mg (range 88-160) and 139.79 mg (SD = 22.94) respectively, for regorafenib, and 160 mg (range 139-160) and 159.49 mg (SD = 2.99) respectively, for placebo (18).

Among the placebo patients who crossed over to open-label treatment with regorafenib (data cut-off 08 June 2015), the median treatment duration with regorafenib was 30.9 weeks (mean 46.6 weeks) (mean daily dose of regorafenib was 140.27 mg). The median treatment duration with regorafenib, for regorafenib-treated patients randomised to the regorafenib treatment group during both double-

blind and open-label treatment (n=132), was [redacted] weeks (mean [redacted] weeks) (mean daily dose of regorafenib was [redacted] mg). The median treatment duration with regorafenib, for all regorafenib-treated patients across both study periods (n=190) was [redacted] weeks (mean [redacted] weeks) (mean daily dose of regorafenib was [redacted]mg) (14).

Provide the information specified in sections 4.12.2–4.12.4.

4.12.2 In a table, summarise adverse reactions reported in the studies listed in section 4.2. For each intervention group, give the number with the adverse reaction and the frequency, the number in the group, and the percentage with the reaction. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse reaction.

Adverse events that started or worsened during treatment (including during 30 days after the last dose) were considered 'treatment emergent' (TEAE). If open-label treatment started within this 30 day window, then only AEs occurring until and including the first day of open-label dose were included in the double-blind primary safety analysis (18).

The majority of patients experienced at least one TEAE during the double-blind period of the study (regorafenib, n=132 [100%]; placebo, n=61 [92%]). A high rate of TEAEs in both groups is expected for this pre-treated advanced/metastatic GIST patient population. The most commonly occurring TEAEs were associated with disorders of the gastrointestinal system ([redacted]), general and administrative site conditions ([redacted]), skin and subcutaneous tissues ([redacted]), and vascular system ([redacted]). A similar pattern was observed in the secondary analyses in all regorafenib-treated patients i.e. TEAEs experienced by 100% of all regorafenib-treated patients (gastrointestinal disorders ([redacted]), skin and subcutaneous tissues ([redacted]), general and administrative site conditions ([redacted]), and vascular system ([redacted]).

The most commonly reported TEAEs (≥10%; any grade) are summarised in Table 25. These are presented as those 1) occurring during the double-blind period 2) for patients treated at any time with regorafenib and 3) for the subgroup of patients who received regorafenib for > 1 year. In the regorafenib arm, in any analyses, the most commonly occurring TEAEs were Palmar-Plantar Erythrodysaesthesia Syndrome (PPES; otherwise known as the hand-foot skin reaction (HFSR)), hypertension, fatigue, and diarrhoea.

Table 25. TEAEs (all grade) occurring in ≥10% regorafenib patients during GRID study (NCI CTCAE; SAF) (14;18)

	Double-blind treatment (data cut-off 26 January 2012)		**Data cut-off 08 June 2015**	
	Regorafenib + BSC	**Placebo + BSC**	**Regorafenib-treated at any time during study**	**Subgroup treated with regorafenib for >1 year**
	N=132 n (%)	**N=66 n (%)**	**N=190 n (%)**	**N=75 n (%)**
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Blood and Lymphatics Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac	[redacted]	[redacted]	[redacted]	[redacted]
Ear and Labyrinth	[redacted]	[redacted]	[redacted]	[redacted]
Endocrine Hypothyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal Abdominal pain Constipation Diarrhoea Dyspepsia Mucositis oral Nausea Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
General and Administrative Site Conditions Fatigue Fever Oedema limb Pain	[redacted]	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Infection and Infestations Bronchial infection Rash pustular Upper respiratory infection	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]
Investigations Alanine aminotransferase increased (ALT)	[redacted]	[redacted]	[redacted]	[redacted]

	Double-blind treatment (data cut-off 26 January 2012)		Data cut-off 08 June 2015	
	Regorafenib + BSC	Placebo + BSC	Regorafenib-treated at any time during study	Subgroup treated with regorafenib for >1 year
	N=132 n (%)	N=66 n (%)	N=190 n (%)	N=75 n (%)
Aspartate aminotransferase increased (AST) Blood bilirubin increased Platelet count decreased Weight Loss	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and Nutrition Anorexia Hyperglycaemia Hypokalaemia	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and Connective Tissue Arthralgia Back pain Myalgia Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]
Nervous System Dysgeusia Headache Paraesthesia	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders Insomnia			[redacted]	[redacted]
Renal and urinary Proteinuria	[redacted]	[redacted]	[redacted]	[redacted]
Reproductive system and breast disorders			[redacted]	[redacted]
Respiratory, Thoracic and Mediastinal Cough Dyspnoea Hoarseness Voice alteration	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue Alopecia Palmar-Plantar Erythrodysaesthesia Syndrome Pruritus Rash maculopapular	[redacted]	[redacted]	[redacted]	[redacted]
Vascular Hypertension	[redacted]	[redacted]	[redacted]	[redacted]

BSC=Best supportive care; TEAE=Treatment-emergent adverse event; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0; A patient may have experienced more than one TEAE.

The incidence of grade 3, 4, or 5 TEAEs (84.7% vs 88%), was similar among patients treated at any time or for > 1 year with regorafenib. The most common

grade 3 TEAEs by CTCAE term were hypertension, PPES (HFSR), and diarrhoea. The most common grade 4 TEAE was neutrophil count decreased.

Most of the TEAEs in regorafenib-treated patients were considered drug-related. In the double-blind study phase, drug-related adverse events were reported in 130 (98%) patients in the regorafenib group and 45 (68%) patients in the placebo group. [redacted]. In all analyses, the most common drug-related AEs for regorafenib-treated patients were PPES (HFSR), hypertension, fatigue, diarrhoea, and oral mucositis.

Drug-related hand-foot skin reaction is also commonly associated with other multi targeted kinase inhibitors (33;47). In GRID, this adverse event was generally manageable with dose modifications and proper care of the affected skin area.

Adverse events of Special Interest (AESIs) and comparison with use in other indications

The safety profile of regorafenib is consistent across indications (GIST and metastatic colorectal cancer mCRC) (10). The toxicity profile was typical for a small molecule that induces inhibition of the VEGFR and other tyrosine kinase-mediated pathways: hypertension, skin (hand-foot syndrome, rash) and gastrointestinal toxicities (diarrhoea, mucositis). Haematologic toxicity is comparably limited.

Although known in this drug class, PPES (HFSR) and hypertension were reported substantially more often in GIST, than in mCRC. Given the longer exposure (median 22.9 weeks) in patients with GIST versus patients with mCRC (10.0 weeks), an explanation can be aggravation of the drug induced toxicity that has evolved during the early phase of treatment. HFSR events are generally mild to moderate in severity, easily manageable with dose interruptions and/or dose reductions, and are reversible in nature.

Adverse events of special interest included: acute cardiac events, hypertension, liver dysfunction, severe proteinuria and renal failure, clinically significant bleeding, and skin reactions.

- Acute cardiac and ischaemic events were rare, occurring in 8 (4.2%) patients: One event of cardiac arrest (grade 5, possibly related; 7 events of acute coronary syndrome (grade 2, n=2; grade 3, n=5). All events were SAEs, and two were reported as drug-related. The majority of acute coronary syndrome events were managed with dose interruptions; none led to permanent discontinuation and none required dose reduction.

- Hypertension is a known class effect for this type of drug. Similar to other therapies targeting the VEGF/VEGFR pathway, the higher occurrence of hypertension in regorafenib-treated patients is probably related to antiangiogenic effects (33;47), and can be managed with dose modification and appropriate anti-hypertensive intervention. In the GRID study, overall, 65.3% of patients treated with regorafenib at any time had a reported TEAE of hypertension. Only one event of hypertension led to permanent discontinuation (worsening hypertension, drug-related grade 4 SAE). Hypertension was managed in some cases (13.2% of patients) by dose interruption; only 6 patients (3.2%) required dose reduction.

- Liver dysfunction was an expected event, but occurred infrequently. [redacted] Associated laboratory findings included a low incidence of grade 3 events of increased ALT ([redacted]), increased AST ([redacted]), and increased bilirubin ([redacted]). Grade 4 events of increased values for these analytes occurred in 2 ([redacted]) of patients for ALT and 1 ([redacted]) of patients for increased bilirubin (there were no reports of Grade 4 increased AST).

- Severe proteinuria is a known toxicity of this drug class, but occurred infrequently.

[redacted].

- Bleeding events - also known to be a class effect of this class of drug – were reported for 21.1% of regorafenib-treated patients. Most bleeding events were grade 1. The most common bleeding events were epistaxis, intraabdominal haemorrhage, and rectal haemorrhage (4 patients, 2.1%). One fatal gastric haemorrhage event was reported in context of disease progression.

- Hand skin foot reaction was observed in the majority of patients treated at any time with regorafenib (126 patients, 66.3%). Most were managed by dose reductions or interruptions; only 2 (1.1%) patients discontinued due to PPES (HFSR).

Serious adverse events (SAEs)

Serious adverse events were reported in 38 (29%) of 132 patients in the regorafenib group and 14 (21%) of 66 patients in the placebo group during the double-blind phase. In the secondary analyses, the incidence of serious adverse events (SAEs) was similar among patients treated at any time or for > 1year with regorafenib (54.2% vs. 52.0%). In all safety analyses, most SAEs were reported in the SOCs gastrointestinal, general and administrative site conditions, and infections and infestations.

[redacted].

Laboratory parameters

The vast majority of laboratory abnormalities were grade 1–2. Overall, the laboratory toxicity profile was consistent with known effects for this class of drug and with effects observed in the earlier phases of development of regorafenib.

The most common haematologic abnormality in patients treated with regorafenib at any time was anaemia (144 [77.0%] patients). Grade 3 events of anaemia were reported for 15 (8.0%) patients (no grade 4 events reported). The overall incidence of 'platelet count decreased' (all grades) was 18.2% (grade 4, n=1; grade 3, n=2).

The most common biochemical and renal abnormalities by CTCAE term (>40%) in patients treated with regorafenib at any time included: hyperglycaemia (93.0%), AST increased (67.6%), hypertriglyceridaemia (63.3%), hypoalbuminaemia (62.0%), hypophosphatemia (61.2%), alkaline phosphatase increased (57.4%), and ALT increased (48.9%).

The high incidence of hypophosphatemia is known for this class of drug, and was the most common grade 3 biochemical abnormality (22.9%).

[redacted]

Adverse events leading to withdrawal

AEs that led to permanent discontinuation of treatment were low. In the double-blind phase of the study, 9 patients discontinued due to an AE in the regorafenib-treated group (6.1%) versus 5 patients in the placebo group (7.6%). [redacted]

Most adverse events were manageable by dose modification without the need to discontinue treatment. [redacted]. The most frequent TEAEs leading to dose interruption (>5% of patients treated at any time) were PPES

(HFSR) (52 [27.4%]), hypertension (25 [13.2%]), diarrhoea (17 [8.9%]), fatigue (14 [7.4%]), and ALT increased (10 [5.3%]).

[redacted]. The most frequent TEAEs leading to dose reduction (>5% of patients treated at any time) were PPES (HFSR) (58 [30.5%]) and diarrhoea (13 [6.8%]).

Deaths

Overall, 5 deaths were reported as related to regorafenib treatment by investigators (cardiac arrest, acute hepatic failure, acute kidney injury, colonic perforation, and thromboembolic event).

[redacted].

Subgroup analyses (14)

Treatment-emergent AEs were evaluated by subgroups of geographic region, prior line of treatment, age, sex, race, baseline BMI, and ECOG performance status. In general, there were no major imbalances in incidence of TEAEs across the subgroups.

Main observed differences were:

- Asian subjects and the Asian geographic region had a higher incidence of PPES (HFSR) [redacted]

[redacted]. However, the Asian subgroups were small, therefore results must be interpreted with caution.

- Men had a higher incidence of hypertension than women.
- Patients with ECOG performance status 0 had a higher incidence of hypertension.
- [redacted]
- Patients with 4 or more lines of prior therapy had a higher incidence of PPES (HFSR)
- [redacted].

Open-label phase (14)

Overall, the AEs reported in the open-label period were similar to those observed in patients treated with regorafenib in the double-blind period, with the most commonly occurring AEs being PPES (HFSR), hypertension, fatigue, and diarrhoea.

Long-term safety (14)

The safety profile of patients on long-term regorafenib treatment (> 1 year; n=75) was comparable with the safety profile of the overall patient population, with no unexpected safety findings in this group of long-term treatment responders. [redacted].

For most AEs, the interval-specific event rates do not completely decrease to 0% in long-term regorafenib treatment, emphasising the need for the regular clinical monitoring of these patients.

[redacted].

For hypothyroidism, the decreasing but not completely absent event rates over time emphasise the label-defined regular monitoring recommendation of thyroid function during regorafenib treatment.

Of note, long-term responders showed around a [redacted] incidence rate in drug-related grade 3 events as compared to the overall patient population, mainly due to respective increases in grade 3 PPES (HFSR) and hypertension rates. The majority of these grade 3 events occurred within first months of treatment. Treatment discontinuation rates due to regorafenib-related events were comparable between long-term responders and overall patient population ([redacted]% vs [redacted]%), indicating that these events could be adequately managed by dose modifications.

4.12.3 Provide details of any studies that report additional adverse reactions to those reported in section 4.2. Include the following.

- Details of the methodology used for the identification, selection and quality assessment of the studies. See instructions in sections 4.1, 4.2 and 4.6.
- Examples of search strategies for specific adverse reactions or generic adverse-reaction terms. Key aspects of quality criteria for adverse reaction data can found in Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in an appendix.

- Details of the methodology of the studies. See instructions in sections 4.3–4.5 for the type of information required.
- Adverse reactions. In a table provide details of adverse reactions for each intervention group. For each group, give the number with the adverse reaction and the frequency, the number in the group, and the percentage with the reaction. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse reaction.

No supportive studies were considered with regard to the safety profile of regorafenib in metastatic and/or unresectable GIST which has progressed after therapy with at least imatinib and sunitinib.

4.12.4 Provide a brief overview of the safety of the technology in relation to the decision problem.

Regorafenib has been licenced and marketed since 2012 (US) / 2013 (Europe).

Adverse reactions in the GRID study were in line with the expected profile in a population of patients with GIST who have been previously treated with imatinib and sunitinib. In GRID, the majority of patients experienced at least one TEAE during the double-blind period of the study (regorafenib, n=132 [100%]; placebo, n=61 [92%]). A high rate of TEAEs in both groups is expected for this pre-treated advanced/metastatic GIST patient population.

AEs were also consistent with the known safety profile of regorafenib observed in metastatic colorectal cancer (mCRC) (10) and the drug class inducing inhibition of the VEGFR and other tyrosine kinase-mediated pathways e.g. skin (hand-foot syndrome, rash) and gastrointestinal toxicities (diarrhoea, mucositis).

Overall, treatment with regorafenib was not associated with a substantial reduction in patient reported quality of life compared to placebo. Most adverse events were manageable by dose modification without the need to discontinue treatment. AEs that led to permanent discontinuation of treatment were low.

HFSR events are generally mild to moderate in severity, easily manageable with dose interruptions and/or dose reductions, and are reversible in nature.

The most serious adverse drug reactions in patients receiving regorafenib were haemorrhage, severe liver injury, and gastrointestinal perforation. Although most cases of bleeding events in patients treated with regorafenib were mild to moderate in severity, this remains a disadvantage; however, it is deemed an acceptable AE in view of the nature of the disease and the lack of other available treatment options (10).

The safety profile of patients on long-term regorafenib treatment (> 1 year; n=75) was comparable with the safety profile of the overall patient population, with no unexpected safety findings. The majority of AEs occurred within first months of treatment with significantly decreased event rates in subsequent months. There remains a need, however, to continue regular clinical monitoring of these patients, as reflected in the 'Special warnings and precautions for use' section of the Summary of Product Characteristics (SmPC; see Appendix 1).

No major imbalances in incidence of TEAEs were observed across patient subgroups (e.g. geographic region, prior line of treatment, age, sex, race, baseline BMI, and ECOG performance status), suggesting that regorafenib-treatment can be administered in a broad spectrum of patients.

The safety of regorafenib is therefore demonstrated to be manageable in the context of the patient population in UK clinical practice defined in the decision problem, for whom there is a poor prognosis and no other standard treatment option.

4.13 *Interpretation of the clinical effectiveness and safety evidence*

When concluding the clinical effectiveness and safety evidence, provide the information specified in sections 4.13.1 and 4.13.2.

4.13.1 A statement of principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology.

Clinical evidence for the use of regorafenib in patients with unresectable or metastatic GIST who have progressed on or are intolerant to prior treatment with imatinib and sunitinib is based on the results of the pivotal phase 3 GRID study. This prospective, randomised, double-blind, placebo-controlled multicentre trial, showed a clinically relevant and significant prolongation of PFS, and disease control benefits in this poor prognosis patient population.

Median PFS was longer in the regorafenib group (+119 days) than in those treated with placebo group (4.8 months vs. 0.9 months) and regorafenib was associated with a 73% risk reduction of disease progression or death compared to treatment with placebo (hazard ratio [HR] 0.27, 95% CI 0.19–0.39; p<0.0001). The treatment effect of regorafenib was robust - consistent across all pre-specified subgroups analysed and by the various sensitivity analyses performed.

Median secondary PFS for the placebo arm (for those who crossed over to regorafenib) and the regorafenib arm was [redacted] days ([redacted] months) and [redacted] days ([redacted] months), respectively.

Median OS time was 529 days (17.4 months) in both treatment groups (HR = 0.909). However, 58 (87.9%) patients in the placebo group crossed over to regorafenib treatment, which could have confounded any potential difference in survival between groups. To correct for the effect of crossover from the placebo to the regorafenib arm on the OS endpoint, the data were analysed using two different correction methods: RPSFT and IPE. When these correction models were employed, median OS time was longer in the regorafenib group (529 days or 17.4 months) than in the placebo group (338 days or 11.1 months IPE [p = 0.00095]; 361 days or 11.9 months RPSFT [p = 0.00286]). The estimated corrected hazard ratio of regorafenib to placebo using the RPSFT and IPE correction methods were 0.616 and 0.586, respectively. Corrected hazard ratios of OS thus demonstrated an extension of survival times under regorafenib treatment relative to placebo.

Analyses of other secondary efficacy variables in the GRID study further substantiated primary efficacy results in demonstrating the efficacy of regorafenib over placebo. Median time to progression (TTP) was significantly longer in the regorafenib arm than in the placebo arm (5.4 months [165 days] versus 0.9 months [28 days], HR 0.248, 95% CI 0.170–0.364; p<0.000001). There was also a trend towards a higher response rate in the regorafenib group (4.5% vs. 1.5% for the placebo group), but the difference between treatment groups was not statistically significant; however, disease control rate (DCR) was significantly higher in the regorafenib group (52.6%) vs. the placebo group (9.1%) (one-sided p<0.000001). This is similar to other effective kinase inhibitors in TKI-resistant disease. TKIs primarily promote stable disease and are most effective in increasing the necrosis inside the tumour without shrinking its actual size.

Adverse events in the GRID study were in line with the expected safety profile in a population of patients with pre-treated advanced/metastatic GIST, and generally consistent with the known safety profile of regorafenib observed in metastatic colorectal cancer (mCRC) (10) and the drug class inducing inhibition of the VEGFR and other tyrosine kinase-mediated pathways e.g. skin (hand-foot syndrome, rash) and gastrointestinal toxicities (diarrhoea, mucositis). Overall, treatment with regorafenib was not associated with a substantial reduction in patient reported quality of life compared to placebo.

Common adverse events included hand-foot skin reaction (HFSR), hypertension, diarrhoea, mucositis and fatigue. These were generally manageable by dose modification without the need to discontinue treatment. AEs that led to permanent discontinuation of treatment were low. The most serious adverse drug reactions in patients receiving regorafenib were haemorrhage, severe liver injury, and gastrointestinal perforation.

Additional safety analyses showed no major imbalances in the incidence of AEs across pre-specified patient subgroups and also in patients who had received regorafenib treatment for over one year, suggesting that regorafenib-treatment can be administered in a broad spectrum of patients and on a long-term basis, if

necessary. The majority of AEs occurred within the first months of treatment with significantly decreased event rates in subsequent months (14). There remains a need, however, for regular clinical monitoring, as reflected in the 'Special warnings and precautions for use' section of the Summary of Product Characteristics (SmPC; see Appendix 1).

A key issue for clinicians involved in treating unresectable or metastatic GIST which has progressed on imatinib and sunitinib, is the poor prognosis for patients at this stage of disease due to the lack of effective treatment options. Regorafenib provides the clinical benefits of delaying disease progression, improving survival, and ameliorating symptoms in this difficult to treat patient population.

The safety profile of regorafenib is deemed acceptable and manageable. Market authorization approval in the EU was received in June 2014 (10)

4.13.2 A discussion of the strengths and limitations of the clinical evidence base for the technology. This should include the following:

- A brief statement on the internal validity of the studies included in the clinical evidence base.
- A brief statement on the external validity of the studies included in the clinical evidence base. Include the relevance of the evidence base to the decision problem and the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice. Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

Provide information about the life expectancy of people with the disease or condition in England and the source of the data. Also provide information on the number of people with the particular therapeutic indication for which the technology is being appraised. If the marketing authorisation includes other therapeutic indications for the technology, provide information about the numbers of people with these diseases or conditions in England and provide the source of the data.

This is to assess whether the technology may be suitable for consideration as a 'life-extending treatment at the end of life' as described in section 6.2.10 of the NICE guide to the methods of technology appraisal. Complete the table below and cross reference to where this information is found in the company submission.

A strength of the evidence base is that it was derived from a well-designed trial i.e. large (relative to this patient population), prospective, randomised, double-blind, placebo-controlled, multicentre, and adequately powered.

A further strength is that the efficacy and safety of regorafenib was corroborated across all subgroup and sensitivity analyses conducted, indicating the robustness of the results and its applicability to a broad spectrum of patients, as would be seen in clinical practice. Regorafenib demonstrated consistent PFS benefits, independent of the number of previous treatments, patient characteristics, and mutation status.

A perceived limitation to the evidence could be that there was no 'active' comparator in the study. Placebo was selected as a medically appropriate control group due to the lack of approved treatment options available to patients with metastatic or unresectable GIST after they have progressed on imatinib and sunitinib. This decision was accepted by the regulatory agencies and is supported by the recommendations in UK and other international guidelines, whereby patients are directed toward regorafenib treatment, BSC or clinical trial participation upon failure of imatinib and sunitinib treatment (26;35;48)

A limitation of the evidence base is that the secondary endpoint of overall survival is confounded by the crossover design of the study. At the time of initiation of the study, the available promising results in studies with regorafenib in metastatic or unresectable GIST previously treated with both imatinib and sunitinib, meant that the conduct of a placebo-controlled phase 3 study without the option for patients randomised to placebo to cross-over to open label regorafenib was unethical. Median OS time was 529 days (17.4 months) in both treatment groups (HR = 0.909). The crossing over of 58 (87.9%) patients from the placebo group to regorafenib

treatment upon disease progression is likely to have confounded this result. In order to correct for this effect of crossover from the placebo to the regorafenib arm, the data were analysed using two different correction methods: RPSFT and IPE. When these correction models were employed, median OS time was longer in the regorafenib group (529 days or 17.4 months) than in the placebo group (338 days or 11.1 months IPE [p = 0.00095]; 361 days or 11.9 months RPSFT [p = 0.00286]). The estimated corrected hazard ratio of regorafenib to placebo using the RPSFT and IPE correction methods were 0.616 and 0.586, respectively. Corrected hazard ratios of OS demonstrated an extension of survival times under regorafenib treatment relative to placebo.

The additional analysis point (08 June 2015; final analysis of overall survival) also provides information on the long-term safety of regorafenib in this patient population, with no unexpected safety findings.

Relevance of the evidence base to the decision problem and the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in routine clinical practice

The decision problem addressed in the submission is the clinical benefit and cost-effectiveness of regorafenib as a treatment in those patients with unresectable or metastatic GIST who have progressed on or are intolerant to prior treatment with imatinib and sunitinib.

Population

It is reasonable to generalise the clinical benefit seen in the GRID trial to potential patients within routine clinical practice in England and Wales. Although GIST can occur at any age, mean age at presentation is 50 – 70 years and it is more common in men than women. This patient profile fits with the baseline demographics of the GRID study, where the median age of patients was 60 years and the male to female ratio was roughly 2:1.

Regorafenib was also seen to be effective and with no imbalances in the incidence of AEs across all subgroups of patients, including geographic region, prior line of

treatment, age, sex, baseline BMI, duration of imatinib treatment, ECOG performance status, and mutational status.

Comparators

Prior to the licensing of regorafenib for patients with unresectable or metastatic GIST who have progressed on or are intolerant to prior treatment with imatinib and sunitinib, there were no standard effective treatment options for patients other than BSC. Placebo was therefore selected as the medically appropriate control group due to lack of other standard treatments. This decision was accepted by the regulatory agencies at the time of study design and marketing approval.

Intervention

In the GRID study, regorafenib was administered at the same dosage as that recommended in the Summary of Product Characteristics, and followed in clinical practice. It is an oral agent, convenient to administer, with a simple dosing regimen (four 40mg tablets once daily for 3 weeks followed by one week off therapy). Oral therapy avoids the patient having to attend hospital for intravenous chemotherapy. No dose adjustment is needed for age, sex, bodyweight, mild or moderate renal or hepatic impairment.

Outcomes

All efficacy and safety assessments in the GRID study were standard variables and methods for clinical studies in oncology. They are widely recognised as valid, reliable, accurate and relevant to clinical practice.

No standard treatment is available for metastatic or unresectable GIST previously treated with both imatinib and sunitinib. This patient population therefore has limited treatment options and a poor prognosis. Outcome measures in the GRID study were based around assessment of treatment effects on delaying disease progression, improvements in survival, amelioration of symptoms, and health-related quality of life, all of which are directly relevant to patients with metastatic or unresectable GIST previously treated with both imatinib and sunitinib, in clinical practice.

The primary efficacy endpoint, PFS, is a standard indicator for the evaluation of anticancer agents and the appropriateness of this endpoint for this study was discussed with the regulatory agencies. Delaying disease progression is an important treatment goal in the management of patients with cancer in general and in patients with advanced GIST, as growing tumour burden is associated with increasing bothersome symptoms, reduced QoL and increased stress.

The GRID study met its primary endpoint of significant improvement in PFS for regorafenib vs. placebo. Regorafenib reduced the risk of disease progression or death by 73% vs. placebo – a 5-fold increase (4.8 vs. 0.9 months; HR=0.268, 95% CI: 0.19-0.39; p<0.0001) in median PFS – in patients with metastatic and/or unresectable GIST who had progressed despite previous treatment with at least imatinib and sunitinib. Subgroup and sensitivity analyses for PFS were consistent and supportive of the overall primary analysis results of PFS, demonstrating regorafenib provides consistent PFS benefits, independent of the number of previous treatments, patient characteristics, and mutation status.

In addition, patients who were initially randomised to placebo in the GRID study experienced PFS benefits after crossing over to receive regorafenib. Median secondary PFS for the placebo arm (for those who crossed over to regorafenib) and the regorafenib arm was 151 days (5 months) and 137 days (4.5 months), respectively. Continuing treatment with regorafenib may therefore be clinically beneficial, as it appears to delay further disease progression.

Overall survival is often the gold standard endpoint in the evaluation of new therapies in many cancers. However, the choice of OS as the primary endpoint was impractical in the GRID study due to the availability of early promising results with regorafenib in this patient population and the necessity of a cross-over design (see earlier in section 4.13.2). As expected, due to the cross-over design, median OS was 529 days (17.4 months) in both treatment groups (HR = 0.909). When correction models were employed, median OS time was longer in the regorafenib group (529 days or 17.4 months) than in the placebo group (338 days or 11.1 months IPE [p = 0.00095]; 361 days or 11.9 months RPSFT [p = 0.00286]). The estimated corrected

hazard ratio of regorafenib to placebo using the RPSFT and IPE correction methods were 0.616 and 0.586, respectively. Corrected hazard ratios of OS demonstrated an extension of survival times under regorafenib treatment relative to placebo.

Tumour response evaluations (RR, DCR, TTP, DOR) are well-recognised endpoints for clinical activity in patients with advanced stage solid tumours and serious or life threatening diseases. Tumour response evaluations were measured using RECIST criteria (v.1.1), which are widely used to evaluate the response to treatment in patients with solid tumours. RECIST v1.1 was modified and clarified relevant to GIST tumour assessments. In advanced disease where life expectancy is reduced and there is no cure, relief of physical symptoms and maintenance of function become primary objectives of medical intervention. Disease-specific measures offer the advantages of being more likely to be sensitive to the impact of drug therapy. The analyses of secondary efficacy variables in the GRID study were consistent with the primary efficacy results in demonstrating the efficacy of regorafenib over placebo for the treatment of metastatic GIST in patients who have been previously treated with imatinib and sunitinib.

Patient-reported outcomes were measured in this study using the EORTC QLQ-C30 and EQ-5D, which are validated tools applicable for international clinical trial settings and for use in a wide range of cancer patient populations, irrespective of specific diagnosis. It is important that new cancer treatments do not significantly impact patient quality of life and that the achieved benefits of treatment are not outweighed by risks and major deterioration of patient quality of life. In the GRID study, regorafenib had a similar impact on patients' HRQoL compared with placebo.

The safety assessments used in this study included those considered standard of care for patients with metastatic and/or unresectable gastrointestinal stromal tumours (GIST) and were appropriate for patient safety and for assessing toxicity. The safety profile and patient tolerability of regorafenib was evaluated at every study visit throughout the GRID study. Adverse reactions in the GRID study were in line with the expected profile in a population of patients with GIST who have been previously treated with imatinib and sunitinib. Most adverse events were manageable

by dose modification without the need to discontinue treatment. Adverse events observed in GRID were typical for this drug class, the most common AEs being hand-foot skin reaction (HFSR), hypertension, diarrhoea, mucositis and fatigue.

In summary, the above review of the evidence base in relation to key factors of the decision problem - e.g. population, outcomes - demonstrates clearly the relevance and applicability of the results of the GRID study to routine clinical practice in the UK.

End of life criteria

In the current clinical practice in England, no active treatment is recommended for patients with unresectable or metastatic GIST whose disease has progressed on, or who are intolerant to, previous treatment with imatinib and sunitinib. Best supportive care is therefore the only treatment option available, alternative to regorafenib.

A median OS of 12.2 months was found in a recent retrospective study based on regorafenib-treated patients with advanced and refractory GIST in England (44). In a retrospective study considering the evidence from 10 European institutions a median OS of 2.4 months (range 1.8–2.9) was found for adult patients with documented metastatic GIST who had been treated with BSC as third-line therapy after progression on first-line imatinib and second-line sunitinib (31).

In the GRID trial, the median OS for regorafenib arm was 17.4 month compared with 11.9 and 11.1 months for the placebo + BSC arm when RPSFT and IPE crossover corrections were applied, respectively (see section 4.13.2) (14) The difference in median OS between regorafenib and placebo + BSC was therefore found to range between 5.5 and 6.3 months.

No country specific incidence rates for GIST are available, however recent estimates quoted for the United Kingdom range from 1.32 to 1.50 per 100,000 people (49;50), corresponding to about 700-850 new cases per year in England (50). Of these 700-850 patients per year, between 50 and 60 are estimated to be eligible for a further TKI treatment after failure of imatinib and sunitinib treatments (see section 6 for further details).

All the data available for regorafenib supporting the end-of-life criteria are displayed in Table 26.

Table 26. End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median OS for patients treated with BSC: • 11.1 months (placebo + BSC when using IPE crossover correction) (11) • 11.9 months (placebo + BSC when using RPSFT crossover correction) (11)
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Median OS • 17.4 months (regorafenib + BSC) vs. 11.1 months (placebo + BSC when using IPE crossover correction) (11) • 17.4 months (regorafenib + BSC) vs. 11.9 months (placebo + BSC when using RPSFT crossover correction) (11)
The treatment is licensed or otherwise indicated for small patient populations	• Metastatic and/or unresectable GIST after failure with imatinib and sunitinib treatments: average of 58 patients per year over 5 years (19;28;32;33) • Metastatic colorectal cancer (CRC) previously treated with/or not considered candidate for available therapies: average of 953 patients per year over 5 years (51-53)

4.14 *Ongoing studies*

4.14.1 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.

The final analysis of the GRID study (in terms of overall survival and long-term safety) occurred in June 2015 and the data are reported earlier in section 4.

No relevant ongoing studies or updated analyses of existing studies are anticipated to provide additional evidence within the next 12 months for regorafenib in metastatic and/or unresectable patients with GIST who have progressed after therapy with at least imatinib and sunitinib.

This is confirmed by hand-searching all records for 'regorafenib and GIST' on the www.clinicaltrials.gov website.

5 Cost effectiveness

Section 5 provides detailed guidance on the level of information that should be provided in the evidence submission template about the cost effectiveness of the appraised technology.

When completing the template, also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

5.1 *Published cost-effectiveness studies*

Identification of studies

5.1.1 Describe the strategies used to retrieve cost-effectiveness studies relevant to decision-making in England from published NICE technology appraisals, the published literature and from unpublished data held by the company. Justify the methods used with reference to the decision problem and the NICE reference case. Provide sufficient detail to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used. Provide the search strategy used in an appendix.

A full systematic review of the published literature was conducted to identify cost-effectiveness studies relevant to the decision problem.

The objective of the search was to identify all relevant cost-effectiveness studies from the published data. A range of databases indexing published research was searched, for studies examining the cost-effectiveness of treatments in adults with unresectable and/or metastatic GIST, who have failed to respond to both imatinib and sunitinib treatment regimens.

Similar to the clinical evidence review, the economic evidence literature review was conducted from database inception to 21 December 2011 and then updated in three phases:

- An update from 21 December 2011 up to July 2013

- An update from 21 July 2013 to 06 May 2016
- A further update from 06 may 2016 to 19 December 2016

The search covering the period database inception to 19 December 2016 was aimed to identify cost-effectiveness studies relevant to the scope of the decision problem:

- MEDLINE
- MEDLINE (R) In-Process
- EMBASE
- EconLIT
- NHS EED

Search strategies included subject index headings (e.g. MeSH & Emtree terms) where applicable and free text terms. Economic evaluation study design filters were applied to the searches of the MEDLINE, MEDLINE (R) In-Process, and EMBASE databases.

In addition, proceedings from three major conferences were searched, for relevant abstracts/posters with results of recent trials:

- American Society of Clinical Oncology (ASCO) (ASCO-GI specific and ASCO Annual meeting) (2009-2011; 2012-2013; 2014-2016)
- European Society for Medical Oncology (ESMO) (ESMO-GI specific and Annual conference) (2009-2011; 2012-2013; 2014-2016)
- International Society For Pharmacoeconomics and Outcomes Research (ISPOR Annual conference) (2009-2011; 2012-2013; 2014-2016)

The searches were limited to articles published in the English language. Full details of the search strategy including search terms employed and the databases searched are provided in Appendix 11.

A set of inclusion and exclusion criteria (Table 27) was developed and applied to the search results, after duplicates across the various databases were removed in a graduated and systematic review: first, two individuals independently reviewed the titles and abstracts against the criteria and any disparity in the decision to include was reviewed by a third party; second, included abstracts were ordered and the full texts were reviewed against the criteria; third, all full text publications were either excluded with reason or included and extracted.

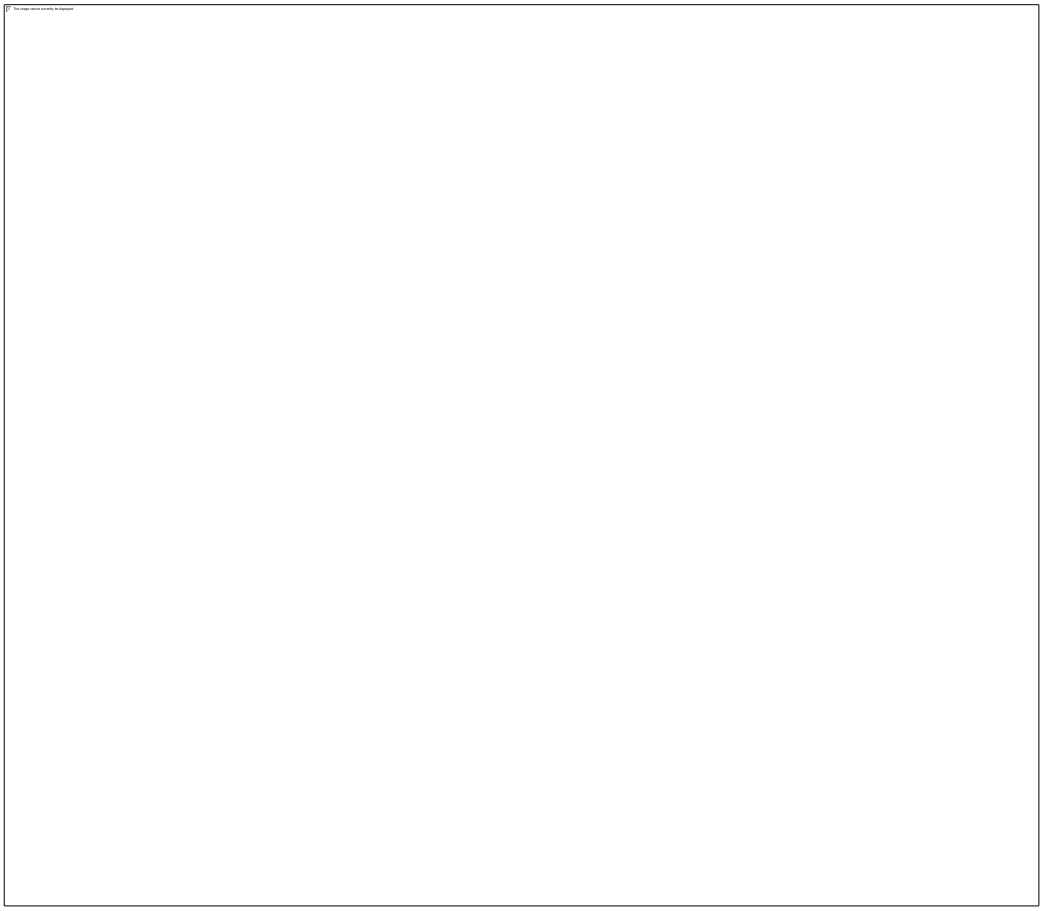
Table 27. Inclusion and exclusion criteria for cost-effectiveness publications

	Inclusion criteria	Exclusion criteria
Study design	• Study design appropriate to report the cost of illness and/or resource use for GIST (cost studies analyses, database studies collecting cost or resource use data [including claims databases and hospital records], cross-sectional studies [including surveys] containing cost data, cohort studies containing cost data, longitudinal studies containing cost data, RCT containing piggy-back economic evaluation, cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses, cost-minimisation analyses, budget impact models, cost consequence studies)	• Literature and systematic reviews • Database studies or epidemiology studies, not collecting cost data • RCTs (with no piggy-back economic evaluations) • Studies published in non-English language (with/without English abstracts)
Patient population	• Studies including adult patients (aged ≥18 years) • Studies reporting data in countries of interest (US, Canada, Australia, France, Germany, Italy, Spain, UK, Brazil, Mexico, Japan, China, Korea)	• Studies in children or adolescents • Studies conducted in animals or *in vitro*
Disease/ therapy	• Studies including patients with metastatic, advanced, and/or unresectable GIST, defined as such using the study author's definition • Studies of third-line patients (who have failed two pharmacological therapies). However, as it is was anticipated that studies focused on third-line patients were rare, studies in first- and second-line patients were only excluded at the final stage of the second pass (at the first pass stage there was no exclusion based on therapy line)	• Studies that did not include patients with a specific GIST diagnosis (including gastrointestinal leiomyosarcoma that appeared to behave as GIST, soft-tissue sarcoma that appeared to behave as GIST, oesophageal leiomyosarcoma, gastric leiomyoma, gastric leiomyoblastoma, small intestinal leiomyoma and leiomyosarcoma, colonic and rectal leiomyoma and eiomyosarcoma, gastrointestinal autonomic nerve tumour, eiomyoma and leiomyosarcoma of omentum and mesentery, retroperitoneal leiomyosarcoma)
Intervention	• Regorafenib	• Any other intervention
Comparator	• Placebo/BSC	• Any other comparator

BSC = Best Supportive Care

The PRISMA diagram (Figure 14) illustrates the number of publications identified and included/excluded at each stage of the review. A total of two publications were finally included and data extracted from.

Figure 14. PRISMA flow diagram of the included economic studies



Description of identified studies

5.1.2 Provide a brief overview of each cost-effectiveness study only if it is relevant to decision-making in England. Describe the aims, methods and results for each study. Each study's results should be interpreted with reference to a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than 1 study is identified, please present the information in a table as suggested below.

Sanz-Granda et al. (2015) is an economic study based on Spanish healthcare settings (54). This study was considered not relevant to the decision-making in England and Wales.

Pitcher et al. (2016) is a UK based cost-utility analysis aimed at evaluating the cost-effectiveness of regorafenib compared with placebo for patients receiving treatment for unresectable or metastatic GIST after failure/ intolerance to imatinib and sunitinib in an English setting. In this study a partitioned survival model was adopted to determine the transition of patients through the three health states – i.e. progression-free, progressed, and death (55).

A summary of the study relevant to the decision-making in England is reported in Table 28.

Table 28. Summary list of published cost-effectiveness studies relevant to the decision- making in England

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Pitcher, 2016 (UK)§ (55)	2016	A partitioned survival model was used to model three health states: progression-free, progressed, and dead, over a lifetime horizon.	NA	• QALYs using IPE crossover adjustment method: – Regorafenib: 1.717 – Placebo: 0.969 • QALYs using RPSFT crossover adjustment method: – Regorafenib: 1.717 – Placebo: 1.080	• Costs Using IPE crossover adjustment method – Regorafenib: £36,258 – Placebo: £10,513 • Costs using RPSFT crossover adjustment method – Regorafenib: £36,258 – Placebo: £10,659	ICERs per QALY gained: For IPE: £34,420 For RPSFT, £40,188
QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio §Results presented at ISPOR 19th Annual European Congress						

5.1.3 Provide a complete quality assessment for each relevant cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[2] or

[2] 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

Philips et al. (2004)[3]. Please provide these assessments in an appendix.

A complete quality assessment of the cost-effectiveness studies is reported in Appendix 12.

5.2 *De novo analysis*

This section should be read with the NICE guide to the methods of technology appraisal, section 5.2.

Patient population

5.2.1 State which patient groups are included in the economic evaluation and how they reflect the population defined in the scope and decision problem for the NICE technology appraisal, marketing authorisation/CE marking, and the population from the trials. If there are differences, please provide the rationale. Explain the implications of this for the relevance of the evidence base to the decision problem. For example, indicate if the population in the economic model is different from that described in the (draft) summary of product characteristics (SmPC) or information for use (IFU) and included in the trials.

The target patient population is adults with metastatic and/or unresectable GIST who have previously been treated with at least imatinib and sunitinib. The cohort starts at age 60, corresponding to the median age of patients in the GRID trial (8). The mean age of patients in the GRID study was 58.2 years (95% CI 18 – 87) (8).

Model structure

5.2.2 Describe the model structure and provide a diagram of the model submitted, including the following:

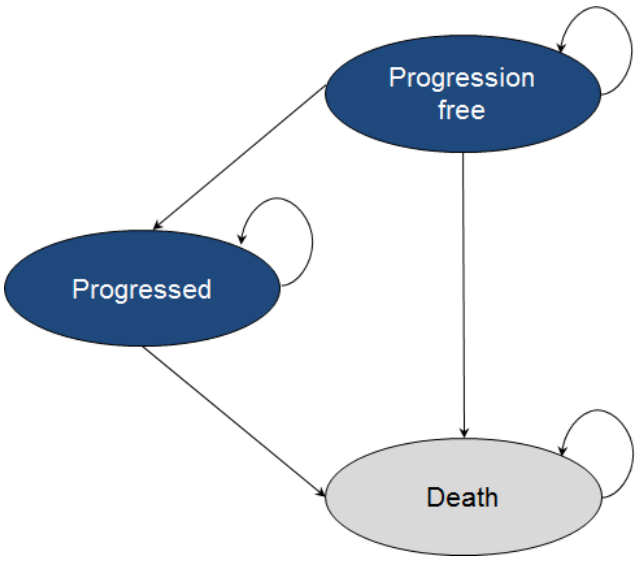
[3] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

- Type of de novo analysis (for example, decision tree, Markov model, discrete event simulation model).
- Justification of the chosen structure in line with the clinical pathway of care described in section 3.3.
- How the model structure and its health states capture the disease or condition for patients identified in section 3.3.
- Where appropriate, state the cycle length and whether a half-cycle correction has been applied.

A commonly used oncology model structure is used as the basis for the economic evaluation. Three main health states are considered: progression-free, progressed and death. A partitioned survival model is used to determine the proportion of the cohort of patients in the three health states at different points in time. This model type is the most suitable since it can use Kaplan-Meier survival curves from the GRID trial directly.

Figure 15 shows the three main health states and the possible transitions between them.

Figure 15. Three-state state partitioned survival model



Patients' transitions through health states are determined using the Kaplan-Meier survival curves for overall survival (OS) and progression-free survival (PFS). The

PFS curve defines the proportion of patients who are in the progression-free health state, while one minus the OS curve defines the proportion of patients who are dead. Hence, the remainder of patients are allocated to the progressed health state so that the total proportion of patients across the three health states adds up to one.

Kaplan-Meier data is only available for the duration of the GRID trial. In order to extrapolate the survival data beyond the trial duration, five parametric models were fitted to the Kaplan-Meier curves in line with the methods recommended by NICE Decision Support Unit (12). These curves were tested for statistical fit and clinical plausibility.

The model uses a 28-day cycle length to correspond with the regorafenib treatment regimen consisting of three weeks on treatment followed by one week off treatment. Half-cycle correction is also applied in the model.

5.2.3 Complete the table below presenting the features of the de novo analysis. Compare and justify your chosen values with the methods specified by NICE in the reference case (see the NICE guide to the methods of technology appraisal, section 5, table 5.1).

Features of the de novo analysis are presented in Table 29.

Table 29. Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	40 years	Long enough to capture all the expected lifetime benefits
Were health effects measured in QALYs; if not, what was used?	Yes	In accordance with NICE methods guide
Discount of 3.5% for utilities and costs	Yes	In accordance with NICE methods guide
Perspective (NHS/PSS)	Payer (NHS, PSS)	In accordance with NICE methods guide
PSS, personal social services; QALYs, quality-adjusted life years		

Intervention technology and comparators

5.2.4 If the intervention and comparator(s) are not implemented in the model as per their marketing authorisations/CE marking, describe how and

why there are differences. Make it clear whether the intervention and comparator(s) included in the model reflect the decision problem. If not, briefly describe how and why, cross-referencing to the decision problem section in your submission.

The intervention investigated by this model is regorafenib once daily (recommended dose 160 mg per day) in four week cycles; three weeks on treatment, followed by one week off treatment in addition to BSC.

There is currently no standard, approved or recommended third-line treatment for GIST in patients having failed on both imatinib and sunitinib. A physician survey of 15 GIST physicians in England and Wales was conducted in 2013. Recent interviews with two consultant oncologists in GIST management were carried out in 2016 to assess whether the findings from the previous survey were still valid within the current clinical practice. In line with the decision problem, BSC is used as the primary comparator. Throughout this chapter, reference to the treatment arms regorafenib plus BSC and BSC alone are simplified to regorafenib and placebo, respectively.

5.2.5 If a treatment continuation rule has been assumed for the intervention and comparator(s), provide the rationale for the continuation rule and where it is referenced (for example, [draft] SmPC, European public assessment report, comparator use, clinical practice, or clinical trial protocols). Please note that this refers to clinical continuation rules and not patient access schemes. If a treatment continuation rule is included in the model that is not stated in the (draft) SmPC or information for use (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 implementing the continuation rule (for example, any additional monitoring required)

- the robustness and plausibility of the end point 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 people for whom the technology is particularly cost effective
- issues about withdrawal of treatment for people whose disease does not respond and other equity considerations.

In the GRID study, treatment with regorafenib that provided clinical benefit to a patient experiencing disease progression could be continued based on the investigator's opinion and following consultation with the sponsor. For patients receiving placebo experiencing disease progression, active treatment with regorafenib was offered (crossover option) (36).

However, this treatment continuation rule based on the investigator's opinion is not standard practice in England and Wales. This is further confirmed by the results from the 2013 physician survey, validated by two consultant oncologists in 2016, in which the average proportion of patients experiencing progression who would continue TKI treatment post-progression resulted being about 25.3%. Therefore, no treatment with regorafenib post-progression is included in the base case.

When continuing active treatment post-disease progression, acquisition costs for the active treatment need to be considered. The mean exposure to treatment post-progression was calculated by subtracting the mean time under treatment in the regorafenib arm during the double-blind phase of the GRID study, i.e. 15.026 weeks, from the mean time under actual treatment in both double-blind and open-label phases for patients randomised to the regorafenib arm, i.e. [redacted] weeks. The mean duration of treatment post-progression in the regorafenib arm resulted being equal to

[redacted] weeks ([redacted] days). This is equivalent to approximately 9 cycles of treatment with regorafenib. Drug acquisition costs for regorafenib are reported in sections 5.5.

5.3 *Clinical parameters and variables*

This section should be read with the NICE guide to the methods of technology appraisal, section 5.7.

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical evidence section of the submission (section 4). Cross-references to the clinical evidence section should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as justification for the approach. The answers should clearly specify the approach taken in the base case analysis.

Provide the information specified in sections 5.3.1–5.3.4.

5.3.1 Describe how the clinical data were incorporated into the model, also commenting on the following factors:

- Whether intermediate outcome measures were linked to final outcomes (for example, if a change in a surrogate outcome was linked to a final clinical outcome). If so, explain how the relationship was estimated, what sources of evidence were used, and what other evidence there is to support it.
- Whether costs and clinical outcomes are extrapolated beyond the trial follow-up period(s). If so, explain and justify the assumptions that underpin this extrapolation, particularly the assumption that was used about the longer-term difference in effectiveness between the intervention and its comparator. For the extrapolation of clinical outcomes, present graphs of any curve fittings to patient-level data or Kaplan–Meier plots and the methods and results of any internal and external validation

exercises. The NICE Decision Support Unit[4] has published technical support document 14, which provides additional information on the implementation of methods and reporting standards for extrapolation with patient level data.

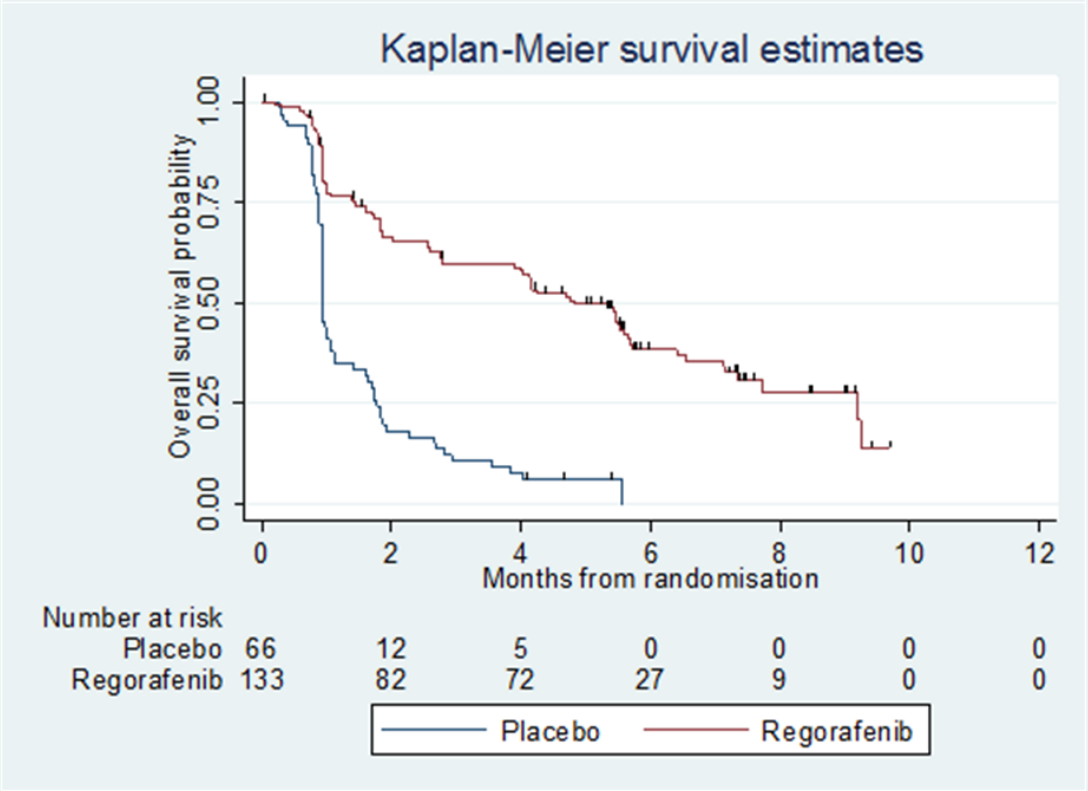
Parametric fittings of the Kaplan-Meier data extrapolated beyond the trial time horizon were used to inform state transitions in the model. This allows for evaluation of clinical outcomes over a longer time horizon than that observed in the trial. The parametric extrapolations are described further in section 5.3.2.

5.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix and describe the details of the transformation of clinical outcomes or any other relevant details here.

The PFS data used in the model were taken directly from the patient-level data in the GRID trial. Cross-over of patients from the placebo arm to the regorafenib arm was allowed after disease progression; therefore no cross-over corrections were needed for the PFS data from the GRID study. The PFS Kaplan-Meier curve from GRID is shown in Figure 16.

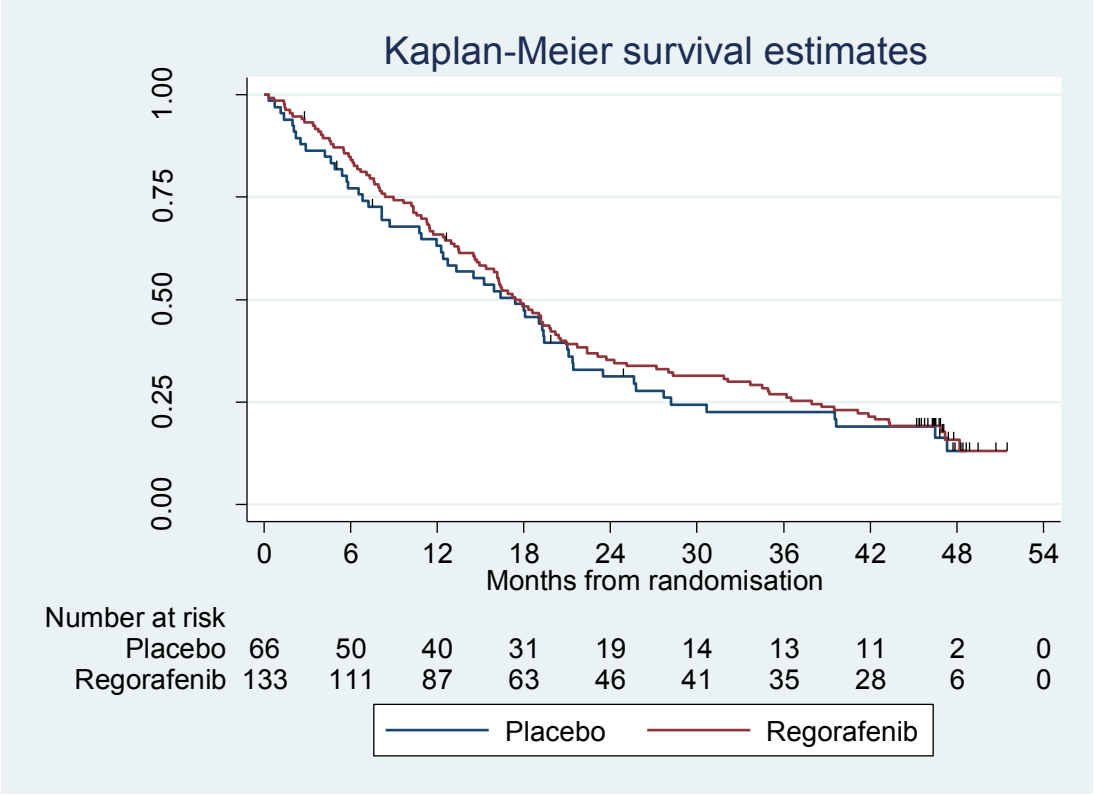
[4] Although the Decision Support Unit is funded by NICE, technical support documents are not formal NICE guidance or policy.

Figure 16. Kaplan-Meier estimates of the progression-free survival in GRID



OS data used in the model were taken directly from the patient-level data in the GRID trial. OS Kaplan-Meier curves for regorafenib and placebo are shown in Figure 17.

Figure 17. Kaplan-Meier estimates of the probability of survival in GRID (unadjusted) – 2015 OS data update



Due to the crossover-option trial design, 87.9% (n=58/66) of patients in the placebo arm crossed over onto open-label regorafenib treatment after progression. This implied the observed OS in the placebo arm to be confounded by the benefits of treatment with regorafenib after cross-over. To adjust for crossover and simulate placebo patients not crossing over to active treatment, OS data for the GRID placebo arm had to be adjusted.

Crossover corrections based on the IPE method (56) and the RPSFT method (57) were carried out as recommended by NICE Decision Support Unit (9)

A further method, the Inverse Probability of Censoring Weights (IPCW), was considered but not used due to the high proportion of placebo patients crossing over to regorafenib, a factor which is responsible for introducing high levels of bias in treatment effect estimates (9)

The IPE-adjusted and RPSFT-adjusted OS curves are shown in Figure 18 and Figure 19, respectively. The IPE and RPSFT methods were implemented in Stata

(58). The IPE method was implemented using the Weibull parametric failure time model, as in the study by Morden et al (13) similarly, the RPSFT method was implemented using the logrank test, also recommended by Morden et al (13)

The IPE method was ultimately selected as the base case crossover adjustment method since Morden's study of 1,000 simulated datasets showed that this method performed particularly well in terms of reducing bias in the estimates of the true treatment effect (13). In line with the methodological approach recommended by NICE Decision Support Unit (9), recensoring was applied in order to avoid bias for the IPE and RPSFT methods. Results from this crossover correction were used in the cost-effectiveness analyses presented in sections 5.7 and 1.1. Recensoring was not applied for the IPE and RPSFT crossover corrections presented in the GRID clinical study report.

Figure 18. Kaplan-Meier estimates of the probability of survival using the IPE crossover adjustment method for the placebo arm – 2015 OS data update

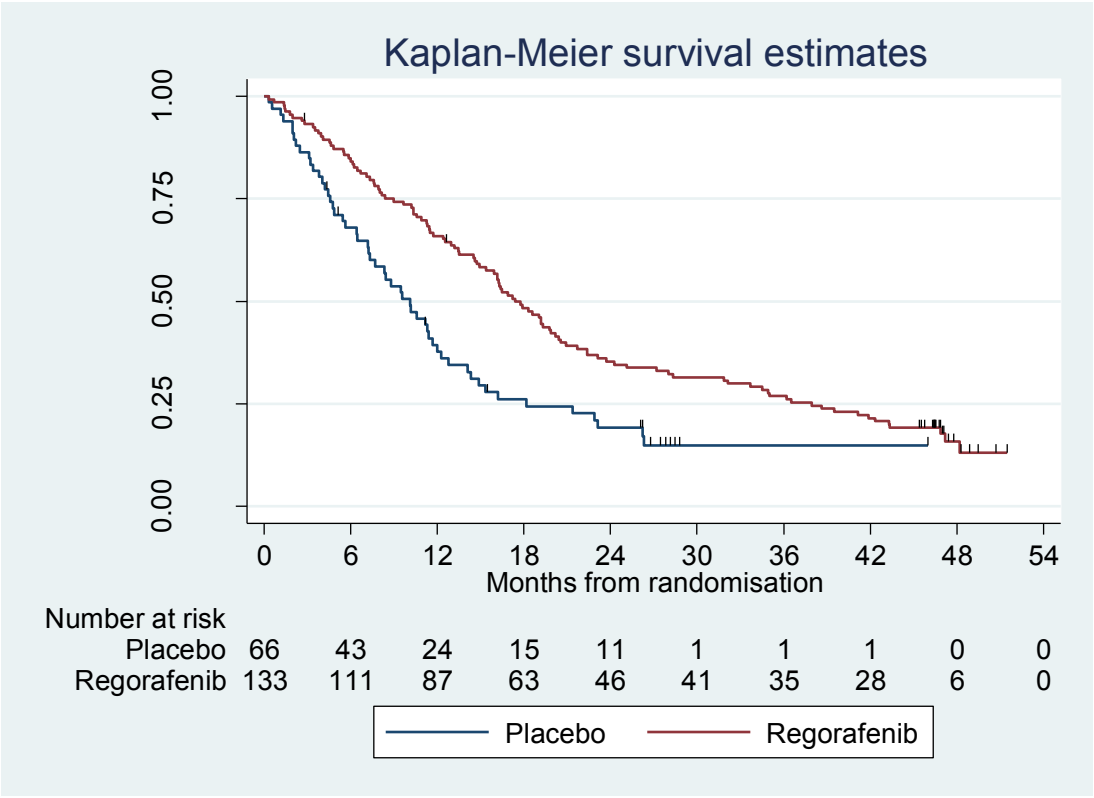
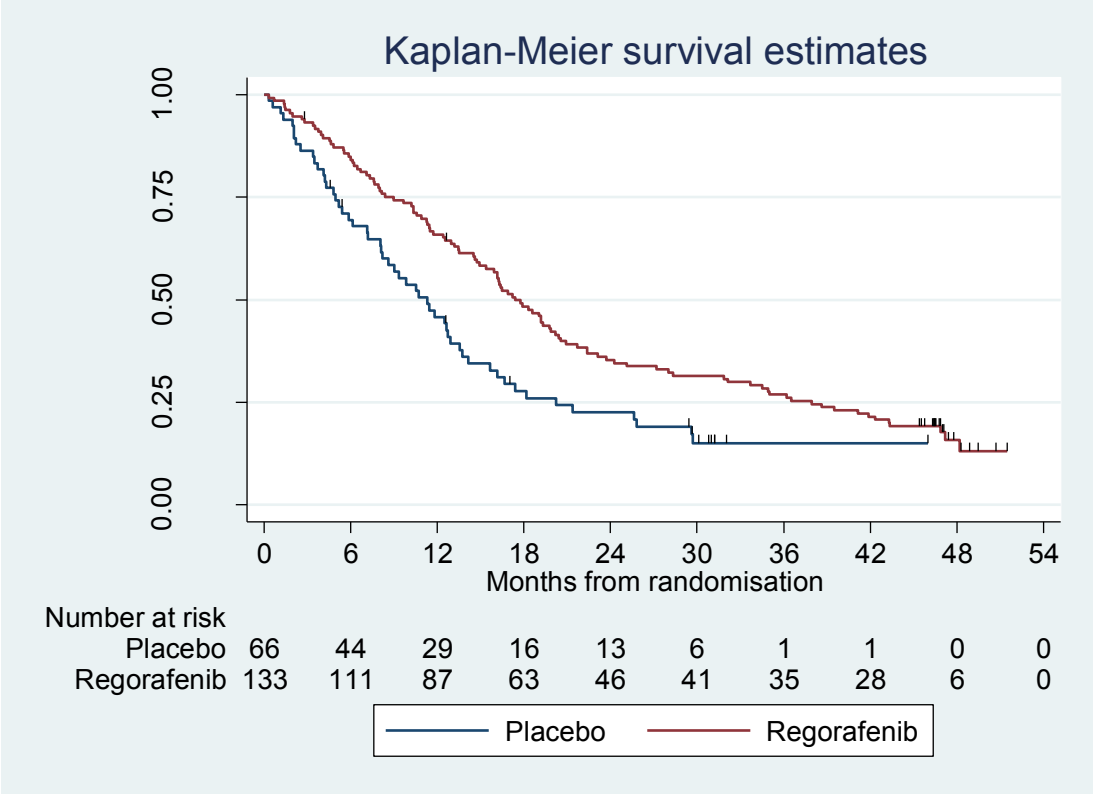


Figure 19. Kaplan-Meier estimates of the probability of survival using the RPSFT crossover adjustment method for the placebo arm – 2015 OS data update



Hazard ratios of regorafenib versus BSC generated from the unadjusted, IPE-adjusted, and RPSFT- adjusted recensored OS data are presented in Table 30. In addition to the adjustments undertaken for crossover, the Cox model used to estimate hazard ratios was also stratified by region and prior anti-cancer drug group as per the primary analysis (18).

Table 30. Hazard ratios of probability of survival in GRID

Crossover Adjustment	Hazard Ratio
Unadjusted	0.909
IPE (Weibull model, recensoring)	0.[redacted]
RPSFT (logrank test, recensoring)	0.[redacted]

Note: HRs for all three methods are stratified by region and prior anti-cancer drug variables

The extrapolation in this model was entirely parametric. Extrapolation of the GRID trial OS and PFS data was evaluated using five different parametric models: Weibull, exponential, loglogistic, Gompertz and lognormal.

Visual inspection to assess the fitting of the five parametric models to the GRID Kaplan-Meier data was conducted. However, due to the uncertainty associated with this approach, conclusions on the best fitting model could not be drawn. An alternative approach based on the assessment of the Akaike's Information Criterion (AIC) and the Bayesian Information Criterion was adopted.

The AIC and BIC provide a useful statistical test of the relative fit of alternative parametric models (12). Both criteria are a measure of the relative quality of a statistical model by trading off the model fit with the number of model parameters (the lower the AIC/BIC, the better the model). Therefore, the selection of the most appropriate extrapolation method is based on its statistical fit determined using AIC and BIC.

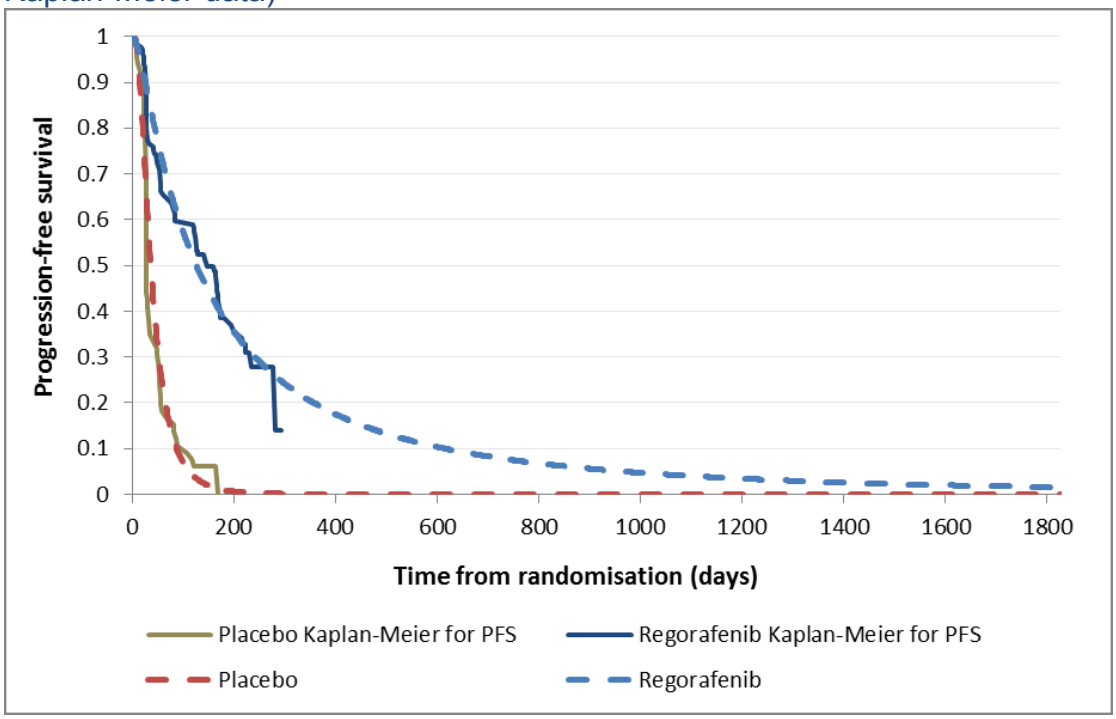
As seen in Table 31, the lognormal curve provides the lowest AIC for regorafenib progression-free survival, and the log-logistic gives the minimum AIC for progression-free survival on placebo. Due to the different shapes of different parametric models, the same parametric model type should be chosen for the two treatment arms (12). In order to use the AIC and BIC and keep the same parametric model in both arms, the sum of the AIC and the sum of the BIC across the two treatment arms were used to inform the parametric model choice (Table **31**). For the base case analysis, the lognormal extrapolation of the data was selected for the progression-free survival curves for both the regorafenib and placebo arms.

Table 31. AICs for different parametric models for progression-free survival extrapolation

Parametric Model	**AIC**			**BIC**		
	Placebo	Regorafenib	SUM AIC	Placebo	Regorafenib	SUM BIC
Exponential	170.886	349.477	520.363	173.078	352.368	525.446
Loglogistic	139.045	348.561	487.605	143.424	354.341	497.765
Weibull	162.487	350.95	513.437	162.487	356.731	519.218
Lognormal	142.055	343.396	**485.45**	146.434	349.177	**495.611**
Gompertz	172.009	351.475	523.484	176.388	357.255	533.643

The base case scenario (lognormal model) is shown in Figure 20.

Figure 20. Lognormal model for progression-free survival (compared to the GRID Kaplan-Meier data)



Fitting of the five parametric models for overall survival are presented in Figure 21 for IPE-adjusted placebo and Figure 22 for regorafenib.

Figure 21. Parametric models for overall survival (compared with GRID Kaplan-Meier data)

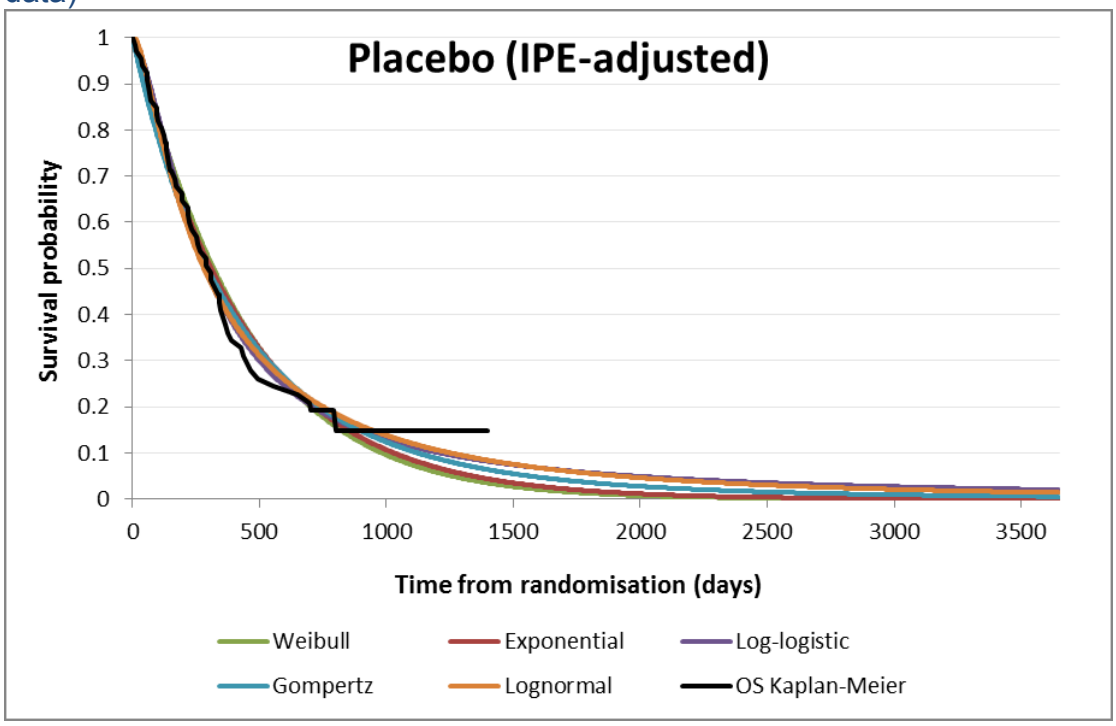


Figure 22. All possible extrapolated models fitted to KM curve for regorafenib (using GRID data)

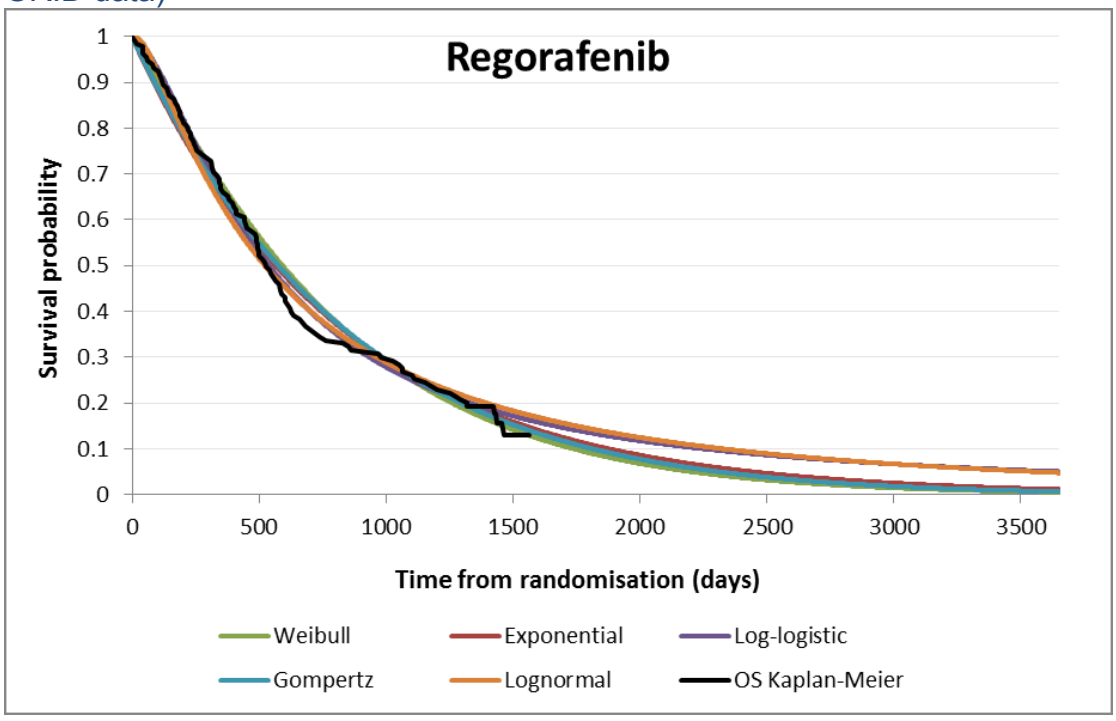


Table 32 and Table 33 present the AIC and BIC for the assessed extrapolations of the OS data. The loglogistic model gives the minimum AIC for regorafenib OS and

for both the RPSFT and IPE methods used in the placebo arm. In terms of BIC, the exponential model provides the minimum BIC for both the RPSFT and IPE corrections. However, the difference between the BIC values for the exponential and loglogistic models results being smaller compared to the other parametric models. Hence, the loglogistic model was selected for use in the model base case.

Table 32. AICs for different parametric models for OS extrapolation

Parametric Model	**Regorafenib**	**Placebo**		**Sum AIC (placebo + regorafenib)**	
		RPSFT	*IPE*	*RPSFT*	*IPE*
Exponential	390.96	196.66	195.24	587.62	586.21
Loglogistic	**388.92**	**195.74**	**193.24**	**584.66**	**582.16**
Weibull	391.25	198.43	196.92	589.67	588.17
Lognormal	393.24	197.25	194.77	590.49	588.01
Gompertz	392.85	198.39	196.89	591.23	589.74

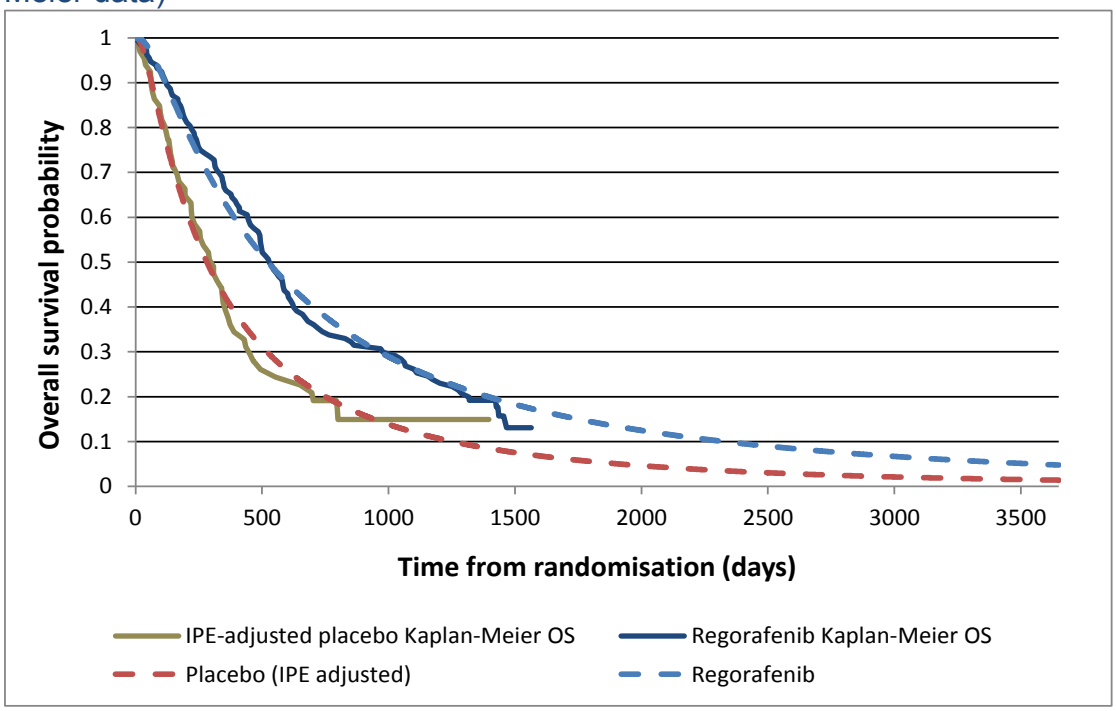
Table 33.BICs for different parametric models for OS extrapolation

Parametric Model	**Regorafenib**	**Placebo**		**Sum BIC (placebo + regorafenib)**	
		RPSFT	*IPE*	*RPSFT*	*IPE*
Exponential	**393.85**	**198.85**	**197.43**	**592.7**	**591.28**
Loglogistic	394.7	200.12	197.62	593.97	591.47
Weibull	397.03	202.81	201.3	596.66	595.15
Lognormal	399.02	201.63	199.14	595.48	592.99
Gompertz	398.63	202.77	201.27	596.62	595.12

The fitting of the five parametric models was validated by two consultant oncologists based in England and specialised in the management of metastatic or unresectable GIST during the 2016 survey. From a clinical perspective, the log-logistic model looked clinically plausible along with the Weibull and Gompertz models.

The loglogistic models used for regorafenib and the IPE-adjusted placebo along with the Kaplan-Meier OS data from GRID are shown in Figure 23. This is the model base case.

Figure 23. Loglogistic model for overall survival (compared to the GRID Kaplan-Meier data)



Use of the hazard ratio applied to the parametric model for the regorafenib arm to determine the OS curve for placebo (rather than extrapolating the regorafenib and placebo arms separately) was also explored. The proportional hazards (PH) assumption was tested using Schoenfeld residuals on the unadjusted data. If the PH assumption is satisfied, then the residuals should not be correlated with survival time. The null hypothesis and the PH assumption were tested through Stata. We found a p-value of 0.4138 and 0.6536 for OS and PFS, respectively, suggesting that the PH assumption cannot be rejected. Therefore, one of the options explored in the OWSA is to use the hazard ratio applied to the parametric model for the regorafenib arm to determine the OS in the placebo arm.

Because of the availability of patient-level-data for the two treatment arms in the GRID study, parametric models fitted separately to the individual PFS and OS curves were used for the base case analysis. The selection of the best fitting model followed the assessment of the single parametric functions applied to the Kaplan-Maier curves for the regorafenib and placebo arms. As recommended by NICE Decision Support Unit, the same “type” of model was used for both the treatment arms (12).

Adverse event rates

Drug-related grade 3 and 4 adverse events reported in at least 3% of patients were included in the model. These adverse events were hypertension, hand-foot skin reaction (HFSR) and diarrhoea. The incidence of these adverse events during the double-blind period in GRID is shown in Table 34 (8).

Table 34. Drug-related grade 3-4 adverse events in GRID occurring in at least 3% of patients

Adverse Event (Grade 3-4)	Incidence during double-blind period in GRID, n (%)	
	Placebo (N=66)	Regorafenib (N=132)
Hypertension	2 (3)	31 (24)
Hand-foot skin reaction	0 (0)	26 (20)
Diarrhoea	0 (0)	7 (5)

For use in the model, these rates were adjusted for the time spent in the double-blind period. Table 10-1 in the GRID Amended CSR (18) reported that placebo arm and regorafenib arm patients spent a mean of 9.1 and 20.2 weeks in the double-blind period, respectively (8). This led to the per cycle rates shown in Table 35.

Table 35. Incidence rate per cycle of grade 3-4 adverse events included in the model

Adverse Event (Grade 3-4)	Estimated incidence rate per cycle (%)	
	Placebo	Regorafenib
Hypertension	1.35	5.16
Hand-foot skin reaction	0	4.25
Diarrhoea	0	1.07

Despite these adverse events normally resolve in less than four weeks, a conservative approach was adopted in the cost-effectiveness analyses by assuming their duration would last for a whole treatment cycle.

5.3.3 If there is evidence that (transition) probabilities may change over time for the treatment effect, condition or disease, confirm whether this has 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.

Transition probabilities in the model vary over time based on the extrapolation of the GRID trial OS and PFS data evaluated using five different parametric models: Weibull, exponential, loglogistic, Gompertz and lognormal.

5.3.4 If clinical experts have assessed the applicability of the clinical parameters or approximated any of the clinical parameters, provide the following details :

- 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 whose opinion was sought
- the background information provided and its consistency with all 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).

Physicians surveyed in 2013 were randomly selected based on the following screening points:

- The approximate number of adult metastatic/unresectable GIST patients personally and directly managed by each physician in the last six months before the survey
- The number of adult metastatic or unresectable GIST patients managed by physicians who have failed (i.e. progressed on, are intolerant to, or otherwise unsuitable for) imatinib

- The number of adult metastatic or unresectable GIST patients managed by physicians who have failed (i.e. progressed on, are intolerant to, or otherwise unsuitable for) sunitinib
- The number of adult metastatic or unresectable GIST patients managed by physicians who have failed (i.e. progressed on, are intolerant to, or otherwise unsuitable for)both imatinib and sunitinib
- The country in which the physician was based
- The profession or specialisation of the physician and her/his grade

In 2016, results of the previous physician survey conducted in 2013 on resources consumption for the treatment of GIST in England and Wales were validated by two consultant oncologists based in England and specialised in the management of metastatic or unresectable GIST. No specific clinical parameters were assessed in 2016 except for long-term overall survival predictions.

5.4 *Measurement and valuation of health effects*

This section should be read with the NICE guide to the methods of technology appraisal, section 5.3.

The NICE Decision Support Unit[4] has published several technical support documents that provide additional information on measuring and valuing health benefits in economic evaluation:

- An introduction to the measurement and valuation of health for NICE submissions (technical support document 8).
- The identification, review and synthesis of health state utility values from the literature (technical support document 9).
- The use of mapping methods to estimate health state utility values (technical support document 10).

- Alternatives to EQ-5D for generating health state utility values (technical support document 11).
- The use of health state utility values in decision models (technical support document 12).

Health-related quality-of-life data from clinical trials

5.4.1 If health-related quality-of-life (HRQL) data were collected in the clinical trials identified in section 4, comment on whether the data are consistent with the reference case. Consider the following points, but note that this 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.

Two quality of life questionnaires were administered during the GRID trial: the EQ-5D and the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30). Both datasets were used to estimate health-state utilities. The mapping algorithm applied to the EORTC data and the results obtained from it are described in section 5.4.2.

EQ-5D

The analysis included patient data collected during the GRID study. Data from patients with both baseline EQ-5D assessment and at least one post-baseline assessment was used in the analysis. The Patient Reported Outcome Analysis Set (PROAS) was used. Two methods were used to generate health-state utilities: a paired-samples comparison and a repeated measures analysis.

The paired-samples comparison based on t tests was used initially to assess within subject difference in EQ-5D utility at baseline in the progression-free state (day 1 of

cycle 1) and the first post-progression observation. The selection of first follow-up visit subsequent to the diagnosis of first disease progression, excluding observations made on the same day as progression was identified (and before patient knowledge of progression), was made to evaluate the impact of progression on the health utility including patient awareness of progression (40).

In total, there were 77 patients with an EQ-5D assessment at baseline and at least one assessment post-progression. The mean utilities in the progression-free and progressed health states using the paired-samples comparison are shown in Table 36.

Table 36. EQ-5D health state utilities from the paired samples comparison

Health state	Mean utility	Observations, N	SD	SE
Progression-free	0.767	77	0.221	0.025
Progressed	0.647	77	0.343	0.039

SD = standard deviation; SE = standard error
Source: GRID utility assessment based on EQ-5D (provided by Bayer)

An alternative EQ-5D paired samples comparison was performed where the progression-free state was split into regorafenib and placebo arms. For this analysis, the first measurement post-baseline had to be used (instead of baseline) for the progression-free state in order to incorporate the treatment effect. The results of this analysis are shown in Table 37.

Table 37. EQ-5D health state utilities from the paired samples comparison splitting by treatment in the progression-free state

Health state	Mean utility	Subjects	SD	SE
Progression Free - Placebo	0.583	12	0.341	0.098
Progression Free - Regorafenib	0.702	27	0.281	0.054
Progressed Disease	0.649	49	0.320	0.046

SD = standard deviation; SE = standard error

As a sensitivity analysis, a repeated measures analysis was also performed. The repeated-measures analysis consists in correlating repeated observations from distinct patients using the EQ-5D index score as the dependent variable.

For the sensitivity analysis, four health-states were included: progression-free, at progression, progressed and discontinued open-label phase. A linear mixed model

with a first-order, autoregressive covariance structure was employed with subject identity modelled as a random effect. The results of this analysis are shown in Table 38.

Table 38. EQ-5D health state utilities from the repeated measures analysis

Health state	Mean utility	SE	95% CI
Progression free	0.743	0.016	0.712, 0.775
Progressed	0.703	0.023	0.657, 0.748

SE = standard error; CI = confidence interval
Source: GRID utility assessment based on EQ-5D (provided by Bayer)

An alternative EQ-5D repeated measures analysis was also performed by splitting the progression-free state into the regorafenib and placebo arms. The utility values from this analysis are shown in Table 39. Note that in this analysis, the regorafenib arm has a slightly lower mean utility than the placebo arm.

Table 39. EQ-5D health state utilities from the repeated measures analysis splitting by treatment in the progression-free state

Health state	Mean utility	SE	95% CI
Progression Free - Regorafenib	0.741	0.018	0.706, 0.777
Progression Free - Placebo	0.750	0.027	0.698, 0.802
Progressed Disease	0.681	0.023	0.637, 0.725

SE = standard error; CI = confidence interval

Since health state utility generally decreases over time due to age and tumour burden, the repeated measured analysis may be biased due to the fact that there were more measurements taken for patients in the progression-free state. There were also no clinically meaningful differences in EQ-5D between the two treatment groups.

Because of the high number (88%) of patients in the placebo arm crossing over to regorafenib, the repeated measures analysis did not contain a homogeneous progressed population for estimating utility of these subjects. As a consequence of the crossover period, the repeated measure analysis would contain the utility observations that occurred in the initial diagnosis of progressed disease, but also the utility observations during the active treatment phase with regorafenib (40).

The EQ-5D paired-samples comparison data (Table 36) was used in the base case, without splitting by treatment, as it provided a more robust utility estimate for both the progressed and non-progressed subjects compared to the repeated measures analysis.

The EQ-5D is the preferred data for generating utilities in the NICE reference case unless EQ-5D data are either unavailable or considered inappropriate.

Mapping

5.4.2 If applicable, describe the mapping methods used to estimate health state utility values from the quality-of-life data collected in clinical trials. Please include the following information:

- which tool was mapped from and onto which other tool (for example, SF–36 to EQ–5D)
- details of the methodology used
- details of validation of the mapping technique
- if the mapping technique is published or has been used in other NICE technology appraisals for similar diseases or health conditions.

Similarly to the EQ-5D data, paired-samples comparison and repeated measured analysis were applied to the EORTC QLQ-C30 data in order to determine an alternative set of utility data.

The EORTC QLQ-C30 measures quality of life in patients with cancer is commonly included in cancer trials. In order to use outcomes from the EORTC QLQ-C30 to determine utilities one must map these outcomes to a generic preference-based measure. This was done by Rowen et al (59) for a UK population. They reduced the EORTC QLQ-C30 to an eight-dimensional descriptive system (EORTC-8D). The eight dimensions correspond to ten questions from the EORTC QLQ-C30. From these ten questions from the EORTC QLQ-C30, one can assign a score to each of the eight dimensions in the EORTC-8D. Then the preference weights reported in Rowen et al (59) can be applied to derive the corresponding health state utility.

This mapping algorithm was applied to the EORTC data from the GRID trial in order to determine the corresponding health-state utilities for the progression free, at progression and progressed health states. The EORTC PROAS dataset contains 185 patients. Of these patients, 133 have non-censored time to progression dates. Of these 133 patients, 78 have both baseline and progressed EORTC data, as required for a paired-samples comparison. The mean utilities in the two health states (progression-free and progressed) are shown in Table 40 for the paired-samples comparison.

Table 40. EORTC-derived utilities using paired-samples comparison

Health state	Mean utility	Observations, N	SD	SE
Progression-free	0.818	78	0.138	0.016
Progressed	0.751	78	0.158	0.018

SD = standard deviation; SE = standard error;

In order to retain a greater number of data points, a repeated measures analysis was also undertaken to produce an alternative estimate of health-state utilities. As with the EQ-5D, a first-order, autoregressive covariance structure was employed with subject identity modelled as a random effect. Only patients with non-censored time to progression dates and an evaluable assessment at baseline and at least one post-baseline assessment were included (133 patients fulfilled this criteria). The resulting health state utilities are shown in Table 41.

Table 41. EORTC-derived utilities using repeated measures analysis

Health state	Mean utility	Observations, N	SE	95% CI
Progression free	0.794	320	0.011	0.771, 0.816
Progressed	0.756	128	0.013	0.730, 0.783

SE = standard error; CI = confidence interval

Health-related quality-of-life studies

5.4.3 Describe how systematic searches for relevant HRQL data were done. Consider published and unpublished studies, including any original research commissioned for the 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 an appendix.

A full systematic review of the published literature was conducted to identify health related quality of life (HRQoL) studies relevant to the decision problem.

The objective of the search was to identify all relevant studies reporting utilities associated with GIST disease states or studies that investigate health related quality of life (HRQoL) outcomes from the published data. A range of databases indexing published research was searched for studies reporting utilities/HRQoL in adults with unresectable and/or metastatic GIST, who have failed to respond to both imatinib and sunitinib treatment regimens.

Similar to the economic evidence review, the HRQoL evidence literature review was conducted from database inception to 21 December 2011 and then updated in three phases:

- An update from 21 December 2011 up to July 2013
- An update from 21 July 2013 to 06 May 2016
- A further update from 06 May 2016 to 19 December 2016

The search covering the period database inception to 19 December 2016 was aimed to identify HRQoL studies relevant to the scope of the decision problem:

- MEDLINE
- MEDLINE (R) In-Process
- EMBASE
- EconLIT
- NHS EED

Search strategies included subject index headings (e.g. MeSH & Emtree terms) where applicable and free text terms. HRQoL evaluation study design filters were

applied to the searches of the MEDLINE, MEDLINE (R) In-Process, and EMBASE databases.

In addition, proceedings from four major conferences were searched, for relevant abstracts/posters with results of recent trials:

- American Society of Clinical Oncology (ASCO) (ASCO-GI specific and ASCO Annual meeting) (2009-2011; 2012-2013; 2014-2016)
- European Society for Medical Oncology (ESMO) (ESMO-GI specific and Annual conference) (2009-2011; 2012-2013; 2014-2016)
- International Society For Pharmacoeconomics and Outcomes Research (ISPOR Annual conference) (2009-2011; 2012-2013; 2014-2016)
- International Society for Quality of Life Research (ISOQoL) (2009-2011; 2012-2013; 2014-2016)

The searches were limited to articles published in the English language. Full details of the search strategy including search terms employed and the databases searched are provided in Appendix 13.

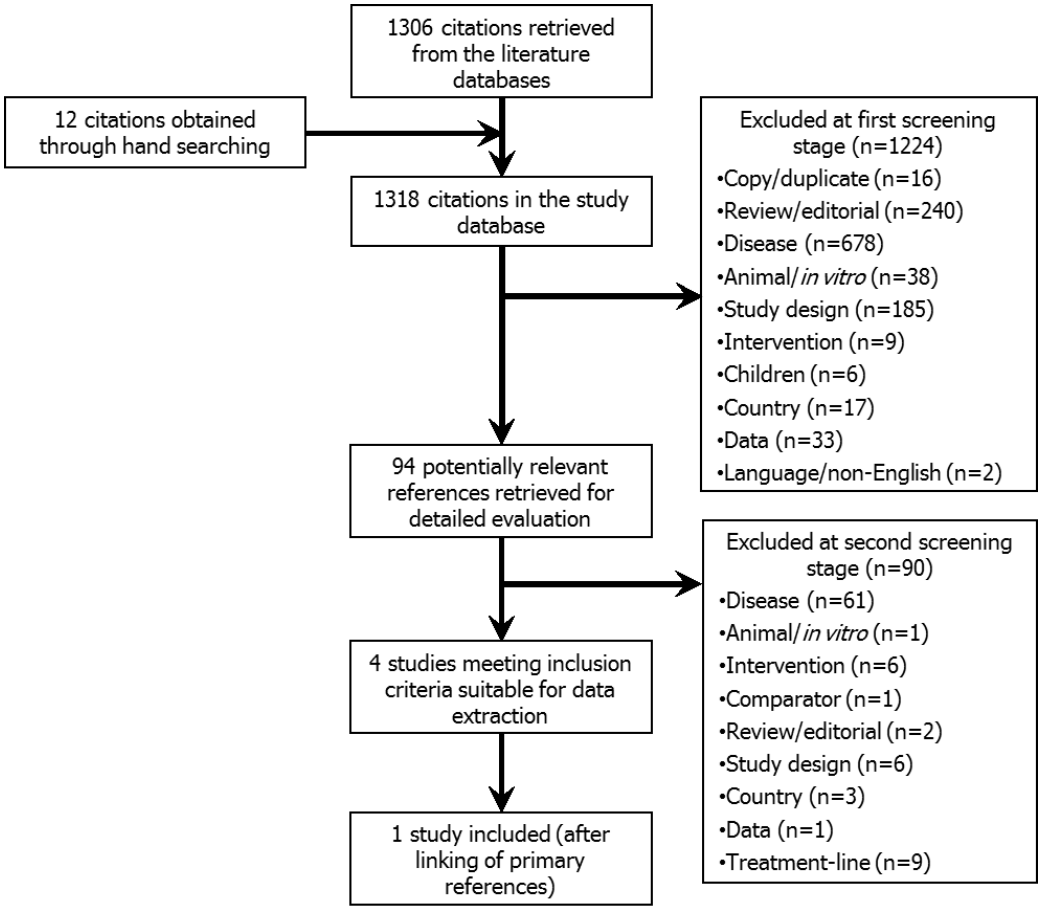
A set of inclusion and exclusion criteria (Table 42) was developed and applied to the search results, after duplicates across the various databases were removed in a graduated and systematic review: first, two individuals independently reviewed the titles and abstracts against the criteria and any disparity in the decision to include was reviewed by a third party; second, included abstracts were ordered and the full texts were reviewed against the criteria; third, all full text publications were either excluded with reason or included and extracted.

Table 42. Inclusion and exclusion criteria for cost-effectiveness publications

	Inclusion criteria	Exclusion criteria
Study design	• Study design appropriate to report the HRQoL/utility associated with GIST (patient preference studies, utility mapping studies, cohort studies / longitudinal studies (retrospective), cohort studies / longitudinal studies (prospective), case control studies, cross sectional studies, analysis of hospital records/databases, cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses)	• Literature and systematic reviews • Database studies or epidemiology studies, not collecting utility data • RCTs (with no piggy-back economic evaluations) • Studies published in non-English language (with/without English abstracts)
Patient population	• Studies including adult patients (aged ≥18 years) • Studies reporting data in countries of interest (US, Canada, Australia, France, Germany, Italy, Spain, UK, Brazil, Mexico, Japan, China, Korea)	• Studies in children or adolescents • Studies conducted in animals or *in vitro*
Disease/ therapy	• Studies including patients with metastatic, advanced, and/or unresectable GIST, defined as such using the study author's definition • Studies of third-line patients (who have failed two pharmacological therapies). However, as it is was anticipated that studies focused on third-line patients were rare, studies in first- and second-line patients were only excluded at the final stage of the second pass (at the first pass stage there was no exclusion based on therapy line)	• Studies that did not include patients with a specific GIST diagnosis (including gastrointestinal leiomyosarcoma that appeared to behave as GIST, soft-tissue sarcoma that appeared to behave as GIST, oesophageal leiomyosarcoma, gastric leiomyoma, gastric leiomyoblastoma, small intestinal leiomyoma and leiomyosarcoma, colonic and rectal leiomyoma and eiomyosarcoma, gastrointestinal autonomic nerve tumour, eiomyoma and leiomyosarcoma of omentum and mesentery, retroperitoneal leiomyosarcoma)
Intervention	• Regorafenib	• Any other intervention
Comparator	• Placebo/BSC	• Any other comparator

The PRISMA diagram (Figure 24) illustrates the number of publications identified and included/excluded at each stage of the review. One publication was finally included and data extracted from.

Figure 24. PRISMA flow diagram of the included HRQoL studies



5.4.4 Tabulate the details of the studies in which HRQL was measured. Include the following, but note that this list is not exhaustive:

- population in which health effects were measured
- information on recruitment (for example, participants of a clinical trial, approximations from clinical experts, utility elicitation exercises including members of the general public or patients)
- interventions and comparators
- sample size
- response rates
- description of health states
- adverse reactions

- appropriateness of health states given the 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.

After full text review, only one article was extracted into Table 43 for inclusion in this submission. This study assessed EQ-5D utility in the progression-free state (day 1 of cycle 1) and first post-progression observation.

Table 43. Summary list of published HRQL studies

Study	Country	Population	Intervention	Sample size	Elicitation method	Health states	Utility score
GRID Poole et al. (2015) (40)	58 years (SD 13.1)	Male: 64.3% Mean age (years): 58 Metastatic Unresectable, associated with disease progression with imatinib and sunitinib (100%)	Regorafenib	185	EQ-5D index score	Mean at baseline (day 1 of cycle 1) from the combined data set	0.769
						Mean at First progression-free state (Progression-free state represented by baseline observation, QoL observations made on day 1 of cycle 1 before commencing blinded treatment)	0.767

Study	Country	Population	Intervention	Sample size	Elicitation method	Health states	Utility score
						Mean at First post-progression State (The first post progression health state suggesting significantly impaired health-related quality of life after confirmed disease progression showed a decrease of -0.120)	0.647

5.4.5 Highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Poole et al. (2015) is the publication of reference for the HRQL findings from the GRID study.

Adverse reactions

5.4.6 Describe how adverse reactions affect HRQL. The effect of adverse reactions on HRQL should be explored regardless of whether they are included in a cost-effectiveness analysis in the base-case analysis. Any exclusion of the effect of adverse reactions on HRQL in the cost-effectiveness analysis should be fully justified.

The three most common adverse events - HFSR, diarrhoea, and fatigue – are generally easily manageable and their effect on the HRQL can be negligible. However, we assumed that EQ-5D values from the repeated measures analysis where the progression-free state was split by treatment arm were representative of the treatment effects and the associated adverse events. Results from this analysis

(Table 39) showed a slightly lower mean utility value for the regorafenib arm compared to placebo.

The cost-effectiveness results based on the utilities reported in Table 39 are presented in section 5.8.9.

Health-related quality-of-life data used in cost-effectiveness analysis

5.4.7 Define what a patient experiences in the health states in terms of HRQL in the cost-effectiveness analysis. Explain how this relates to the aspects of the disease or condition that most affect patients' quality of life.

In the progression-free health state the disease is controlled while on and off treatment, therefore it is reasonable to expect patients' HRQL to remain stable for the whole time spent in this health state.

In the progressed health state a decline in patients' HRQL towards the end of their lives may be experienced. This is not reflected by the utility assigned to this health state which may result into an overestimation of the real HRQL. However, HRQL values for patients who experienced disease progression were applied in both model arms, meaning no incremental difference was applied (40).

5.4.8 Clarify whether HRQL is assumed to be constant over time in the cost-effectiveness analysis. If not, provide details of how HRQL changes over the course of the disease or condition.

The cost-effectiveness analysis assumed HRQL within each health state being constant over time. This is in line with the evidence presented by Poole et al. (2015) indicating that utility remains stable in successive treatment cycles over time within a given health state (40).

5.4.9 If appropriate, describe whether the baseline HRQL assumed in the cost-effectiveness analysis is different from the utility values used for each of the health states. State whether quality-of-life events were taken from this baseline.

Utility values used in the cost-effectiveness analysis for patients in the progression-free health state were based on baseline observations.

A lower utility value for the progressed health state was adopted in the base case analysis consistently with the results from the paired-sample comparison which showed a statistically significant mean difference of -0.120 (p = 0.001) between baseline- and first post-progression utility (40).

5.4.10 If the health state utility values used in the cost-effectiveness analysis have been adjusted, describe how and why they have been adjusted, including the methodologies used.

Health state utility values used in the base case cost effectiveness analysis were based on the paired-samples comparison as reported in section 5.4. Because of the crossover design the repeated measures analysis did not contain a homogeneous progressed population for estimating utility of these subjects. The paired-samples comparison method is therefore preferred to the repeated measured analysis.

5.4.11 Identify any health effects found in the literature or clinical trials that were excluded from the cost effectiveness analysis and explain their exclusion.

No health effects found in the literature or GRID study and excluded from the cost effectiveness analysis were identified.

5.4.12 In a table, summarise the utility values chosen for the cost-effectiveness analysis, referencing values obtained in sections 5.4.1–5.4.6. Justify the choice of utility values, giving consideration to the reference case. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed. See below for a suggested table format.

Table 44. Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Progression-free	0.767 (0.025)	0.718, 0.816	Section 5.4.1 Page 169	See Section 5.4.1
Progressed	0.647 (0.039)	0.571, 0.723	Section 5.4.1 Page 169	See Section 5.4.1
HS, health state; AR, adverse reaction				

5.4.13 If clinical experts assessed the applicability of the health state utility values available or approximated any of values, provide the details (see section 5.3.4).

Not applicable.

5.5 *Cost and healthcare resource use identification, measurement and valuation*

This section should be read with the NICE guide to the methods of technology appraisal, section 5.5.

5.5.1 All parameters used to estimate cost effectiveness should be presented clearly in a table with 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.

The drug acquisition cost assumptions used in this economic analysis are based on the NHS list price and a confidential discounted PAS price and are shown in Table 45.

The drug acquisition costs are based on dosing assumptions of 139.8 mg/day (the mean actual treatment dose from GRID) for 21 days per 28-day (8). Regorafenib comes as 40mg tablets and all regorafenib patients took doses that were multiples of 40mg up to a maximum of 160mg. Seventy-two percent of regorafenib patients

underwent dose modifications during the double-blind phase, which is reflected in the mean dose of 139.8 mg/day.

Bayer is offering a patient access scheme (PAS) in the form of a confidential discount. The discount offered is approximately [redacted]% and reduces the cost per cycle of regorafenib from £3,744 to £[redacted], when no mean dose reduction is considered, and from £3,271 to £[redacted] when mean dose reduction is considered. Table 45 shows the results for all scenarios with and without PAS.

Table 45. Drug costs

Drug	Unit cost	Drug cost per 28-day cycle	Source
Regorafenib 160mg per day (without PAS)	£44.57/40mg tablet	£3,744.00	Bayer UK
Mean Regorafenib dose (dose as in GRID, without PAS)	£44.57/40mg tablet	£3,271.09	Bayer UK for price, Demetri, et al., 2013 (8) for mean dose
Regorafenib 160mg per day (with PAS)	£[redacted]/40mg tablet	£[redacted]	Bayer UK
Mean Regorafenib dose (dose as in GRID, with PAS)	£[redacted]/40mg tablet	£[redacted]	Bayer UK for price, Demetri, et al. 2013 (8) for mean dose

Resource use was determined from a 2013 physician resource use survey of 15 GIST medical oncologists in England and Wales. Physicians included had to be medical oncologists who personally and directly managed at least five patients with metastatic or unresectable GIST over the last six months. Results of the survey were validated in 2016 by two consultant oncologists specialised in the management of metastatic or unresectable GIST. This was to ensure that the assumptions from the earlier survey were still current and relevant.

As mentioned in section 5.2.5, treatment continuation after disease progression is not standard practice in England and Wales. This was further confirmed in the two physician surveys which showed that only 25.3% of patients with metastatic or unresectable GIST who have already failed on imatinib and sunitinib would continue receiving TKI treatment after disease progression. Therefore, the base case considers active treatment acquisition costs only until disease progression.

According to the survey, the main tests used on metastatic/unresectable GIST patients after previous treatment with imatinib and sunitinib are CT scans, MRI scans, full blood counts and liver function tests. Table 46 shows the average proportion of patients taking each test prior to treatment. Tests are performed in fewer patients starting BSC instead of a TKI such as regorafenib.

Table 46. Resource use prior to treatment

Test	Proportion of 3rd line patients receiving test prior to treatment with a TKI, Mean (SE)	Proportion of 3rd line patients receiving test prior to BSC, Mean (SE)
CT scan	0.85 (0.079)	0.24 (0.070)
MRI scan	0.12 (0.031)	0.01 (0.005)
Full blood count	0.92 (0.065)	0.56 (0.100)
Liver function test	0.92 (0.062)	0.49 (0.111)

SE = standard error; TKI = Tyrosine Kinase Inhibitor

These tests are often continued on an ongoing basis, although regular CT and MRI scans are not often continued in the post-progression state. See Table 47 and Table 48 for the progression-free and the post-progression states, respectively.

Table 47. Regular tests given to patients in the progression-free state

Test	Patients on a TKI		Patients on BSC	
	Percentage of physicians responding that patients would be given the test regularly	Average frequency (weeks between tests), Mean (SE)	Percentage of physicians responding that patients would be given the test regularly	Average frequency (weeks between tests), Mean (SE)
CT scan	100%	12.1 (1.44)	60%	18.9 (3.26)
MRI scan	73%	19.9 (4.00)	27%	18.0 (2.58)
Full blood count	93%	6.4 (1.90)	67%	10.9 (2.36)
Liver function test	93%	6.4 (1.90)	60%	11.2 (2.61)

SE = standard error; TKI = Tyrosine Kinase Inhibitor
Source: Physician survey of 15 medical oncologists treating GIST

Table 48. Regular tests given to patients in the post-progression state

Test	Percentage of physicians responding that patients would be given the test regularly, %	Average frequency (weeks between tests), Mean (SE)
CT scan	20%	14.5 (6.84)
MRI scan	7%	8.0 (-)
Full blood count	67%	8.8 (1.88)
Liver function test	60%	9.4 (2.03)

SE = standard error
Source: Physician survey of 15 medical oncologists treating GIST

The majority of physicians responded that outpatient visits are the most common form of regular monitoring and telephone consultations are not very common. See Table 49 for the average frequency of outpatient visits by health state.

Table 49. Frequency of outpatient visits based on health state

Health state	Percentage of physicians responding that patients would be monitored on an outpatient basis	Average frequency (weeks between visits), Mean (SE)
Progression-free on a TKI	100%*	6.2 (0.86)
Progression-free on BSC	100%	7.9 (0.77)
Progressed disease on BSC	100%	6.9 (0.97)

SE = standard error; TKI = Tyrosine Kinase Inhibitor
Source: Physician survey of 15 medical oncologists treating GIST
* Two physicians responded that they didn't know; we assume the total number of physicians is 13 for this category

Average frequencies by health state for tests and monitoring outpatient visits were used to calculate the corresponding probabilities over a four-week treatment cycle.

Regular medication for pain management is also fairly common in this stage of metastatic or unresectable GIST. See Table 50 for a summary of the results of the pain management section of the physician survey conducted in 2013.

Table 50. Pain management in the progressed-free and progressed health states

Treatment	Average proportion of patients treated with pain medication by health state and medicine	
	Progression-free Mean (SE)	Progressed disease Mean (SE)
Co-codamol, 2 tablets QDS (each containing 8mg codeine)	0.18 (0.039)	0.22 (0.043)
Tramadol, 100mg QDS	0.12 (0.028)	0.14 (0.036)
Paracetamol, 1g QDS	0.33 (0.074)	0.38 (0.085)
Morphine sulphate, 30mg immediate release every 4 hours	0.20 (0.057)	0.29 (0.065)
Dexamethasone, 4mg OD	0.11 (0.022)	0.19 (0.043)

SE = standard error
Source: Physician survey of 15 medical oncologists treating GIST

Patients may also be given palliative surgical resection or palliative radiotherapy to relieve or prevent symptoms. The results of the physician survey (shown in Table 51) indicate that use of palliative surgical resection or palliative radiotherapy does not depend on whether or not a patient is on a TKI and increases slightly in progressed disease.

Table 51. Palliative care interventions by health state

Palliative intervention	Average proportion of patients who receive the palliative care intervention, Mean (SE)		
	Progression-free on a TKI	Progression-free on BSC with no TKI	Progressed disease
Palliative surgical resection	0.10 (0.024)	0.10 (0.031)	[redacted] (0.033)
Palliative radiotherapy	0.20 (0.053)	0.20 (0.061)	[redacted] (0.063)

SE = standard error; TKI = Tyrosine Kinase Inhibitor
Source: Physician survey of 15 medical oncologists treating GIST

The units costs associated with the resource use described above can be found in Table 52.

Table 52. Unit costs associated with health state resource use

Item	Cost (£)	Source	Assumption
Regular tests			
CT scan	40.23	NHS Reference costs 2015-16	Cost per scan (IMAG); code RD26Z - Computerised Tomography Scan of three areas, with contrast;
MRI scan	146.61	NHS Reference costs 2015-16	Cost per scan *(weighted average of all MRI – adult; codes: RD01A, RD02A, RD03Z,RD04Z,RD05Z,RD06Z,RD07 Z)*
Full blood count	3.10	NHS Reference costs 2015-16	Cost per test (DAPS); code DAPS05 - Haematology
Liver function test	1.18	NHS Reference costs 2015-16	Cost per test (DAPS); code DAPS04 - Clinical Biochemistry
Regular monitoring visit			
Outpatient visit (regular monitoring)	93.00	2016/17 National Tariff; OP	Cost of outpatient attendance Attendances - code 370 WF01A Follow Up Attendance - Single Professional
Pain management			
Co-codamol	0.89	MIMS, January 2017	Cost per 30-tab pack (non-proprietary), 8mg codeine phosphate per tab
Tramadol	2.87	MIMS, January 2017	Cost per 100-cap pack, 50mg per cap (non-proprietary)
Paracetamol	2.19	MIMS, January 2017	Cost per 100-tab pack, 500mg per tab (non-proprietary)
Morphine sulphate immediate release	5.31	MIMS, January 2017	Cost per 56-tab pack, 10mg per tab (Sevredol®)
Dexamethasone	42.85	MIMS, January 2017	Cost per 50-tab pack, 2mg per tab (non-proprietary)
Palliative care			
Palliative surgical resection	3,943.21	NHS Reference costs 2015-16	Single intervention for malignant GI Tract disorder *(weighted average; code: FZ92D, FZ92E, FZ92F)*
Palliative radiotherapy-	160.59	NHS Reference costs 2015-16	Cost per medical specialist palliative care attendance *(weighted average adult; code: SD01A, SD02A, SD03A, SD04A)*

Resource identification, measurement and valuation studies

5.5.2 Describe how relevant cost and healthcare resource use data for England were identified. Include the search strategy and inclusion criteria, and consider published and unpublished studies to demonstrate how relevant cost and healthcare resource use data for England were identified. The search strategy used should be provided in an appendix. If the systematic search yields limited data for England,

the search strategy may be extended to capture data from other countries. Please give the following details of included studies:

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

Resource use was identified and validated through a physician survey of 15 GIST medical oncologists from England and Wales. Findings from this survey were further validated in 2016 by two consultant oncologists. Costs for use in the economic analysis are presented in section 5.5.5.

5.5.3 When describing how relevant unit costs were identified, comment on whether NHS reference costs or payment-by-results (PbR) tariffs are appropriate for costing the intervention being appraised. Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the PbR tariff. Provide the relevant Healthcare Resource Groups and PbR codes and justify their selection with reference to section 2.

Unit costs associated with resource use presented in section 5.5.1 and included in the cost-effectiveness analysis were retrieved from the following appropriate sources of data:

- NHS reference costs 2015/16
- Personal Social Services Research Unit 2015
- Monthly Index of Medical Specialties (MIMS) 2017
- 2016/17 National Tariff

- Drug tariff 01/2017

5.5.4 If clinical experts assessed the applicability of the cost and healthcare resource use values available, or approximated any of the values used in the cost-effectiveness analysis, provide the details (see section 5.3.4).

As reported in section 5.5.2, healthcare resource use values were provided by 15 GIST medical oncologists in England and Wales during a survey conducted in 2013. Data were further validated by two consultant oncologists in 2016. Cost of end-of-life care extracted from Abel et al. (2012) were also confirmed by the two physicians.

Intervention and comparators' costs and resource use

5.5.5 In a table, summarise the cost and associated healthcare resource use of each treatment. A suggested format for a table is provided below. Cross refer to other sections of the submission; for example, drugs costs should be cross-referenced to section 2.3.1. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 5.2.2.

A summary of the costs and associated resource use of each treatment is reported in Table 53.

Table 53. Input costs per cycle associated with the technology in the economic model

Item	Regorafenib mean (CI)	Reference in submission	BSC mean (CI)	Reference in submission
Drug costs§	£3,271.09 (£2,616.87; £3,925.30)	Section 5.5.1	-	-
Management costs				
One-time costs for regorafenib	£55.72 (£44.58; £66.86)	Section 5.5.1	-	-
One-time costs post-progression	£[redacted] (£[redacted]; £[redacted])	Section 5.5.1	£[redacted] (£[redacted]; £[redacted])	Section 5.5.1

Item	Regorafenib mean (CI)	Reference in submission	BSC mean (CI)	Reference in submission
Regorafenib + BSC while progression-free	£124.21 (£99.37; £149.05)	Section 5.5.1	-	-
BSC while progression-free	-	-	£80.07 (£64.05; £96.08)	Section 5.5.1
BSC post-progression	£88.98 (£71.18; £106.78)	Section 5.5.1	£88.98 (£71.18; £106.78)	Section 5.5.1
End of life costs	£8,736.53 (£8,052.12; £9,422.00)	Section 5.5.8	£8,736.53 (£8,052.12; £9,422.00)	Section 5.5.8
Additional one-time costs for BSC	-	-	£13.82 (£11.05; £16.58)	Section 5.5.1
Adverse Events Costs				
HFSR	£0.00	Section 5.5.7	£0.00	Section 5.5.7
Diarrhea	£7.02 (£5.62; £8.43)	Section 5.5.7	£7.02 (£5.62; £8.43)	Section 5.5.7
Hypertension	£11.86 (£9.48; £14.23)	Section 5.5.7	£11.86 (£9.48; £14.23)	Section 5.5.7

CI = confidence interval
§ Drug costs based on 139.8 mg dose reduction

Further explanation on how the costs per cycle included in the model were calculated is reported in sections 5.5.6 and 5.5.7.

Health-state costs and resource use

5.5.6 Summarise and tabulate the costs included in each health state. A suggested format for a table is provided below. Cross refer 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 5.2.2.

Table 54 shows the resulting health state costs. The one-time costs consist of test costs prior to starting treatment and palliative surgical resection and palliative radiotherapy. However, palliative surgical resection and palliative radiotherapy costs are only applied in the progressed disease state since the resource use is the same in the progression-free state regardless of whether the patient is taking a TKI.

For each treatment arm, one-time costs in the progression-free health state were estimated as the sum of the unit cost of each test (Table 52) weighted by the corresponding proportion of patients undergoing the single test (Table 46). Similarly, one-time costs in the progressed health state were obtained as the sum of the unit costs of palliative care interventions (Table 52) weighted by the proportion of patients requiring palliative care (Table 43).

Regular per cycle costs consist of regular outpatient monitoring visits, regular tests and medication for pain management. For each treatment arm and health state, unit cost of regular outpatient monitoring visits and regular tests (Table 52) applied in the model were weighted by the corresponding average probabilities per cycle (see section 5.5.1). Similarly, for each treatment arm and health state, costs of pain management per cycle were based on the unit costs for pain management (Table 52) weighted by the corresponding average proportion of patients requiring medications for the treatment of pain (Table 50).

Table 54. Health state costs per cycle included in the model

Cost component		**Progression-free state on a TKI (£), Mean (SE)**	**Progression-free state on BSC with no TKI (£), Mean (SE)**	**Progressed disease (£), Mean (SE)**
One-time costs	Tests	55.72 (5.53)	13.82 (2.93)	N/A
	Palliative resection	Not included	Not included	[redacted] (129.38)
	Palliative radiotherapy	Not included	Not included	[redacted] (10.11)
	Total one-time costs	**55.72 (5.53)**	**13.82 (2.93)**	[redacted] **(129.77)**
Regular per cycle costs	Regular tests	45.45 (5.46)	14.81 (4.08)	8.35 (36.00)
	Regular outpatient monitoring visits	60.49 (9.16)	46.91 (4.73)	53.68 (8.15)
	Pain management	18.27 (2.97)	18.35 (2.97)	26.95 (3.77)
	Total per cycle costs	**124.21 (11.07)**	**80.07 (6.92)**	**88.98 (37.11)**

SE = standard error

All standard errors associated with cost and resource use inputs have been calculated assuming independence of variables. Although independence is unlikely, the result is a larger standard error, hence a wider confidence interval for costs and therefore overall more conservative.

Adverse reaction unit costs and resource use

5.5.7 Summarise and tabulate the costs for each adverse reaction listed in section 4.12 and included in the de novo cost-effectiveness analysis. These should include the costs of therapies identified in section 2.3. A suggested format for a table is provided below. Cross refer to other sections of the submission for the resource costs.

Grade 3 and 4 adverse events (AEs) reported in at least 3% of patients were included in the model: hand-foot skin reaction (HFSR), diarrhoea, and hypertension. Bayer UK provides a free of charge HSFR kit in order to assist in the management of this adverse event, hence a zero cost was associated with this in the model. The treatment of diarrhoea consists of drug treatment with loperamide. The drug unit costs and calculations are presented in Table 55.

Table 55. Treatment costs associated with diarrhoea

Drug	**Loperamide**
Cost per pack	£2.15
No. tabs per pack	30.00
mg per tab	2.00
Cost per mg	£0.04
Average daily dose (mg)	7.00
Average weekly dose (mg)	49.00
Cost per cycle	**£7.02**

Source: (60)

It was previously reported that the management of hypertension in this therapeutic area consists of treatment with an ACE inhibitor once daily and is associated with two annual GP visits and two annual district nurse appointments (61). Ramipril 10mg was used in the model as it is the most commonly dispensed ACE inhibitor by pharmacy contractors in England (60). The drug unit costs and calculations are presented in Table 56 and the management costs are detailed in Table 57. These generated a cost per patient per cycle of £11.86.

Table 56. Drug costs associated with hypertension treatment

Drug	Ramipril
Cost per pack*	£1.24
No. tabs per pack	28.00
mg per tab	10.00
Cost per mg	£0.004
Average daily dose (mg)	10.00
Average weekly dose (mg)	70.00
Cost per cycle	**£1.24**

Source: (60)

Table 57. Management costs associated with hypertension treatment

Management	Cost	Reference
GP visit	£44	PSSRU Unit costs of Health & Social Care 2015, pg. 177 - Table 10.8b (62)
District nurse visit	£25	PSSRU Unit costs of Health & Social Care 2015, pg. 175 - Table 10.7 (62)

The cost for the GP visit could be updated to the more recent amount reported in PSSRU 2016. However, no cost associated with the district nurse visit is reported in PSSRU 2016. For this reason we decided to use a consistent source of costs – i.e. PSSRU 2015 - for both types of visit.

Miscellaneous unit costs and resource use

5.5.8 Describe and tabulate any additional costs and healthcare resource use that have not been covered elsewhere (for example, costs relating to subsequent lines of therapy received after disease progression, personal and social services costs). If none, please state.

End-of life costs

End-of-life costs were taken from the study conducted by Abel et al (63) This was a study on a cohort of hospice patients in South-West England. The details of the costs and patient numbers in the study are presented in Table 58. The costs were adjusted for inflation using the Hospital and Community Health Services (HCHS) index (21) (Table 59).

Table 58. End-of-life costs reported in Abel et al (63)

	Cost (£)	Lower CI (£)	Upper CI (£)	Patients
Death in hospital	11,299	9,161	13,436	108
Death outside of hospital	7,730	7,079	8,381	556

CI = confidence interval

Table 59. Adjustment of end-of-life costs for inflation

Year	Pay & Price Index (base 1987/8=100)
2011/12	282.5
2012/13	287.3
2013/14	290.5
2014/15	293.1
2015/16	297.00

Although the weighted cost is already presented in the paper, it was also calculated using the costs in Table 58, which were weighted based on the number of patients and then inflated using the index shown in Table 59 to generate an end-of-life cost of £8,736 which was used in this economic analysis.

5.6 *Summary of base case de novo analysis inputs and assumptions*

This section should be read with the NICE guide to the methods of technology appraisal, section 5.11.1.

Summary of base case de novo analysis inputs

5.6.1 Tabulate all variables included in the cost-effectiveness analysis, detailing the values used, range (for example, confidence interval, standard error or distribution) and source. Cross refer to other parts of the submission. Complete the table below that summarises the variables applied in the economic model.

A summary of variables used in the model applied in the model for the base case de novo analysis is reported in Table 60.

Table 60. Summary of variables applied in the economic model (per cycle)

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Regorafenib cost	£[redacted]	(£[redacted]-£[redacted])	Table 45
One-time costs for regorafenib	£56	(£45-£67)	Table 54
Regorafenib + BSC while progression-free	£124	(£99-£149)	Table 54
BSC while progression-free	£80	(£64-£96)	Table 54
BSC post-progression	£89	(£71-£107)	Table 54
End of life costs	£8,736	(£8,052-£9,422)	Table 58
Diarrhoea costs	£7	(£6-£8)	Table 55
Hypertension costs	£12	(£9-£14)	Table 56
Progression-free state utility	0.767	(0.718-0.816)	Table 36
Post-progression state utility	0.647	(0.571-0.723)	Table 36
Discount rate (costs)	3.5%	(0-6%)	Table 29
Discount rate (benefits)	3.5%	(0-6%)	Table 29

5.6.2 For the base-case de novo analysis the company should ensure that the cost-effectiveness analysis reflects the NICE reference case as closely as possible. Describe the rationale if an input chosen in the base-case de novo analysis:

- deviates from the NICE reference case or
- is taken from other sources (such as the published literature) rather than data from clinical trials of the technology (when available).

The NICE reference case was followed as closely as possible.

Assumptions

5.6.3 Provide a list of all assumptions used in the de novo economic model and justify each assumption.

All the assumptions used in the de novo economic model are reported in Table 61.

Table 61. Model assumptions – base case analysis

Assumption	Reason	Section
Health state assumptions		
Initially all patients begin in the progression free on treatment health state and are assigned progression free disease utility and costs of treatment while on therapy.	This is in line with trial	5.2.2
Patients discontinuing treatment prior to progression are not assigned a cost of active treatment and are assigned progression free utility and other routine costs. Patients can move to the death state based on the OS curve. As there are no cost or outcome implications, the placebo arm does not track patients between on treatment and off treatment states.	This is in line with trial	5.2.2
While in the progressed state patients are assigned progression state disease utility and costs of disease management. In the progressed state patients are not assigned costs of regorafenib treatment. Patients can only move from the progressed state to the death state.	Treatment with regorafenib should continue as long as benefit is observed or until unacceptable toxicity occurs	5.2.2
Other assumptions		
Time horizon of 40 years	This should be sufficiently long to capture all the lifetime benefits.	5.2.2
BSC as the only comparator	There are no approved treatments for patients in the given indication for regorafenib.	5.2.4
IPE crossover adjustment	Crossover causes significant bias in the effectiveness estimate if uncorrected. The IPE method provided the least bias for crossover adjustment.	5.3.2
Log-logistic function used for long term extrapolation of OS	This provided the best statistical fit according to the AIC.	5.3.2
Same utilities used for each treatment arm	No statistically significant treatment effect was found between treatment arms in the utility analyses, therefore the same utilities were applied in both arms.	5.4.1
Resource use based on 2013 physician survey	Physicians were oncologists that had practiced in the area of GIST. The resource use assumptions were then re-evaluated by clinical experts in 2016, and changes to resource use assumptions were explored in scenario analyses.	5.5.1

5.7 *Base-case results*

This section should be read with the NICE guide to the methods of technology appraisal, sections 5.7.4 and 5.11.2–5.11.3.

5.7.1 Provide the results of the analysis. In particular, results should include, but are not limited to, the following:

- the link between clinical- and cost-effectiveness results
- costs, quality-adjusted life years (QALYs) and incremental cost per QALY
- disaggregated results such as life years gained, costs associated with treatment, costs associated with adverse reactions, and costs associated with follow-up or subsequent treatment.

Please refer to section 5.7.2 for the full set of results.

Base-case incremental cost effectiveness analysis results

5.7.2 When presenting the results of the base case incremental cost effectiveness analysis in the table below, list the interventions and comparator(s) from least to most expensive. Present incremental cost-effectiveness ratios (ICERs) compared with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance. If the company has formally agreed a patient access scheme with the Department of Health, present the results of the base-case incremental cost-effectiveness analysis with the patient access scheme.

In the model base case using the list price the incremental cost per QALY of regorafenib plus BSC versus BSC alone is £[redacted]/QALY gained (Table 62) with regorafenib being more expensive by £[redacted] and more effective by 0.748 QALYs using the log-logistic extrapolation for OS.

Table 62. Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (LYs)	ICER (£) incremental (QALYs)
Placebo + BSC	10,671	1.474	0.969					
Regorafenib	[redacted]	2.521	1.717					
				[redacted]	1.047	0.748	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Using the PAS price of regorafenib, the incremental cost per QALY of regorafenib plus BSC versus BSC alone is £34,476 /QALY gained (Table 63) with regorafenib being more expensive by £25,786 and more effective by 0.748 QALYs using the log-logistic extrapolation for OS.

Table 63. Base-case results (with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (LYs)	ICER (£) incremental (QALYs)
Placebo + BSC	10,671	1.474	0.969					
Regorafenib	36,457	2.521	1.717					
				25,786	1.047	0.748	24,623	34,476
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

The proportion of patients alive from the models at selected time points are presented in Table 64 and compared with corresponding values from the GRID trial. The similarity between the two sets of data shows that the model closely mirrors the clinical evidence.

Clinical outcomes from the model

5.7.3 For the outcomes highlighted in the decision problem (see section 3), provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials, as suggested in the table below. Discuss reasons for any differences between the modelled results in the cost-effectiveness analysis and the observed results in the clinical trials (for example, adjustment for crossover).

The model accurately represents the data from the trial, as shown in Table 64 below.

Table 64. Summary of model results compared with clinical data

Outcome	Time horizon	Placebo + BSC		Regorafenib + BSC	
		Clinical trial result	Model result	Clinical trial result	Model result
Overall survival	1 year	0.38	0.42	0.65	0.66
	2 years	0.19	0.20	0.35	0.39
	3 years	0.15	0.12	0.26	0.26
Progression-free survival	168 days	n/a	n/a	0.43	0.44

5.7.4 Provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying 1 for each comparator.

Table 65. Markov traces over time (in one-year increments) – regorafenib and placebo

Day	Regorafenib			BSC		
	Progression-free	Progressed	Death	Progression-free	Progressed	Death
1	[redacted]	[redacted]	[redacted]	1.0000	0.0000	0.0000
29	[redacted]	[redacted]	[redacted]	0.6410	0.3297	0.0293
57	[redacted]	[redacted]	[redacted]	0.2620	0.6600	0.0781
85	[redacted]	[redacted]	[redacted]	0.1098	0.7554	0.1348
113	[redacted]	[redacted]	[redacted]	0.0497	0.7563	0.1940
141	[redacted]	[redacted]	[redacted]	0.0241	0.7235	0.2524
169	[redacted]	[redacted]	[redacted]	0.0125	0.6795	0.3080
197	[redacted]	[redacted]	[redacted]	0.0068	0.6332	0.3600
225	[redacted]	[redacted]	[redacted]	0.0038	0.5882	0.4079
253	[redacted]	[redacted]	[redacted]	0.0023	0.5459	0.4518
281	[redacted]	[redacted]	[redacted]	0.0014	0.5069	0.4917
309	[redacted]	[redacted]	[redacted]	0.0009	0.4712	0.5280
337	[redacted]	[redacted]	[redacted]	0.0006	0.4387	0.5608
365	[redacted]	[redacted]	[redacted]	0.0004	0.4091	0.5906

5.7.5 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.

Table 66. QALY accrued over time: (in one-year increments) – regorafenib and placebo

Day	Regorafenib			BSC		
	Progression-free	Progressed	Death	Progression-free	Progressed	Death
1						
29	[redacted]	[redacted]	[redacted]	0.0483	0.0082	0.0000
57	[redacted]	[redacted]	[redacted]	0.0266	0.0246	0.0000
85	[redacted]	[redacted]	[redacted]	0.0109	0.0351	0.0000
113	[redacted]	[redacted]	[redacted]	0.0047	0.0375	0.0000
141	[redacted]	[redacted]	[redacted]	0.0022	0.0367	0.0000
169	[redacted]	[redacted]	[redacted]	0.0011	0.0348	0.0000
197	[redacted]	[redacted]	[redacted]	0.0006	0.0326	0.0000
225	[redacted]	[redacted]	[redacted]	0.0003	0.0303	0.0000
253	[redacted]	[redacted]	[redacted]	0.0002	0.0281	0.0000
281	[redacted]	[redacted]	[redacted]	0.0001	0.0261	0.0000
309	[redacted]	[redacted]	[redacted]	0.0001	0.0243	0.0000
337	[redacted]	[redacted]	[redacted]	0.0000	0.0226	0.0000
365	[redacted]	[redacted]	[redacted]	0.0000	0.0210	0.0000

Disaggregated results of the base case incremental cost effectiveness analysis

5.7.6 Provide details of the disaggregated QALYs and costs by health state, and of resource use predicted by the model in the base case incremental cost effectiveness analysis by category of cost. The tables that should be completed summarising the disaggregated results (for example, QALY gain by health state, costs by health state, predicted resource use by category of cost) are presented below.

A summary of the QALY gain by health state is reported in Table 67.

Table 67. Summary of QALY gain by health state

Health state	QALY Regorafenib	QALY Placebo	Increment	Absolute increment	% absolute increment
Progression-free	0.566	0.095	0.471	0.471	52%
Post Progression	1.412	0.981	0.431	0.431	48%
Total	1.978	1.076	0.902	Total absolute increment	100%

QALY, quality-adjusted life year; HS1, health state 1; HS2, health state 2

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

Summaries of costs by health state when considering no PAS and PAS are presented in Table 68 and Table 69.

Table 68. Summary of costs by health state (without PAS)

Health state	Cost Regorafenib (£)	Cost Placebo (£)	Increment (£)	Absolute increment (£)	% absolute increment
Progression-free	[redacted]	224	[redacted]	[redacted]	[redacted]%
Post Progression	[redacted]	2,041	[redacted]	[redacted]	[redacted]%
Death	[redacted]	8,406	[redacted]	[redacted]	[redacted]%
Total	[redacted]	10,671	[redacted]	Total absolute increment	[redacted]%

HS1, health state 1; HS2, health state 2

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

Table 69. Summary of costs by health state (with PAS)

Health state	Cost Regorafenib (£)	Cost Placebo (£)	Increment (£)	Absolute increment (£)	% absolute increment
Progression-free	25,796	224	25,572	25,572	97%
Post Progression	2570	2,041	529	529	2%
Death	8,091	8,406	-315	315	1%
Total	36,457	10,671	25,786	Total absolute increment	100%

HS1, health state 1; HS2, health state 2

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

Summaries of predicted resource use by category of costs when considering no PAS and PAS are presented in Table 70 and Table 71.

Table 70. Summary of predicted resource use by category of cost (without PAS)

Item	Cost Regorafenib (£)	Cost Placebo (£)	Increment (£)	Absolute increment (£)	% absolute increment
Drug costs - progression-free	[redacted]	0	[redacted]	[redacted]	[redacted]%
Drug costs - post-progression	[redacted]	0	[redacted]	[redacted]	[redacted]%
Additional one-time cost post-progression	[redacted]	472	[redacted]	[redacted]	[redacted]%
Adverse event costs	[redacted]	3	[redacted]	[redacted]	[redacted]%
Monitoring costs	[redacted]	1,789	[redacted]	[redacted]	[redacted]%
End-of-life costs	[redacted]	8,406	[redacted]	[redacted]	[redacted]%
Total	[redacted]	10,671	[redacted]	Total absolute increment	[redacted]%

Table 71. Summary of predicted resource use by category of cost (with PAS)

Item	Cost Regorafenib	Cost Placebo	Increment	Absolute increment	% absolute increment
Drug costs - progression-free	24,592	0	24,592	24,592	93%
Drug costs - post-progression	0	0	0	0	0%
Additional one-time cost post-progression	466	472	-7	7	0%
Adverse event costs	11	3	7	7	0%
Monitoring costs	3,297	1,789	1,508	1,508	6%
End-of-life costs	8,091	8,406	-315	315	1%
Total	36,457	10,671	25,786	Total absolute increment	100%

5.8 *Sensitivity analysis*

This section should be read with the NICE guide to the methods of technology appraisal, sections 5.7 and 5.8.

One-way sensitivity analysis (OWSA) and probabilistic sensitivity analysis (PSA) were performed to explore the effect of parameter uncertainty. Scenario analysis was performed to explore assumptions in the model.

Probabilistic sensitivity analysis

5.8.1 All inputs used in the analysis will be estimated with a degree of imprecision. As specified in the NICE guide to the methods of technology appraisal, probabilistic sensitivity analysis 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. In non-linear decision models, probabilistic methods provide the best estimates of mean costs and outcomes. The mean value, distribution around the mean, and the source and rationale for the supporting evidence should be clearly described for each parameter included in the model. The distributions for probabilistic sensitivity analysis should not be arbitrarily chosen, but should represent the available evidence on the parameter of interest, and their use should be justified.

PSA was conducted to simultaneously take into account the uncertainty associated with parameter values. The implementation of PSA involved assigning particular parametric distributions and repeatedly sampling mean parameter values.

The variables included in the PSA are presented in Table 72. The extrapolated data were sampled during the PSA; this was performed using the covariance matrix for each distribution type for PFS and OS in each arm to generate sampled values for the parameters for each distribution according to their covariance structure. However, this does not consider structural uncertainty. The probabilities of HFSR and diarrhoea in the placebo arm were not varied in the PSA since there were zero

events, making it difficult to estimate the standard error. These probabilities were varied in the OWSA and found not to have a large impact on the ICER (see Table 75 and Table 76).

Table 72. Variables tested in PSA

Parameter	Mean	SE	Alpha	Beta	Distribution	Source
Drug costs						
Length of regorafenib treatment post-progression in regorafenib arm (days)	[redacted]	10.29	381.58	0.53	Gamma	GRID CSR, mean actual time under treatment of Regorafenib+BSC in the DB+OL phase minus the mean actual time under treatment in the DB phase only (table 10-1 and 10-2). (14)
Management costs						
Regorafenib + BSC while progression-free (£ per cycle)	£124.21	12.67	96.04	1.29	Gamma	Physician survey
BSC while progression-free (£ per cycle)	£80.07	8.17	96.04	0.83	Gamma	Physician survey
BSC post-progression (£ per cycle)	£88.98	9.08	96.04	0.93	Gamma	Physician survey
End of life costs (£)	£8,737	349	625.01	13.98	Gamma	Abel et al (2012) (63)
Adverse event costs (Grades 3-4 only)						
Diarrhoea (£ per cycle)	£7.02	0.72	96.04	0.07	Gamma	Physician survey
Hypertension (£ per cycle)	£11.86	1.21	96.04	0.12	Gamma	Physician survey
Utility inputs						
Utility in progression-free state *	0.77	0.025	218.55	66.39	Beta	EQ-5D data collected in GRID trial
Post-progression state*	0.65	0.039	96.50	52.65	Beta	EQ-5D data collected in GRID trial
Adverse events probability per patient (Grades 3-4 only)						
Regorafenib HFSR	0.19697	0.035	25.803	105.197	Beta	GRID CSR Table 10-6 (18)
Regorafenib diarrhoea	0.05303	0.020	6.947	124.053	Beta	GRID CSR Table 10-6 (18)

Parameter	Mean	SE	Alpha	Beta	Distribution	Source
Regorafenib hypertension	0.23485	0.037	30.765	100.235	Beta	GRID CSR Table 10-6 (18)
Placebo hypertension	0.03030	0.015	3.9697	127.0303	Beta	GRID CSR Table 10-6 (18)

*Utilities for both the regorafenib arm and placebo arm were tested, however were not found to be statistically different. Therefore a conservative approach was taken to apply the same utility value for both arms. These values were sampled separately in the PSA (40)

Provide the information specified in sections 5.8.2–5.8.4.

5.8.2 The distributions and their sources for each parameter should be clearly stated if different from those presented in section 5.5, including the derivation and value of 'priors'. If any parameters or variables were omitted from the probabilistic sensitivity analysis, please provide the rationale for the omission(s).

No parameters or variables were omitted in the probabilistic sensitivity analysis.

5.8.3 Present the incremental cost effectiveness results of a probabilistic sensitivity analysis (including 95% confidence intervals). Include scatter plots and cost-effectiveness acceptability curves showing the probability that the treatment is cost effective if the incremental cost-effectiveness ratio ICER is £20,000 to £30,000 per QALY gained. Describe how the probabilistic ICER(s) were calculated and provide the rationale.

Simulations with 3,000 iterations produced the average results shown in Table 73 below.

Table 73. Average results from PSA (with and without PAS)

	Regorafenib + BSC			Placebo + BSC			Incremental			ICER (£/QALY)
	LYs	QALYs	Costs	LYs	QALYs	Costs	LYs	QALYs	Costs	
List Price	2.546	1.735	£[redacted]	1.500	0.986	£11,434	1.046	0.749	£[redacted]	£[redacted]
PAS price	2.536	1.727	£37,813	1.500	0.984	£11,447	1.036	0.742	£26,366	£35,514

Figure 25 and Figure 27 show the cost-effectiveness plane without and with the PAS price. Figure 26 and Figure 28 show the cost-effectiveness acceptability curve (CEAC) without and with the PAS price. At a willingness to pay of £50,000 per QALY gained regorafenib was [redacted]% likely to be cost-effective at its list price and 81% likely at its PAS price.

Figure 25. Cost-effectiveness plane showing per patient incremental cost and QALYs (without PAS)

Figure 26. CEAC based on willingness-to-pay per QALY (without PAS)

[redacted]

Figure 27. Cost-effectiveness plane showing per patient incremental cost and QALYs (with PAS)

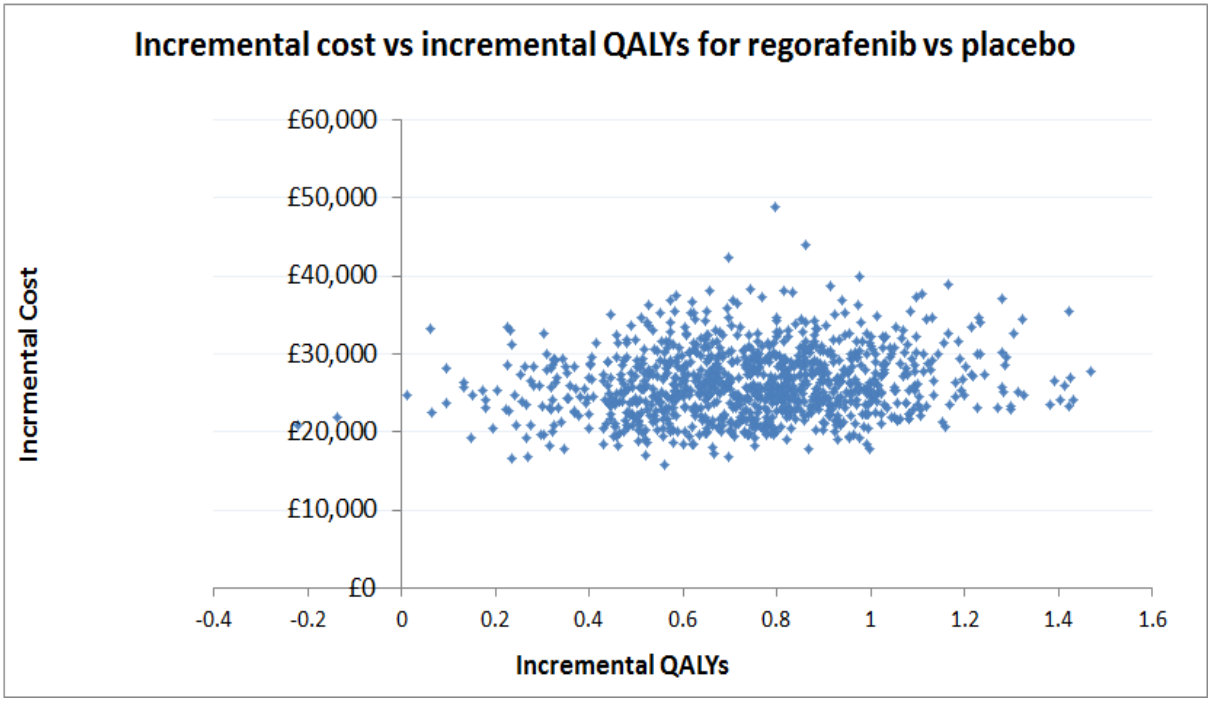
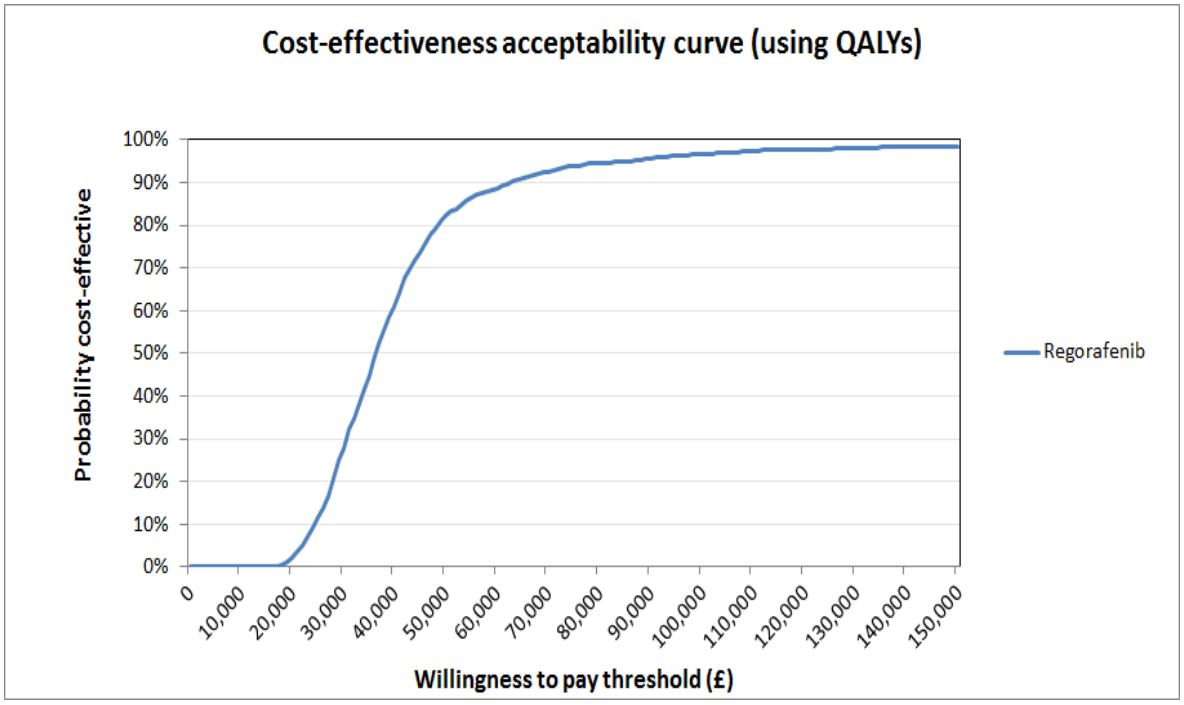


Figure 28. CEAC based on willingness-to-pay per QALY (with PAS)



5.8.4 Describe and explain, if any, the variation between the incremental cost effectiveness analysis results estimated from the base-case analysis (section 5.6) and the probabilistic sensitivity analysis.

Incremental cost effectiveness analysis results estimated from the probabilistic sensitivity analysis are consistent with those found in the base-case analysis.

Deterministic sensitivity analysis

5.8.5 Identify which variables were subject to deterministic sensitivity analysis, how they were varied, and the rationale behind this. If any parameters or variables listed in section 5.6.1 were omitted from sensitivity analysis, please provide the rationale.

The values used for the lower and upper OWSA analysis are shown in Table 74 with full results in Table 75 (using the list price for regorafenib), and Table 76 (using the PAS price).

The top 15 model drivers are shown in the tornado diagram in Figure 29 in terms of incremental cost per QALY (at the list price for regorafenib), the tornado diagram using the PAS price is shown in Figure 30. For both, the highest impact was observed when the drug acquisition cost for regorafenib was varied. This provided an ICER varying between £[redacted] and £[redacted] per QALY gained when applying the list price and between £27,900 and £41,052 per QALY gained when using the PAS price. Variation of the discount rate for the utilities and costs were also important in determining the ICER.

Table 74. Inputs used for lower, upper and scenario OWSA analysis

Variable	Input values used in OWSA		Source
	Lower input	Upper input	
Discount rate costs	0.00	0.06	Assumption
Discount rate utilities	0.00	0.06	Assumption
Additional one-time costs regorafenib	£44.58	£66.86	± 20% base case value
Regorafenib + BSC management costs while progression-free	£99.37	£149.05	± 20% base case value
BSC management costs while progression-free	£64.05	£96.08	± 20% base case value
BSC management costs post-progression	£71.18	£106.78	± 20% base case value
End of life costs	£8,052.12	£9,422	Abel et al (63)
Diarrhoea cost	£5.62	£8.43	± 20% base case value
Hypertension cost	£9.48	£14.23	± 20% base case value
HFSR probability on regorafenib	0.13	0.26	Base case ± 2 SE
Diarrhoea probability on regorafenib	0.01	0.09	Base case ± 2 SE
Hypertension probability on regorafenib	0.16	0.31	Base case ± 2 SE
Hypertension probability on placebo	0.00	0.06	Base case ± 2 SE
Utility of progression-free health state - Regorafenib	0.72	0.82	Base case ± 2 SE
Utility of progression-free health state - Placebo	0.72	0.82	Base case ± 2 SE
Utility of progressed health state	0.57	0.72	Base case ± 2 SE

SE= standard error

5.8.6 Present the results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Results of the deterministic sensitivity analysis are presented in Table 75 and Table 76.

Table 75. Full OWSA results (without PAS)

	Low variation			High variation		
Variable	**Inc Cost (£)**	**Inc QALYs**	**ICER (£/QALY)**	**Inc Cost (£)**	**Inc QALYs**	**ICER (£/QALY)**
Regorafenib drug cost (2616.87, 3925.3)	[redacted]	0.7479	[redacted]	[redacted]	0.7479	[redacted]
Discount rate utilities (0, 0.06)	[redacted]	0.9021	[redacted]	[redacted]	0.6763	[redacted]
Discount rate costs (0, 0.06)	[redacted]	0.7479	[redacted]	[redacted]	0.7479	[redacted]
Utility of progressed health state (0.57, 0.72)	[redacted]	0.7127	[redacted]	[redacted]	0.7832	[redacted]
Utility of progression-free health state - Regorafenib (0.72, 0.82)	[redacted]	0.7131	[redacted]	[redacted]	0.7828	[redacted]
Utility of progression-free health state - Placebo (0.72, 0.82)	[redacted]	0.7540	[redacted]	[redacted]	0.7419	[redacted]
Regorafenib + BSC management costs while progression-free (99.37, 149.05)	[redacted]	0.7479	[redacted]	[redacted]	0.7479	[redacted]
BSC management costs post-progression (71.18, 106.78)	[redacted]	0.7479	[redacted]	[redacted]	0.7479	[redacted]
BSC management costs while progression-free (64.05, 96.08)	[redacted]	0.7479	[redacted]	[redacted]	0.7479	[redacted]
End of life costs (8052.12, 9422)	[redacted]	0.7479	[redacted]	[redacted]	0.7479	[redacted]
Additional start-up costs regorafenib (44.58, 66.86)	[redacted]	0.7479	[redacted]	[redacted]	0.7479	[redacted]
Hypertension probability on regorafenib (0.16, 0.31)	[redacted]	0.7479	[redacted]	[redacted]	0.7479	[redacted]
Hypertension cost (9.48, 14.23)	[redacted]	0.7479	[redacted]	[redacted]	0.7479	[redacted]
Diarrhoea probability on regorafenib (0.01, 0.09)	[redacted]	0.7479	[redacted]	[redacted]	0.7479	[redacted]
Hypertension probability on placebo (0, 0.06)	[redacted]	0.7479	[redacted]	[redacted]	0.7479	[redacted]
Diarrhoea cost (5.62, 8.43)	[redacted]	0.7479	[redacted]	[redacted]	0.7479	[redacted]
HFSR cost (0, 0)	[redacted]	0.7479	[redacted]	[redacted]	0.7479	[redacted]
HFSR probability on regorafenib (0.13, 0.26)	[redacted]	0.7479	[redacted]	[redacted]	0.7479	[redacted]

Variable	Low variation			High variation		
	Inc Cost (£)	Inc QALYs	ICER (£/QALY)	Inc Cost (£)	Inc QALYs	ICER (£/QALY)
HFSR probability on placebo (0, 0)	[redacted]	0.7479	[redacted]	[redacted]	0.7479	[redacted]
Diarrhoea probability on placebo (0, 0)	[redacted]	0.7479	[redacted]	[redacted]	0.7479	[redacted]
Death utility (0, 0)	[redacted]	0.7479	[redacted]	[redacted]	0.7479	[redacted]
OS regorafenib vs placebo unadjusted HR (0.79, 1.53)	[redacted]	0.7479	[redacted]	[redacted]	0.7479	[redacted]
OS regorafenib vs placebo RPSFT HR (1.2, 2.37)	[redacted]	0.7479	[redacted]	[redacted]	0.7479	[redacted]
OS regorafenib vs placebo IPE HR (1.28, 2.53)	[redacted]	0.7479	[redacted]	[redacted]	0.7479	[redacted]

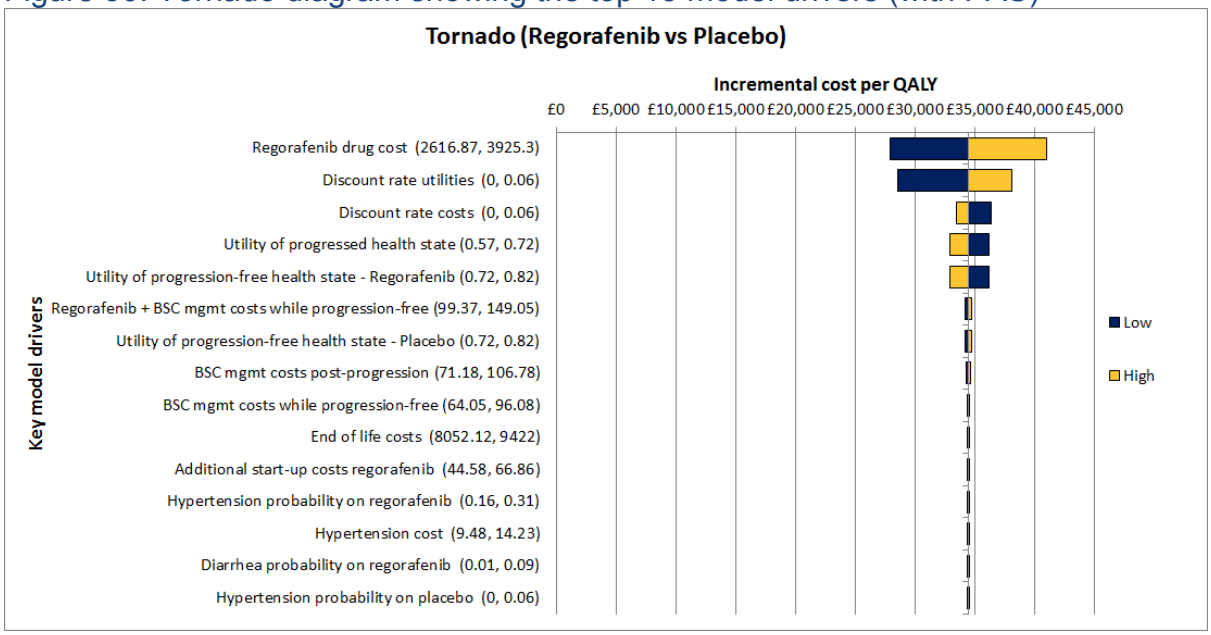
Table 76. Full OWSA results (with PAS)

Variable	Low variation			High variation		
	Inc Cost (£)	Inc QALYs	ICER (£/QALY)	Inc Cost (£)	Inc QALYs	ICER (£/QALY)
Regorafenib drug cost (2616.87, 3925.3)	20,867.86	0.7479	27,900.23	30,704.73	0.7479	41,052.08
Discount rate utilities (0, 0.06)	25,786.30	0.9021	28,584.71	25,786.30	0.6763	38,129.03
Discount rate costs (0, 0.06)	27,212.11	0.7479	36,382.46	25,007.69	0.7479	33,435.16
Utility of progressed health state (0.57, 0.72)	25,786.30	0.7127	36,180.32	25,786.30	0.7832	32,925.31
Utility of progression-free health state - Regorafenib (0.72, 0.82)	25,786.30	0.7131	36,158.84	25,786.30	0.7828	32,943.12
Utility of progression-free health state - Placebo (0.72, 0.82)	25,561.41	0.7479	34,175.48	26,011.18	0.7479	34,776.83
Regorafenib + BSC management costs while progression-free (99.37, 149.05)	25,786.30	0.7540	34,198.45	25,786.30	0.7419	34,758.40
BSC management costs post-progression (71.18, 106.78)	25,679.38	0.7479	34,333.21	25,893.21	0.7479	34,619.10
BSC management costs while progression-free (64.05, 96.08)	25,824.87	0.7479	34,527.73	25,747.72	0.7479	34,424.58
End of life costs (8052.12, 9422)	25,810.96	0.7479	34,509.14	25,761.59	0.7479	34,443.12
Additional start-up costs regorafenib (44.58, 66.86)	25,775.15	0.7479	34,461.26	25,797.44	0.7479	34,491.05
Hypertension probability on regorafenib (0.16, 0.31)	25,784.26	0.7479	34,473.43	25,788.49	0.7479	34,479.09
Hypertension cost (9.48, 14.23)	25,784.95	0.7479	34,474.36	25,787.64	0.7479	34,477.95
Diarrhoea probability on regorafenib (0.01, 0.09)	25,785.75	0.7479	34,475.42	25,786.86	0.7479	34,476.91
Hypertension probability on placebo (0, 0.06)	25,785.74	0.7479	34,475.41	25,786.86	0.7479	34,476.91
Diarrhoea cost (5.62, 8.43)	25,786.14	0.7479	34,475.95	25,786.45	0.7479	34,476.36
HFSR cost (0, 0)	25,786.30	0.7479	34,476.15	25,786.30	0.7479	34,476.15
HFSR probability on regorafenib (0.13, 0.26)	25,786.30	0.7479	34,476.15	25,786.30	0.7479	34,476.15
HFSR probability on placebo (0, 0)	25,786.30	0.7479	34,476.15	25,786.30	0.7479	34,476.15
Diarrhoea probability on placebo (0, 0)	25,786.30	0.7479	34,476.15	25,786.30	0.7479	34,476.15
Death utility (0, 0)	25,786.30	0.7479	34,476.15	25,786.30	0.7479	34,476.15
OS regorafenib vs placebo unadjusted HR (0.79, 1.53)	25,786.30	0.7479	34,476.15	25,786.30	0.7479	34,476.15
OS regorafenib vs placebo RPSFT HR (1.2, 2.37)	25,786.30	0.7479	34,476.15	25,786.30	0.7479	34,476.15
OS regorafenib vs placebo IPE HR (1.28, 2.53)	25,786.30	0.7479	34,476.15	25,786.30	0.7479	34,476.15

Figure 29. Tornado diagram showing the top 15 model drivers (without PAS)

[redacted]

Figure 30. Tornado diagram showing the top 15 model drivers (with PAS)



5.8.7 For technologies whose final price or acquisition cost has not been confirmed, sensitivity analysis should be done over a plausible range of prices. This may also include the price of a comparator that includes a confidential patient access scheme.

Not applicable.

Scenario analysis

5.8.8 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.

Scenario analysis was performed on key areas of uncertainty in the model, these included areas where assumptions could be challenged. Further details on the sensitivity and scenario analyses are presented in sections 5.8.6 and 5.8.9, respectively.

5.8.9 Present the results of scenario analysis. Include details of structural sensitivity analysis.

Scenario analysis 1 – Overall survival extrapolation using the Weibull and Gompertz parametric model

The AIC indicated that the log-logistic function was the best fitting parametric function to GRID study OS data, and so this was selected as the base case. Expert reviewers suggested that the Weibull and Gompertz models should be tested, despite their lack of statistical fit. Other parametric functions were also tested as part of the OWSA (see Table 75 and Table 76).

When the Weibull parametric model was selected for overall survival extrapolation both the incremental costs and the incremental QALYs decreased. Because of the large impact on incremental QALYs, the net effect was an increase in the ICER to £[redacted] using regorafenib list price and £39,679 using the PAS price. The results for this scenario are summarised in Table 77, and the cost breakdown is shown in Table 78. Using the log-normal and exponential model did not cause a significant change in the ICER compared to the base case as long term survival estimates remained similar to the log-logistic model and therefore detailed results are not reported here.

Table 77. Scenario analysis 1a - Overall survival extrapolation with Weibull

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.057	1.171	0.886
	PFLYs	0.705	0.124	0.581
	QALYs	1.415	0.773	0.643
	Costs	£[redacted]	£10,412	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.057	1.171	0.886
	PFLYs	0.705	0.124	0.581
	QALYs	1.415	0.773	0.643
	Costs	£35,921	£10,412	£25,509
	Incremental cost per QALY			**£39,679**

Table 78. Scenario analysis 1a - Cost breakdown for overall survival with Weibull extrapolation

	Component	Regorafenib + BSC	Placebo + BSC	Incremental
List price	Drug costs - progression-free	£[redacted]	£0	£[redacted]
	Drug costs - post-progression	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£3	£[redacted]
	Monitoring costs	£[redacted]	£1,438	£[redacted]
	End-of-life costs	£[redacted]	£8,499	-£[redacted]
	Total cost	£[redacted]	£10,412	£[redacted]
PAS price	Drug costs - progression-free	£24,446	£0	£24,446
	Drug costs - post-progression	£0	£0	£0
	Additional one-time cost post-progression	£466	£472	-£6
	Adverse event costs	£10	£3	£7
	Monitoring costs	£2,757	£1,438	£1,319
	End-of-life costs	£8,243	£8,499	-£257
	Total cost breakdown	£35,921	£10,412	£25,509

When the Gompertz parametric model was selected for overall survival extrapolation both the incremental costs and the incremental QALYs decreased. Because of the large impact on incremental QALYs, the net effect was an increase in the ICER to £[redacted] using regorafenib list price and £44,124 using the PAS price. The results for this scenario are summarised in Table 79, and the cost breakdown is shown in Table 80.

Table 79. Scenario analysis 1b - Overall survival extrapolation with Gompertz extrapolation

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.068	1.285	0.783
	PFLYs	0.706	0.124	0.582
	QALYs	1.422	0.846	0.576
	Costs	£[redacted]	£10,505	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.068	1.285	0.783
	PFLYs	0.706	0.124	0.582
	QALYs	1.422	0.846	0.576
	Costs	£35,939	£10,505	£25,434
	Incremental cost per QALY			**£44,124**

Table 80. Scenario analysis 1b - Cost breakdown for overall survival with Gompertz extrapolation

	Component	Regorafenib + BSC	Placebo + BSC	Incremental
List price	Drug costs - progression-free	£[redacted]	£0	£[redacted]
	Drug costs - post-progression	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£3	£[redacted]
	Monitoring costs	£[redacted]	£1,569	£[redacted]
	End-of-life costs	£[redacted]	£8,461	-£[redacted]
	Total cost	£[redacted]	£10,505	£[redacted]
PAS price	Drug costs - progression-free	£24,457	£0	£24,457
	Drug costs - post-progression	£0	£0	£0
	Additional one-time cost post-progression	£466	£472	-£6
	Adverse event costs	£10	£3	£7
	Monitoring costs	£2,769	£1,569	£1,200
	End-of-life costs	£8,238	£8,461	-£223
	Total cost	£35,939	£10,505	£25,434

Scenario analysis 2 – RPSFT crossover correction methods

As explained earlier, the IPE method was the preferred method over the RPSFT method for adjusting for crossover bias as it reduces bias when estimating the true treatment effect as explored in Morden et al (13). Furthermore, the RPSFT method makes the additional assumption that estimates are rank-preserving, this may not be

plausible as some patients may be more or less likely to benefit on treatment than others due to biological factors (13).

In this scenario analysis the RPSFT method (with recensoring) was explored, and three different OS survival models were fitted:

3a: Log-logistic

3b: Weibull

3c: Gompertz

The log-logistic model provided the best statistical fit according to the AIC (see Table 32).

We report the results for both Weibull and Gompertz parametric functions, in addition to the best fitting log-logistic function to maintain consistency with the analysis performed in the above scenario.

Table 81 to Table 86 below show the results when the crossover adjustment method was changed with each OS parametric function. RPSFT with the log-logistic function increased the ICER to £[redacted] per QALY gained with the list price and £40,252 with the PAS price. Changing the OS parametric function to Weibull increased the ICER further to £[redacted] with the list price and £44,884 with the PAS price. This increased to £[redacted] with the list price and £49,953 with the PAS price when the OS parametric function was changed to Gompertz.

Table 81. Scenario analysis 2a - RPSFT with OS extrapolation using Log-logistic extrapolation

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.521	1.646	0.876
	PFLYs	0.710	0.124	0.586
	QALYs	1.717	1.080	0.637
	Costs	£[redacted]	£10,818	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.521	1.646	0.876
	PFLYs	0.710	0.124	0.586
	QALYs	1.717	1.080	0.637
	Costs	£36,457	£10,818	£25,639
	Incremental cost per QALY			**£40,252**

Table 82. Scenario analysis 2a - Cost breakdown for RPSFT and OS using Log-logistic extrapolation

	Component	Regorafenib + BSC	Placebo + BSC	Incremental
List price	Drug costs - progression-free	£[redacted]	£0	£[redacted]
	Drug costs - post-progression	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£4	£[redacted]
	Monitoring costs	£[redacted]	£1,988	£[redacted]
	End-of-life costs	£[redacted]	£8,354	-£[redacted]
	Total cost	**£[redacted]**	**£10,818**	**£[redacted]**
PAS price	Drug costs - progression-free	£24,592	£0	£24,592
	Drug costs - post-progression	£0	£0	£0
	Additional one-time cost post-progression	£466	£472	-£7
	Adverse event costs	£11	£4	£7
	Monitoring costs	£3,297	£1,988	£1,309
	End-of-life costs	£8,091	£8,354	-£263
	Total cost	£36,457	£10,818	£25,639

Table 83. Scenario analysis 2b - RPSFT with OS extrapolation using Weibull extrapolation

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.057	1.290	0.767
	PFLYs	0.705	0.124	0.581
	QALYs	1.415	0.849	0.566
	Costs	£[redacted]	£10,516	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.057	1.290	0.767
	PFLYs	0.705	0.124	0.581
	QALYs	1.415	0.849	0.566
	Costs	£35,921	£10,516	£25,406
	Incremental cost per QALY			**£44,884**

Table 84. Scenario analysis 2b - Cost breakdown for RPSFT and OS using Weibull extrapolation

	Component	Regorafenib + BSC	Placebo + BSC	Incremental
List price	Drug costs - progression-free	£[redacted]	£0	£[redacted]
	Drug costs - post-progression	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£3	£[redacted]
	Monitoring costs	£[redacted]	£1,576	£[redacted]
	End-of-life costs	£[redacted]	£8,465	-£[redacted]
	Total cost	**£[redacted]**	**£10,516**	**£[redacted]**
PAS price	Drug costs - progression-free	£24,446	£0	£24,446
	Drug costs - post-progression	£0	£0	£0
	Additional one-time cost post-progression	£466	£472	-£6
	Adverse event costs	£10	£3	£7
	Monitoring costs	£2,757	£1,576	£1,181
	End-of-life costs	£8,243	£8,465	-£222
	Total cost	**£35,921**	**£10,516**	**£25,406**

Table 85. Scenario analysis 2c - RPSFT with OS extrapolation using Gompertz extrapolation

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.068	1.391	0.676
	PFLYs	0.706	0.124	0.582
	QALYs	1.422	0.915	0.507
	Costs	£[redacted]	£10,600	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.068	1.391	0.676
	PFLYs	0.706	0.124	0.582
	QALYs	1.422	0.915	0.507
	Costs	£35,939	£10,600	£25,339
	Incremental cost per QALY			**£49,953**

Table 86. Scenario analysis 2c - Cost breakdown for RPSFT and OS using Gompertz extrapolation

	Component	Regorafenib + BSC	Placebo + BSC	Incremental
List price	Drug costs - progression-free	£[redacted]	£0	£[redacted]
	Drug costs - post-progression	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£3	£[redacted]
	Monitoring costs	£[redacted]	£1,693	£[redacted]
	End-of-life costs	£[redacted]	£8,431	-£[redacted]
	Total cost	**£[redacted]**	**£10,600**	**£[redacted]**
PAS price	Drug costs - progression-free	£24,457	£0	£24,457
	Drug costs - post-progression	£0	£0	£0
	Additional one-time cost post-progression	£466	£472	-£6
	Adverse event costs	£10	£3	£7
	Monitoring costs	£2,769	£1,693	£1,076
	End-of-life costs	£8,238	£8,431	-£194
	Total cost	**£35,939**	**£10,600**	**£25,339**

Scenario analysis 3 – Resource use according to clinical expert opinion

Resource use assumptions were originally sourced from a 2013 physician survey of 15 physicians. The results were recently discussed with clinical experts to confirm accuracy and current day validity. The following points were raised by our clinical experts:

- In line with best clinical practice, all patients should receive either a CT or an MRI scan prior to starting treatment, in order to determine whether they need active treatment or BSC.
- For progression-free patients on regular TKI treatment, frequency of CT scan, blood tests and outpatient visits would be about every 12 weeks as patients would typically come into clinic every 12 weeks.
- For progression-free patients on regular BSC and for those patients who have progressed, the frequency of CT scans, MRI would be lower. For the scenario analysis, it is assumed that tests are performed every 24 weeks.
- The frequency of outpatient visits is thought to be lower:
  - Progression-free TKI patients: reduce from 6.2 to 12 weeks
  - Progression-free BSC patients: reduce from 6.9 to 8-12 weeks
- Reduce the proportion of progressed patients receiving either palliative resection or palliative radiotherapy to 5%.

Table 87 to Table 90 below represent the changes applied to resource use according to the clinical experts' opinion defined above.

Table 87. Resource use prior to treatment, values used in base case and scenario analysis

	Base case		Scenario analysis	
Test	**Proportion of 3rd line patients receiving test prior to treatment with a TKI, Mean (SE)**	**Proportion of 3rd line patients receiving test prior to BSC, Mean (SE)**	**Proportion of 3rd line patients receiving test prior to treatment with a TKI, Mean (SE)**	**Proportion of 3rd line patients receiving test prior to BSC, Mean (SE)**
CT scan	0.85 (0.079)	0.24 (0.070)	0.85 (0.0)	0.96 (0.0)
MRI scan	0.12 (0.031)	0.01 (0.005)	0.15 (0.0)	0.04 (0.0)
Full blood count	0.92 (0.065)	0.56 (0.100)	0.92 (0.065)	0.56 (0.100)
Liver function test	0.92 (0.062)	0.49 (0.111)	0.92 (0.062)	0.49 (0.111)

SE = standard error
Source: Physician survey of 15 medical oncologists treating GIST

Table 88. Regular tests given to patients in the progression-free state, values used in base case and scenario analysis

	Average frequency (weeks between tests), Mean (SE)					
	Base case			Scenario analysis		
Test	**Patients on a TKI**	**Patients on BSC**	**Post-progression state**	**Patients on a TKI**	**Patients on BSC**	**Post-progression state**
CT scan	12.1 (1.44)	18.9 (3.26)	14.5(6.84)	12.1 (1.44)	24.0(0.0)	24.0(0.0)
MRI scan	19.9 (4.00)	18.0 (2.58)	8.0(-)	12.0 (0.0)	24.0(0.0)	24.0(0.0)
Full blood count	6.4 (1.90)	10.9 (2.36)	8.8(1.88)	12.0 (0.0)	24.0(0.0)	24.0(0.0)
Liver function test	6.4 (1.90)	11.2 (2.61)	9.4(2.03)	12.0 (0.0)	24.0(0.0)	24.0(0.0)

SE = standard error, NA = Not available
Source: Physician survey of 15 medical oncologists treating GIST

Table 89. Frequency of outpatient visits based on health state, values used in base case and scenario analysis

	Average frequency (weeks between visits), Mean (SE)	
Health state	**Base case**	**Scenario analysis**
Progression-free on a TKI	6.2 (0.86)	12.0 (0.0)
Progression-free on BSC	7.9 (0.77)	12.0 (0.0)
Progressed disease on BSC	6.9 (0.97)	6.9 (0.97)

SE = standard error
Source: Physician survey of 15 medical oncologists treating GIST

Table 90. Palliative care interventions for progressed disease patients, values used in base case and scenario analysis

Palliative intervention	**Average proportion of patients who receive the palliative care intervention Mean (SE)**	
	Base case	**Scenario analysis**
Palliative surgical resection	[redacted] (0.033)	0.05 (0.0)
Palliative radiotherapy	[redacted] (0.063)	0.05 (0.0)

SE = standard error
Source: Physician survey of 15 medical oncologists treating GIST

Table 91 and Table 92 show the results when all the resource use assumptions are applied as per the clinical experts' opinion.

Table 91. Scenario analysis 3 – Results using all clinical expert resource use assumptions

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.521	1.474	1.047
	PFLYs	0.710	0.124	0.586
	QALYs	1.717	0.969	0.748
	Costs	£[redacted]	£10,299	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.521	1.474	1.047
	PFLYs	0.710	0.124	0.586
	QALYs	1.717	0.969	0.748
	Costs	£35,975	£10,299	£25,677
	Incremental cost per QALY			**£34,330**

Table 92. Scenario analysis 3 - Clinical expert resource use assumptions comparison cost breakdown

	Component	Regorafenib + BSC	Placebo + BSC	Incremental
List price	Drug costs progression-free	£[redacted]	£0	£[redacted]
	Drug costs post-progression	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£205	-£[redacted]
	Adverse Event costs	£[redacted]	£3	£[redacted]
	Monitoring costs	£[redacted]	£1,684	£[redacted]
	End-of-life costs	£[redacted]	£8,406	-£[redacted]
	Total cost	**£[redacted]**	**£10,299**	**£[redacted]**
PAS price	Drug costs progression-free	£24,592	£0	£24,592
	Drug costs post-progression	£0	£0	£0
	Additional one-time cost post-progression	£202	£205	-£3
	Adverse Event costs	£11	£3	£7
	Monitoring costs	£3,079	£1,684	£1,395
	End-of-life costs	£8,091	£8,406	-£315
	Total cost	**£35,975**	**£10,299**	**£25,677**

Scenario analysis 4 – Cost of post-progression treatment in the regorafenib + BSC arm

Opposite to other countries, administration of regorafenib after disease progression is not standard clinical practice in the UK. This is further supported by the evidence from Kollàr et al. (2014) which showed a median treatment duration with regorafenib (9.25 months) lower than the median PFS (9.4 months) found in the retrospective study conducted in the UK (44).

Despite the administration of active treatment post-progression is not common practice in the UK, this scenario analysis was aimed at presenting the cost effectiveness results based on the evidence from the GRID study when considering the cost of regorafenib treatment administered after disease progression. In the base case, no post-progression treatment was included as in the trial regorafenib was to be stopped when benefit was lost and patients progress.

The mean exposure to treatment post-progression was calculated by subtracting the mean time under actual treatment in the regorafenib arm during the double-blind phase, i.e. 15.026 weeks, from the mean time under actual treatment in both double-blind and open-label phases for patients randomised to the regorafenib arm, i.e. [redacted] weeks, to obtain a mean post-progression treatment duration in the regorafenib arm of [redacted] weeks ([redacted] days) (Tables 10-1, 10-2 in the GRID Addendum Clinical Study Report) (14). The treatment duration was then multiplied by the weekly cost of treatment with regorafenib based on its mean actual daily dose of [redacted] mg (14). The resulting weekly treatment cost of regorafenib was £3,148 without PAS and £[redacted] with PAS.

When considering the data of the UK population enrolled in the GRID study, a mean actual treatment duration of [redacted] weeks was found for both the double-blind and open-label phases (64). This resulted in a mean post-treatment duration in the regorafenib arm of [redacted] weeks ([redacted] days). This treatment duration is consistent with the mean 8-week duration of TKI treatment post-disease progression resulting from the two physician surveys conducted in 2013 and 2016. The mean actual daily dose for the UK subpopulation was [redacted] mg when considering both the double-

blind and open-label phases (64). In this case, the corresponding weekly cost of treatment with regorafenib was £3,163 without PAS and £[redacted] with PAS.

When adjusting for crossover using the IPE and RPSFT methods, the treatment benefit from receiving regorafenib for those patients who crossed over from the placebo arm is removed. As such, in this scenario the treatment cost of regorafenib for these patients is removed and only applied to the regorafenib arm.

Three scenarios were explored with treatment post-progression in the regorafenib arm continued for:

- [redacted] days (overall SAF population in the GRID study) for all the patients who progressed
- [redacted] days (UK SAF population in the GRID study) for all the patients who progressed
- 56 days (8 weeks) only in 25.3% of the patients who progressed as resulted from the 2013 and 2016 physician surveys for England and Wales

The results are shown in the tables below.

Inclusion of the cost of post-progression treatment for [redacted] days yielded the ICER at £[redacted] without the PAS and £55,511 with the PAS. Inclusion of the cost of post-progression treatment for [redacted] days when considering the UK patient population yielded the ICER at £[redacted] without the PAS and £38,917 with the PAS. When considering the inputs from the standard clinical practice in England and Wales – e.g. 25.3% of patients continuing treatment with regorafenib for 8 weeks on average after disease progression - the ICER resulted at £[redacted] without PAS and £34,807 with PAS.

Table 93. Scenario analysis 4a - Cost of post-progression treatment ([redacted] days)

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.521	1.474	1.047
	PFLYs	0.710	0.124	0.586
	QALYs	1.717	0.969	0.748
	Costs	£[redacted]	£10,671	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.521	1.474	1.047
	PFLYs	0.710	0.124	0.586
	QALYs	1.717	0.969	0.748
	Costs	**£52,190**	**£10,671**	**£41,519**
	Incremental cost per QALY			**£55,511**

Table 94. Scenario analysis 4a - Cost of post-progression treatment cost breakdown ([redacted] days)

	Component	Regorafenib + BSC	Placebo + BSC	Incremental
List price	Drug costs - progression-free	£[redacted]	£0	£[redacted]
	Drug costs - post-progression	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£3	£[redacted]
	Monitoring costs	£[redacted]	£1,789	£[redacted]
	End-of-life costs	£[redacted]	£8,406	-£[redacted]
	Total cost	**£[redacted]**	**£10,671**	**£[redacted]**
PAS price	Drug costs - progression-free	£23,665	£0	£23,665
	Drug costs - post-progression	£16,660	£0	£16,660
	Additional one-time cost post-progression	£466	£472	-£7
	Adverse event costs	£11	£3	£7
	Monitoring costs	£3,297	£1,789	£1,508
	End-of-life costs	£8,091	£8,406	-£315
	Total cost	**£52,190**	**£10,671**	**£41,519**

Table 95. Scenario analysis 4b - Cost of post-progression treatment for the UK subpopulation ([redacted] days)

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.521	1.474	1.047
	PFLYs	0.710	0.124	0.586
	QALYs	1.717	0.969	0.748
	Costs	£[redacted]	£10,671	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.521	1.474	1.047
	PFLYs	0.710	0.124	0.586
	QALYs	1.717	0.969	0.748
	Costs	£39,779	£10,671	£29,108
	Incremental cost per QALY			**£38,917**

Table 96. Scenario analysis 4b - Cost of post-progression treatment for the UK subpopulation cost breakdown ([redacted] days)

	Component	Regorafenib + BSC	Placebo + BSC	Incremental
List price	Drug costs - progression-free	£[redacted]	£0	£[redacted]
	Drug costs - post-progression	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£3	£[redacted]
	Monitoring costs	£[redacted]	£1,789	£[redacted]
	End-of-life costs	£[redacted]	£8,406	-£[redacted]
	Total cost	**£[redacted]**	**£10,671**	**£[redacted]**
PAS price	Drug costs - progression-free	£23,778	£0	£23,778
	Drug costs - post-progression	£4,136	£0	£4,136
	Additional one-time cost post-progression	£466	£472	-£7
	Adverse event costs	£11	£3	£7
	Monitoring costs	£3,297	£1,789	£1,508
	End-of-life costs	£8,091	£8,406	-£315
	Total cost	**£39,779**	**£10,671**	**£29,108**

Table 97. Scenario analysis 4c - Cost of post-progression treatment based on physician survey inputs (25.3% of patients treated for 8 weeks with TKI treatment after disease progression)

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.521	1.474	1.047
	PFLYs	0.710	0.124	0.586
	QALYs	1.717	0.969	0.748
	Costs	£[redacted]	£10,671	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.521	1.474	1.047
	PFLYs	0.710	0.124	0.586
	QALYs	1.717	0.969	0.748
	Costs	£36,705	£10,671	£26,034
	Incremental cost per QALY			**£34,807**

Table 98. Scenario analysis 4c - Cost of post-progression treatment based on physician survey inputs (25.3% of patients treated for 8 weeks with TKI treatment after disease progression)

	Component	Regorafenib + BSC	Placebo + BSC	Incremental
List price	Drug costs - progression-free	£[redacted]	£0	£[redacted]
	Drug costs - post-progression	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£3	£[redacted]
	Monitoring costs	£[redacted]	£1,789	£[redacted]
	End-of-life costs	£[redacted]	£8,406	-£[redacted]
	Total cost	**£[redacted]**	**£10,671**	**£[redacted]**
PAS price	Drug costs - progression-free	£23,665	£0	£23,665
	Drug costs - post-progression	£1,175	£0	£1,175
	Additional one-time cost post-progression	£466	£472	-£7
	Adverse event costs	£11	£3	£7
	Monitoring costs	£3,297	£1,789	£1,508
	End-of-life costs	£8,091	£8,406	-£315
	Total cost	**£36,705**	**£10,671**	**£26,034**

Scenario analysis 5 – EQ-5D utilities from the repeated measures comparison

Table 99 shows the results using health state utility values from the EQ-5D repeated measures comparison (see Table 38) instead of the paired-sampled analyses used in the base case.

The repeated measures analysis is a less robust estimate of utility for non-progressed and progressed health states for subjects with GIST. This is because repeated measures would contain observations of utilities that occurred in the initial diagnosis of progressed disease. Furthermore, repeated measures does not contain a homogenous progressed population for estimating utilities of these subjects (40). A linear mixed model with a first-order, autoregressive covariance structure was employed with subject identity modelled as a random effect.

The ICER slightly increased to £[redacted] per QALY with the list price and £33,944 per QALY with the PAS price. The cost breakdown is not shown because it is identical to the base case.

Table 99. Scenario analysis 5a - Results using the repeated measured EQ-5D utilities

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.521	1.474	1.047
	PFLYs	0.710	0.124	0.586
	QALYs	1.801	1.041	0.760
	Costs	£[redacted]	£10,671	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.521	1.474	1.047
	PFLYs	0.710	0.124	0.586
	QALYs	1.801	1.041	0.760
	Costs	£36,457	£10,671	£25,786
	Incremental cost per QALY			**£33,944**

Despite adverse events such as HFSR, diarrhoea and fatigue are easily manageable and their effect on the patient's HRQL can be deemed negligible, a scenario analysis was conducted using lower utility values for regorafenib in the progression-free health state compared to placebo. Utility values from the EQ-5D repeated measures analysis based on the splitting of the progression-free state into regorafenib and

placebo arms (see Table 39) were used. Table 100 displays the results of this scenario analysis.

The ICER resulting from this analysis increased slightly at £[redacted] without the PAS and £34,508 with the PAS.

Table 100. Scenario analysis 5b - Results using the repeated measured EQ-5D utilities based on the splitting of the progression-free health state into treatment arms

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.521	1.474	1.047
	PFLYs	0.710	0.124	0.586
	QALYs	1.760	1.012	0.747
	Costs	£[redacted]	£10,671	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.521	1.474	1.047
	PFLYs	0.710	0.124	0.586
	QALYs	1.760	1.012	0.747
	Costs	£36,457	£10,671	£25,786
	Incremental cost per QALY			**£34,508**

Scenario analysis 6 – Using EORTC from GRID as the utility data source

Table 101 shows the results using health state utility values from the EORTC repeated measures analysis instead of the EQ-5D paired-sampled analysis. The utilities used for this analysis are shown in Table 41.

Another scenario analysis was performed using the EORTC-derived utilities from the paired-samples comparison method. The utilities used for this analysis can be found in Table 40. The results for this scenario analysis can be found in Table 102 below.

The ICER reduced from £[redacted] using regorafenib list price to £31,678 using the PAS price. The cost breakdown is not shown because it is identical to the base case.

Table 101. Scenario analysis 6a - Results from using repeated measures EORTC utilities from the GRID trial

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.521	1.474	1.047
	PFLYs	0.710	0.124	0.586
	QALYs	1.933	1.119	0.814
	Costs	£[redacted]	£10,671	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.521	1.474	1.047
	PFLYs	0.710	0.124	0.586
	QALYs	1.933	1.119	0.814
	Costs	£36,457	£10,671	£25,786
	Incremental cost per QALY			**£31,678**

When using paired-samples comparison of EORTC-derived utilities, the ICER reduced from £[redacted] using regorafenib list price to £31,226 using the PAS price.

Table 102. Scenario analysis 6b - Results using paired-samples comparison of EORTC-derived utilities

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.521	1.474	1.047
	PFLYs	0.710	0.124	0.586
	QALYs	1.941	1.115	0.826
	Costs	£[redacted]	£10,671	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.521	1.474	1.047
	PFLYs	0.710	0.124	0.586
	QALYs	1.941	1.115	0.826
	Costs	£36,457	£10,671	£25,786
	Incremental cost per QALY			**£31,226**

Further information about these methods can be found in section 5.4.

Summary of sensitivity analyses results

5.8.10 Describe the main findings of the sensitivity analyses, highlighting the key drivers of the cost-effectiveness results.

A comprehensive set of sensitivity and scenario analyses was conducted. The following scenarios and parameters had the most impact on the cost-effectiveness of regorafenib and produced large ICERs:

- Using a time horizon of 5 years.

- Using the RPSFT crossover adjustment method with a Gompertz model for long term OS extrapolation.

All sensitivity analyses provided ICERs below £50,000 per QALY gained when using the PAS price.

5.9 *Subgroup analysis*

This section should be read with the NICE guide to the methods of technology appraisal, section 5.10.

When subgroups have been considered in the de novo cost-effectiveness analysis, provide the information specified in sections 5.9.1–5.9.6.

5.9.1 Types of subgroups that are not considered relevant are those based solely on the following factors:

- Individual utilities for health states and patient preference.
- Different treatment costs for individuals according to their social characteristics.
- Subgroups specified according to the costs of providing treatment in different locations in England (for example, when the costs of facilities available for providing the technology vary according to location).

Patients with unresectable or metastatic GIST who progressed on or are intolerant to prior treatment with imatinib and sunitinib already constitute a small, highly pre-treated population with high unmet needs. Bayer have not identified any subgroup of this population that would result in clinically or economically relevant differences in benefit for regorafenib.

5.9.2 Please specify whether analysis of subgroups was carried out and how these subgroups were identified, referring to the scope and decision problem specified for the NICE technology appraisal. When specifying how subgroups were identified, confirm whether they were identified based on a prior expectation of different clinical or cost effectiveness

because of known, biologically plausible mechanisms, social characteristics or other clearly justified factors. Cross refer to the clinical effectiveness section 4.7.

No subgroup analysis was carried out because of the reasons explained in section 5.9.1.

5.9.3 Clearly define the characteristics of patients in the subgroup.

Not applicable.

5.9.4 Describe how the statistical analysis was carried out.

Not applicable

5.9.5 If subgroup analyses were done, please present the results in tables similar to those in section 5.7.

Not applicable.

5.9.6 Identify any obvious subgroups that were not considered and explain why. Please refer to the subgroups identified in the decision problem in section 3.

Not applicable.

5.10 *Validation*

Validation of de novo cost-effectiveness analysis

5.10.1 When describing the methods used to validate and quality assure the model, provide:

- the rationale for using the chosen methods
- references to the results produced and cross-references to the evidence identified in the clinical evidence, measurement and valuation of health effects, and cost and healthcare resource sections.

Model validation

In the course of model development an independent health economic expert, familiar with oncology modelling was consulted. The health economic expert agreed that the modelling approach including the crossover adjustment methods was reasonable and proposed no major changes.

A check of validity was performed by the model developers using a quality control process, and a model audit which was performed by an experienced health economist external to the team who built the model. This involved calculation spot checks, cross checks against source data and extreme value scenarios to check if the model behaved logically.

Clinical validation

The two clinical experts were asked to validate the model inputs and model assumptions. The key points raised by the clinical experts were explored in the scenario analysis. The key points raised were:

- Gompertz and Weibull functions should be explored to reflect alternative long term OS predictions (explored in scenario analyses).
- Some of the resource use assumptions taken from the physician survey conducted in 2013 do not reflect current/best practice. More plausible resource use assumptions should be explored (explored in scenario analyses).
- For patients who progress from BSC to regorafenib the common treatment effect is clinically plausible given the quick progression of patients on the BSC arm (median PFS = 0.9 months).

5.11 *Interpretation and conclusions of economic evidence*

5.11.1 When interpreting and concluding your economic evidence, consider the following:

- 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?
- Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem?
- How relevant (generalisable) is the analysis to clinical practice in England?
- What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?
- What further analyses could be carried out to enhance the robustness or completeness of the results?

Regorafenib was found to be a cost-effective treatment for patients with metastatic/unresectable GIST after treatment failures with imatinib and sunitinib. The base case analysis results produced an ICER of £[redacted] per QALY gained with the list price. Using the PAS price for regorafenib, the incremental cost per QALY gained was reduced to £34,476.

The method of crossover adjustment used (IPE or RPSFT) produced very similar results with an ICER of £[redacted] and £[redacted] per QALY gained at the list price, respectively. When a PAS was applied the respective ICERs were £34,476 and £40,252 per QALY gained. Adjustment using the IPE crossover correction was the preferred method due to less bias in our estimates.

The model is also sensitive to the OS extrapolation method. For example, an increase in the incremental cost per QALY to £[redacted] at the list price and £39,679 with the PAS was observed when the OS extrapolation model type was changed from log-logistic to Weibull. A similar increase was found when Gompertz extrapolation was used to model long term OS.

There are limitations to the model which may affect the cost-effectiveness of regorafenib. Firstly, it is not possible to accurately observe the impact of regorafenib on OS in the trial due to the high percentage of crossover (88%) from the placebo arm, which introduces bias into the effectiveness estimates. In this submission, statistical correction methods, such as the IPE and RPSFT, to adjust for crossover have been implemented in line with NICE Decision Support Unit recommendations (9). These methods assume a common treatment effect, which was deemed possible by our clinical experts and has been used in a previous appraisal in GIST (28).

Furthermore, the inability to separately identify any benefit of post-progression treatment in the regorafenib arm provided a further limitation in our effectiveness estimates. It is unclear whether continued treatment with regorafenib post-progression confers any benefit. Moreover, administration of regorafenib after progression is not standard practice in the UK. This is further supported by the findings from two physician surveys conducted in 2013 and 2016 which showed that 25.3% of patients, on average, would continue TKI treatment after disease progression. According to the two surveys, the average TKI treatment duration post-disease progression is approximately 8 weeks. The incurred cost of such treatment is explored in a scenario analysis where the mean duration of treatment post-progression for the overall SAF population and UK SAF population in the GRID study and in the standard clinical practice in England and Wales were considered.

Overall regorafenib was found to be a cost-effective treatment for adult patients with unresectable or metastatic gastrointestinal stromal tumours who progressed on or are intolerant to prior treatment with imatinib and sunitinib.

6 Assessment of factors relevant to the NHS and other parties

When completing the template, refer to the NICE guide to the methods of technology appraisal section 5.12, and the NICE guide to the processes of technology appraisal.

6.1 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 and cost effectiveness. This will allow 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.

Provide the information specified in sections 6.2–6.10.

6.2 State how many people are eligible for treatment in England. Present results for the full marketing authorisation or CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

Population projections in England for the years 2017 to 2021 were based on the population growth rate estimated based on the 2014 and 2019 demographic projections published by the Office of National Statistics (32). New cases of GIST per year were estimated based on the incidence rate – i.e. 1.5 cases per 100,000 people - reported in the manufacturer submission for NICE TA179 (28). Around 30% of GISTs are metastatic and/or unresectable and 51% of them fail on treatment with imatinib (28). As reported by Demetri et al. (2006), the clinical benefit rate associated with sunitinib is 24.2%, meaning that 75.8% of patients previously treated with imatinib progress on sunitinib (33). Among these patients, 60% are considered eligible for further TKI treatment (32).

Table 103 displays the projected number of patients eligible for further TKI treatment in England.

Table 103. Projected number of patients eligible for treatment with further TKI

	Year				
Patient population	**2017**	**2018**	**2019**	**2020**	**2021**
Total population in England	55,616,680	56,056,912	56,500,629	56,947,859	57,398,628
Incidence of GIST	834	841	848	854	861
Proportion metastatic/unresectable	250	252	254	256	258
Proportion previously treated with imatinib	128	129	130	131	132
Proportion previously treated with imatinib and sunitinib	97	98	98	99	100
Proportion eligible for further TKI treatment	**58**	**59**	**59**	**59**	**60**

6.3 Explain any assumptions that were made about current treatment options and uptake of technologies.

To help understand the economic impact of regorafenib uptake and use, costs were estimated under two scenarios: a world without regorafenib and a world with regorafenib.

In line with the scope of this appraisal, the current alternative treatment option for the regorafenib-eligible patient population is BSC. Regorafenib is assumed to be administered in combination with BSC. It was assumed that uptake of regorafenib would increase over the next 5 years.

6.4 When relevant, explain any assumptions that were made about market share in England.

In a world without regorafenib, BSC was assumed to have 100% of the market share.

In a world with regorafenib, it was anticipated that the market share of regorafenib would increase to [redacted]% by 2021. Estimates of the annual market share for patients

with GIST eligible for treatment with further TKI are reported in Table 104. It was assumed that market share would be gained from BSC only.

Table 104. Market share in a world with regorafenib

	Year				
Patient population	**2017**	**2018**	**2019**	**2020**	**2021**
Regorafenib	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
BSC	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%

6.5 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, administration costs, monitoring costs and the costs of managing adverse reactions).

The use of regorafenib involves no significant costs other than those associated with the acquisition of the drug and the increased frequency of monitoring tests and visits due to its administration.

Costs of managing HFSR are considered as medication kits. These are provided by Bayer to the patients on regorafenib experiencing this specific adverse reaction to the treatment. Costs associated to the management of other adverse reactions, such as diarrhoea and hypertension are negligible, therefore not included in the budget impact calculation.

6.6 State what unit costs were assumed and how they were calculated. If unit costs used in health economic modelling were not based on national reference costs or the payment-by-results tariff, explain how a cost for the activity was calculated.

Unit costs for the acquisition of regorafenib and the monitoring tests and visits prior to treatment and pre- and post-disease progression were sourced as described in section 5.5.1 of this submission.

6.7 If there were any estimates of resource savings, explain what they were and when they are likely to be made.

Displacement of BSC by regorafenib is unlikely to result in resource savings. As such, no resource savings were included in the budget impact analysis.

6.8 State the estimated annual budget impact on the NHS in England.

Table 105 presents the estimated expenditure for years 2017 - 2021 in a world without and with regorafenib. The budget impact analysis indicates that the net cost incurred due to uptake of regorafenib in 2021 would be approximately £[redacted], and that the cumulative cost over 5 years would be approximately £[redacted].

Table 105. Estimated expenditure for the NHS in England over 5 years

Year	World without regorafenib	World with regorafenib	Budget impact
2017	£133,898	£[redacted]	£[redacted]
2018	£134,958	£[redacted]	£[redacted]
2019	£136,026	£[redacted]	£[redacted]
2020	£137,103	£[redacted]	£[redacted]
2021	£138,188	£[redacted]	£[redacted]
Total	**£680,173**	**£[redacted]**	**£[redacted]**

* Total costs reported may deviate from individual components due to rounding differences

6.9 Identify any other opportunities for resource savings or redirection of resources that it has not been possible to quantify.

No other resource savings or displacements of resource have been considered.

6.10 Highlight the main limitations within the budget impact analysis.

The size of the English population from year 2017 to 2021 was based on a population growth rate estimated based on the 2014 and 2019 population projections by the ONS (32). No published data on the proportion of patients eligible for further TKI treatment after imatinib and sunitinib failure was available at the time of the analysis. Inputs provided by 15 medical oncologists from England and Wales, participating to a physician survey in 2013, were used (19).

7 References

Please use a recognised referencing style, such as Harvard or Vancouver. 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]).

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8 Appendices

Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested in the template, but that is considered to be relevant to the submission. Any 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 template. 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 must be made available for relevant clinical studies; the remainder must be available on request. Submission appendices are not normally provided to the Appraisal Committee or published on the NICE website and therefore please send these as separate documents to the main submission. Examples of appendices submitted to NICE are as follows:

Appendix 1: European public assessment report, SmPC/IFU, scientific discussion or drafts (section 2.2)

Appendix 2: Search strategy for relevant studies (section 4.1.2)

Appendix 3: Quality assessment of randomised controlled trials (RCTs) (section 4.6)

Appendix 4: Subgroup analysis (section 4.8)

Appendix 5: Search strategy for indirect and mixed treatment comparisons (section 4.10.1)

Appendix 6: Methods, results, outcomes and quality assessment of the relevant trials in the indirect or mixed treatment comparison (section 4.10.9-10)

Appendix 7: Programming language used in the analysis (section 4.10.13)

Appendix 8: Quality assessment of the relevant non-randomised and non-controlled evidence (see section 4.11.6-9)

Appendix 9: Search strategy for adverse reactions (section 4.12.3)

Appendix 10: Quality assessment of adverse reaction data (section 4.12.3)

Appendix 11: Search strategy for cost-effectiveness studies (section 5.1.1)

Appendix 12: Quality assessment of cost-effectiveness studies (section 5.1.3)

Appendix 13: Search strategy for measurement and valuation of health effects (section 5.4.3)

Appendix 14: Cost and healthcare resource identification, measurement and valuation (section 5.5.2)

Appendix 15: Checklist of confidential information

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Single technology appraisal

Regorafenib for treating advanced gastrointestinal stromal tumours [ID1056]

Dear Lesley,

The Evidence Review Group, Peninsula Technology Assessment Group (PenTAG), and the technical team at NICE have looked at the submission received on 16 March 2017 from Bayer. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **Friday 21 April 2017**. Your response and any supporting documents should be uploaded to NICE Docs.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Abitha Senthinathan, Technical Lead (Abitha.Sentinathan@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.moore@nice.org.uk).

Yours sincerely

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Encl. checklist for confidential information

Section A: Clarification on effectiveness data

Literature searching

A1. On p117 section 4.12 please explain why no literature searches for adverse events were carried out?

A2. For the three literature searches (for the clinical effectiveness, cost effectiveness and health related quality of life) described on pages 48, 143 and 172; Please describe the methods for full text screening - how was this carried out and by who?

Methods

A3. On p75, the company submission reports that analysis of progression-free survival was performed when the predetermined criteria of 144 progression-free events were reached. On p77 of the company submission, for a sensitivity analysis, 122 progression-free events were considered, as originally planned in the protocol. Please clarify why the protocol changed?

Section B: Clarification on cost-effectiveness data

Literature searching

B1. For the cost effectiveness and health effects searches no tables of excluded studies have been included in the appendices. Please could you provide these?

Methods

B1. **Priority question**: Please provide more details on how the iterative parameter estimation (IPE) and rank-preserving structural failure time (RPSFT) methods were implemented, because there are variants on each method. For example, please provide more details of how recensoring was implemented. Also, was the treatment effect of regorafenib assumed to apply only while regorafenib was being taken, or for the whole period from the start of regorafenib treatment to death?

Results

B2. **Priority question**: The company describes the use of regorafenib post-progression in the GRID RCT for the regorafenib and best supportive care treatment arms.

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Please list any other post-progression treatments taken and the number of patients in each arm receiving them?

B3. **Priority question**: Please provide the total mean duration of regorafenib treatment in the regorafenib arm in the GRID trial, where the mean is calculated for all patients randomised in the regorafenib arm?

B4. **Priority question**: Please provide the total mean duration of regorafenib treatment in the best supportive care arm in the GRID trial, where the mean is calculated for all patients randomised in the best supportive care arm?

B5. **Priority question**: Data cut-off for progression-free survival and overall survival is June 2015. This is now nearly two years out of date. Does the company have any more mature data? If so, please provide the relevant clinical results, and an updated cost-effectiveness analysis (and economic model) incorporating the updated data.

B6. On p147, please provide further details on why the Spanish study (Sanz-Granda et al. 2015) was considered not relevant to the UK for the cost-effectiveness searches?

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Single technology appraisal

Regorafenib for treating advanced gastrointestinal stromal tumours [ID1056]

The present document incorporates all responses to the requests of clarification received until May 18th, 2017.

Bayer's new base case is formed by the analyses presented in section 3.

Table of Content

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1. REQUEST FOR CLARIFICATION # 1 – Date: 03/04/2017

Dear [redacted],

The Evidence Review Group, Peninsula Technology Assessment Group (PenTAG), and the technical team at NICE have looked at the submission received on 16 March 2017 from Bayer. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **Friday 21 April 2017**. Your response and any supporting documents should be uploaded to NICE Docs.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact [redacted], Technical Lead ([redacted]@nice.org.uk). Any procedural questions should be addressed to [redacted], Project Manager ([redacted]@nice.org.uk).

Yours sincerely

[redacted]
Associate Director – Appraisals
Centre for Health Technology Evaluation

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Section A: Clarification on effectiveness data

Literature searching

A1. On p117 section 4.12 please explain why no literature searches for adverse events were carried out?

Literature searches for efficacy and safety outcomes for regorafenib and best supportive care (BSC) were carried out in the systematic review. As reported on p53 section 4.2, only one double blind RCT study – e.g. trial NCT01271712 (GRID) - was identified in the literature. This study comparing efficacy and safety of regorafenib plus BSC versus placebo plus BSC is deemed directly relevant to the decision problem. Efficacy and safety outcomes - i.e. general and specific adverse events - were therefore extracted from the identified clinical study (1).

A2. For the three literature searches (for the clinical effectiveness, cost effectiveness and health related quality of life) described on pages 48, 143 and 172; Please describe the methods for full text screening - how was this carried out and by who?

In order to be included in the review, citations had to meet the eligibility criteria defined in the systematic review protocol. Titles and abstracts of citations found through the searches were reviewed by two independent reviewers. For all studies, whenever there was uncertainty about their inclusion for further full text review, revision by an independent reviewer was carried out and any disagreement resolved through reconciliation between the two reviewers. In case resolution based on the abstract alone was not possible, the full-text paper was obtained for further assessment. Following receipt of the full-text papers, inclusion criteria were applied and papers included or excluded accordingly. This process was adopted for all the clinical, economic, and health related quality of life reviews.

Methods

A3. On p75, the company submission reports that analysis of progression-free survival was performed when the predetermined criteria of 144 progression-free events were reached. On p77 of the company submission, for a sensitivity analysis, 122 progression-free events were considered, as originally planned in the protocol. Please clarify why the protocol changed?

The GRID study was originally designed to enrol 170 subjects, but during the screening a higher number of patients were found eligible for inclusion in the study. The final number of subjects enrolled in the study was therefore 199. As a

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consequence, the total number of PFS events required for the analysis of the primary efficacy endpoint was changed from 122, as originally planned in the study protocol, to 144. This increase in numbers was necessary in order to keep the ratio between PFS events and randomised patients equals to 0.72.

Section B: Clarification on cost-effectiveness data

Literature searching

B1. For the cost effectiveness and health effects searches no tables of excluded studies have been included in the appendices. Please could you provide these?

Table 1. List of economic publications retained for full-text review and decision on exclusion with reason

#	Publication	Excluded?	Reason for Exclusion§
1	Amsel et al. 1986 (2)	Yes	Disease
2	Artinyan et al. 2008 (3)	Yes	Treatment line
3	Berndt et al. 1968 (4)	Yes	Disease
4	Blay et al. 2014 (5)	Yes	Review / editorial
5	Blay et al. 2015 (6)	Yes	Study design
6	Blanke et al. 2015 (7)	Yes	Intervention
7	Bloom et al. 1992 (8)	Yes	Disease
8	Bond et al. 2009 (9)	Yes	Treatment line
9	Bond et al. 2009 (10)	Yes	Treatment line
10	Bonetti et al. 2010 (11)	Yes	Disease
11	Casco et al. 1999 (12)	Yes	Disease
12	Chabot et al. 2008 (13)	Yes	Treatment line
13	Chastek et al. 2014 (14)	Yes	Disease
14	Chen et al. 2008 (15)	Yes	Disease
15	Cheung et al. 2009 (16)	Yes	Disease
16	Chevrou et al. 2013 (17)	Yes	Intervention
17	Chiazze et al. 1967 (18)	Yes	Disease
18	Ciapanna et al. 2010 (19)	Yes	Treatment line
19	Contreras-Hernandez et al. 2008 (20)	Yes	Treatment line
20	Correa 1981 (21)	Yes	Disease
21	Dallal et al. 2001 (22)	Yes	Disease
22	Dan et al. 2006 (23)	Yes	Disease
23	Da-Silveira et al. 2008 (24)	Yes	Disease
24	Datar et al. 2012 (25)	Yes	Disease
25	De Mello-Sampayo et al. 2014 (26)	Yes	Review / editorial
26	De Oliveira et al. 2011 (27)	Yes	Disease

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#	Publication	Excluded?	Reason for Exclusion[§]
27	Deger et al. 2015 (28)	Yes	Country
28	Deger et al. 2015 (29)	Yes	Treatment line
29	Devasirvadam 2008 (30)	Yes	Country
30	Di Giulio et al. 2009 (31)	Yes	Disease
31	Draexler et al. 2015 (32)	Yes	Comparator
32	Dretzke et al. 2010 (33)	Yes	Treatment line
33	Dretzke et al. 2010 (34)	Yes	Disease
34	Duggan 1998 (35)	Yes	Disease
35	El Ouagari et al. 2008 (36)	Yes	Treatment line
36	Fan et al. 2005 (37)	Yes	Disease
37	Fendrick et al. 1999 (38)	Yes	Disease
38	Ferrucci 1995 (39)	Yes	Review / editorial
39	Garnica-Rodriguez et al. 2005 (40)	Yes	Disease
40	Guerin et al. 2015 (41)	Yes	Disease
41	Halpern et al. 2009 (42)	Yes	Treatment line
42	Harris et al. 1999 (43)	Yes	Disease
43	Henderson et al. 2010 (44)	Yes	Disease
44	Hislop et al. 2011 (45)	Yes	Treatment line
45	Huse et al. 2007 (46)	Yes	Treatment line
46	Jamil et al. 2010 (47)	Yes	Disease
47	Jo 2010 (48)	Yes	Disease
48	Kang et al. 2013 (49)	Yes	Study design
49	Keun Park et al. 2008 (50)	Yes	Disease
50	Kirchhoff et al. 2011 (51)	Yes	Disease
51	Konigsrainer et al. 2000 (52)	Yes	Disease
52	Kraljickovic et al. 2015 (53)	Yes	Treatment line
53	Kuppusamy et al. 2011 (54)	Yes	Disease
54	Lafeuille et al. 2009 (55)	Yes	Disease
55	Lee et al. 2007 (56)	Yes	Disease
56	Lee et al. 2010 (57)	Yes	Disease
57	Li et al. 2013 (58)	Yes	Disease
58	Look Hong et al. 2014 (59)	Yes	Disease
59	Loureiro et al. 2012 (60)	Yes	Disease
60	Luporsi et al. 2011 (61)	Yes	Disease
61	Lyseng-Williamson et al. 2014 (62)	Yes	Review / editorial
62	Mabasa et al. 2008 (63)	Yes	Treatment line
63	Majer et al. 2013 (64)	Yes	Disease
64	Mir et al. 2016 (65)	Yes	Study design
65	Mortensen et al. 2000 (66)	Yes	Disease

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#	Publication	Excluded?	Reason for Exclusion[§]
66	Nagy et al. 2012 (67)	Yes	Disease
67	Nerich et al. 2016 (68)	Yes	Intervention
68	Norum et al. 1995 (69)	Yes	Disease
69	Ohata et al. 2005 (70)	Yes	Disease
70	Parthan et al. 2012 (71)	Yes	Disease
71	Paz-Ares et al. 2008 (72)	Yes	Treatment line
72	Perrier et al. 2014 (73)	Yes	Treatment line
73	Perrier et al. 2014 (74)	Yes	Treatment line
74	Raikou et al. 2012 (75)	Yes	Disease
75	Ramaswamy et al. 2016 (76)	Yes	Study design
76	Rao et al. 2005 (77)	Yes	Disease
77	Ren et al. 2015 (78)	Yes	Treatment line
78	Roderick et al. 2003 (79)	Yes	Disease
79	Roderick et al. 2003 (80)	Yes	Disease
80	Roelen et al. 2011 (81)	Yes	Disease
81	Rubin et al. 2011 (82)	Yes	Treatment line
82	Sahai et al. 2003 (83)	Yes	Disease
83	Sanon et al. 2012 (84)	Yes	Disease
84	Sanon et al. 2013 (85)	Yes	Disease
85	Schöffski et al. 2016 (86)	Yes	Review / editorial
86	Seal et al. 2014 (87)	Yes	Intervention
87	Serafini et al. 2014 (88)	Yes	Treatment line
88	Shenfine et al. 2009 (89)	Yes	Disease
89	Simonsson et al. 2007 (90)	Yes	Disease
90	Soni et al. 2009 (91)	Yes	Disease
91	Vakil et al. 2009 (92)	Yes	Disease
92	Van Dam 1998 (93)	Yes	Disease
93	van-Vliet et al. 2007 (94)	Yes	Disease
94	Wallace et al. 2002 (95)	Yes	Disease
95	Webb et al. 1997 (96)	Yes	Disease
96	Wenger et al. 2005 (97)	Yes	Disease
97	Whitaker 1998 (98)	Yes	Study design
98	Wilson et al. 2005 (99)	Yes	Treatment line
99	Xie et al. 2008 (100)	Yes	Disease
100	Xie et al. 2008 (101)	Yes	Disease
101	Xie et al. 2009 (102)	Yes	Disease
102	Xinopoulos et al. 2004 (103)	Yes	Disease
103	Yeh et al. 2009 (104)	Yes	Disease
104	Yeh et al. 2010 (105)	Yes	Disease
105	Zfass 1987 (106)	Yes	Review / editorial
106	Zhou et al. 2011 (107)	Yes	Disease

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#	Publication	Excluded?	Reason for Exclusion[§]
107	Zolic et al. 2015 (108)	Yes	Country

[§] "Comparator" refers to studies not including placebo/BSC as a comparator; "Country" refers to studies reporting data from countries not of interest to the decision making in the UK; "Disease" refers to studies not based on patients with a specific GIST diagnosis; "Intervention" refers to studies not including regorafenib as intervention; "Review/editorial" refers to literature, editorial and/or systematic reviews not part of the inclusion criteria; "Study design" refers to studies not appropriate to report cost data and resource use for GIST; "Treatment line" refers to studies considering a line of treatment that is not part of the inclusion criteria

Methods

B1. **Priority question**: Please provide more details on how the iterative parameter estimation (IPE) and rank-preserving structural failure time (RPSFT) methods were implemented, because there are variants on each method. For example, please provide more details of how recensoring was implemented. Also, was the treatment effect of regorafenib assumed to apply only while regorafenib was being taken, or for the whole period from the start of regorafenib treatment to death?

The IPE and RPSFT crossover adjustment methods were implemented using Stata 11 and the strbee program developed by White et al. 2002 (109) (http://ageconsearch.umn.edu/bitstream/115957/2/sjart_st0012.pdf), as described by Morden et al. 2011 (110) (https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/1471-2288-11-4). The commands implemented for IPE and RPSFT were as follows (square brackets represent inputs from data):

IPE:
Strbee *[treatment]*, test(*weibull*) xo0(*[time to crossover] [crossover flag]*) endstudy(*[study follow-up duration]*) ipe

RPSFT:
strbee *[treatment]*, test(*logrank*) xo0(*[time to crossover] [crossover flag]*) endstudy*[study follow-up duration]*)

A logrank test is implemented for the RPSFT method in order to calculate the test statistic for independence between patients' counterfactual event time and the treatment arm to which they were assigned, as recommended by Morden et al. 2011 (110). For the IPE method, where a likelihood-based analysis is undertaken a Weibull distribution is utilised, also consistent with Morden et al. 2011 (110).

Recensoring was implemented directly within the strbee program, using a maximum potential censoring time equal to the duration of study follow up. Recensoring was applied in order to reduce bias from potentially informative censoring as a result of switching (switching itself may potentially be informative if it is related to prognosis).

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Recensoring is applied in a manner consistent with Morden et al. 2011 (110), and discussed further in White et al. 2002 (109).

The entire data for overall survival was used for the crossover adjustment; the assumption is therefore that treatment effect of regorafenib is applied from initiation of treatment until death, regardless of discontinuation. The treatment effect of regorafenib is therefore likely reduced as it will be an average of patients on and off treatment. Only placebo patients who crossover to regorafenib have their survival times adjusted, non-crossers and those in the regorafenib arm are unchanged.

Results

B2. **Priority question**: The company describes the use of regorafenib post-progression in the GRID RCT for the regorafenib and best supportive care treatment arms. Please list any other post-progression treatments taken and the number of patients in each arm receiving them?

Table 2 reports the most up-to-date available list of systemic anti-cancer therapies administered during the GRID study follow-up.

Table 2. Systemic anti-cancer therapy during follow-up (Full analysis set) – 2017 data cut-off

[redacted]

B3. **Priority question**: Please provide the total mean duration of regorafenib treatment in the regorafenib arm in the GRID trial, where the mean is calculated for all patients randomised in the regorafenib arm?

The total mean duration of double blind and open label regorafenib treatment in the GRID trial for all patients randomised in the regorafenib arm was [redacted] ± [redacted] weeks (111). However, this value has not to be considered as the mean actual time spent on regorafenib as it also includes time spent off treatment and treatment interruptions.

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In the cost-effectiveness analysis, only the actual time spent on treatment should be considered. In the GRID trial, the total actual mean duration of double blind and open label regorafenib treatment for all patients randomised in the regorafenib arm was [redacted] ± [redacted] weeks (111).

B4. **Priority question**: Please provide the total mean duration of regorafenib treatment in the best supportive care arm in the GRID trial, where the mean is calculated for all patients randomised in the best supportive care arm?

The total mean duration of open label regorafenib treatment in the GRID trial for all patients randomised in the best supportive care arm was 46.626 ± 48.857 weeks (111). However, as explained in question B3, this value has not to be considered as the mean actual time spent on regorafenib as it also includes time spent off treatment and treatment interruptions.

When considering the time spent on treatment, only the actual time spent on open label regorafenib should be considered for this study arm. In the GRID trial, the total actual mean duration of open label regorafenib treatment for all patients randomised in the best supportive care arm was [redacted] ± [redacted] weeks (111).

B5. **Priority question**: Data cut-off for progression-free survival and overall survival is June 2015. This is now nearly two years out of date. Does the company have any more mature data? If so, please provide the relevant clinical results, and an updated cost-effectiveness analysis (and economic model) incorporating the updated data.

The final analysis for progression-free survival (PFS) was performed at primary completion with data cut-off date of 26 January 2012. The primary completion date for this study was the date when approximately 144 patients had a PFS event. Progression-free survival data are complete for placebo with the Kaplan-Meier reaching 0 by time of data cut off, as well as for the majority of regorafenib patients. Since the abovementioned cut-off date, no data for the primary endpoint was further collected.

The final overall survival (OS) analysis was performed when approximately 160 deaths occurred as specified in the study protocol. The latest published data cut-off available at the time of the NICE submission was therefore 08 June 2015, when a total of 162 events had occurred. An update of the OS data has been carried out in response to this request (April 2017) and clinical outcomes are presented in Figure 1.

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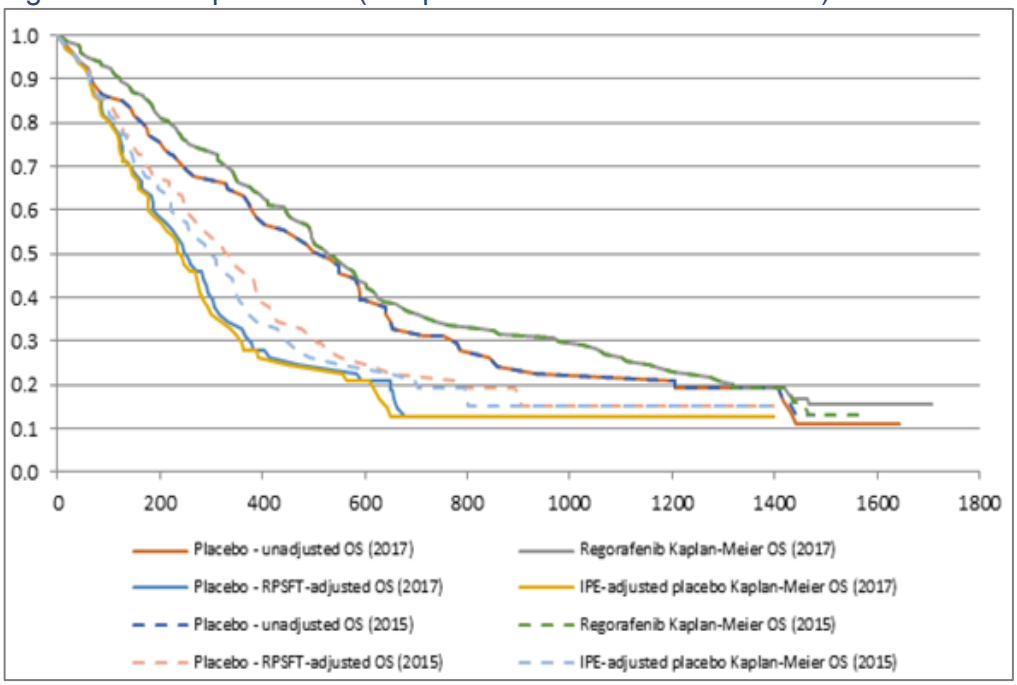
Figure 1. OS Kaplan Meier (comparison of 2015 and 2017 data)



The number of patients at risk in each arm for the 2015 and 2017 data cut is presented in Table **3**.

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Table 3. Number of patients at risk by treatment arm

Data cut	Arm	Day									
		0	*200*	*400*	*600*	*800*	*1000*	*1200*	*1400*	*1600*	*1800*
2017	Regorafenib	133	108	83	57	44	39	31	22	4	0
	Unadjusted placebo	66	49	37	25	16	13	13	8	1	0
	RPSFT placebo	66	37	17	12	1	1	1	0	0	0
	IPE placebo	66	37	15	12	1	1	1	0	0	0
2015	Regorafenib	133	108	83	57	44	39	31	21	0	0
	Unadjusted placebo	66	49	37	25	16	13	13	8	0	0
	RPSFT placebo	66	43	24	15	11	1	1	0	0	0
	IPE placebo	66	41	21	14	8	1	1	0	0	0

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The unadjusted Kaplan-Meier OS outcomes are relatively unchanged from the 2015 data (dashed lines). The adjusted (both RPSFT and IPE) OS outcomes are slightly reduced for placebo. This is a result of the greater follow-up time allowing for a longer potential censoring date within the crossover adjustment calculation.

Updated parametric fits to both the unadjusted, and adjusted, updated KM data are presented in Figure 2 to Figure 4 below.

Figure 2. Parametric models for OS (compared with GRID Kaplan-Meier data) – regorafenib arm

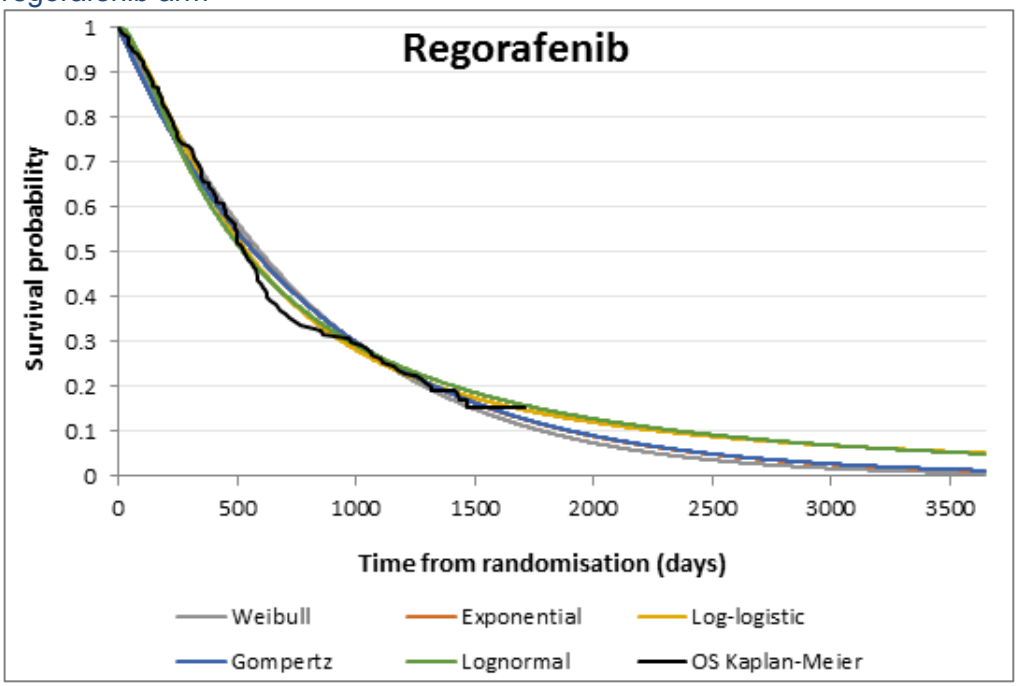

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Figure 3. Parametric models for OS (compared with GRID Kaplan-Meier data) – placebo arm (RPSFT-adjusted)

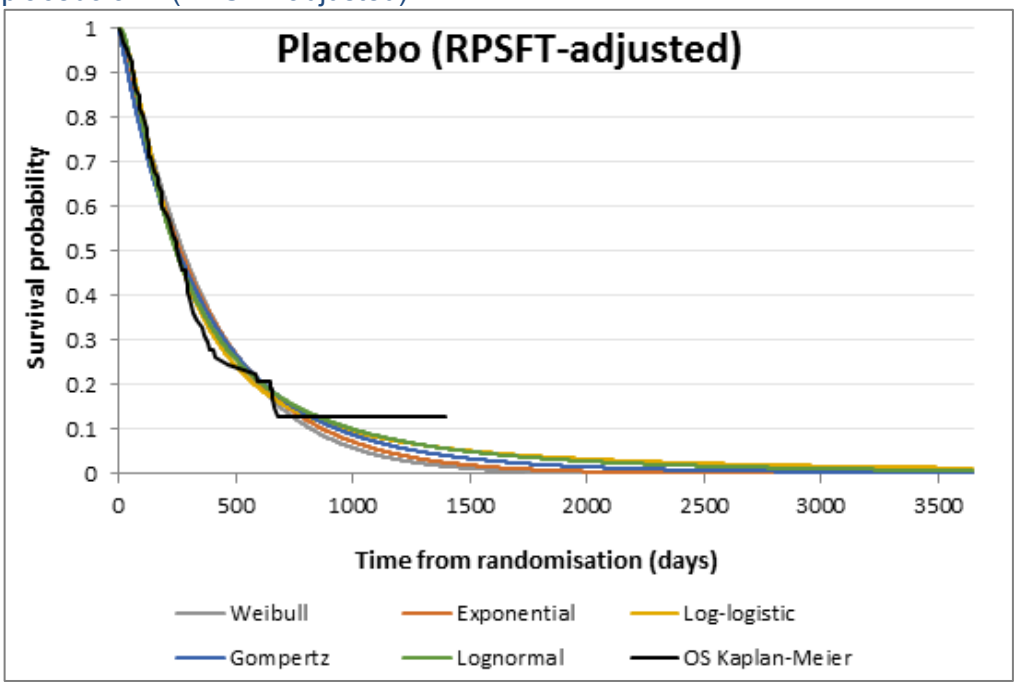

Figure 4. Parametric models for OS (compared with GRID Kaplan-Meier data) – placebo arm (IPE-adjusted)

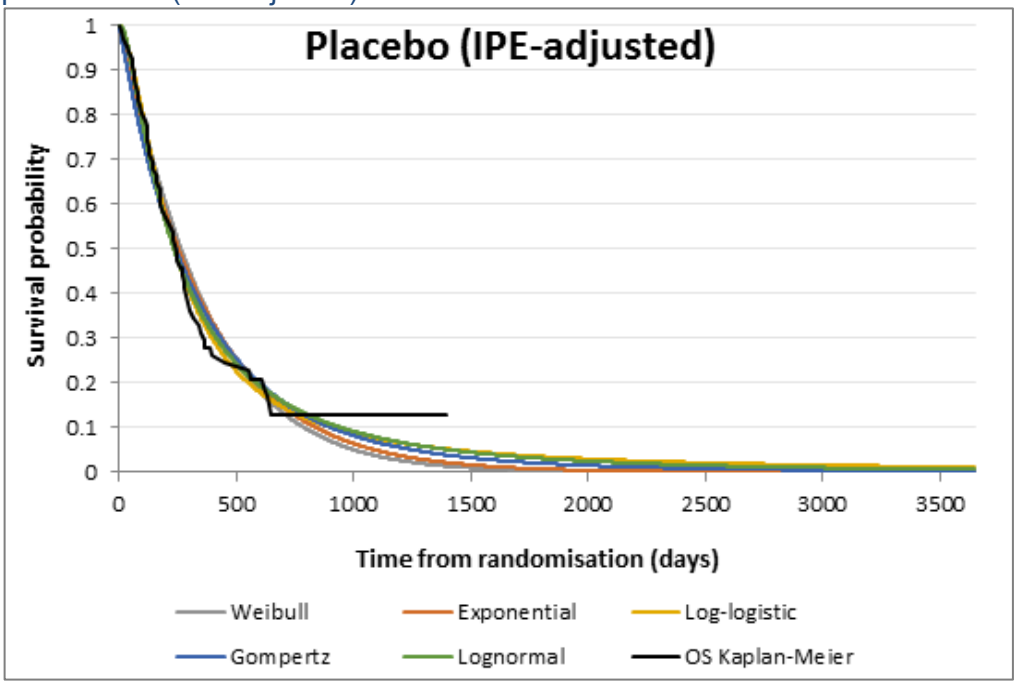

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Table 4 and Table 5 present the AIC and BIC for the assessed extrapolations of the OS data. The loglogistic model gives the minimum AIC for regorafenib OS and for both the RPSFT and IPE methods used in the placebo arm.

Table 4. AIC for different parametric models for OS extrapolation

Parametric Model	Regorafenib + BSC	Placebo + BSC			Sum AIC (placebo + regorafenib)		
		Un-adjusted	RPSFT	IPE	Un-adjusted	RPSFT	IPE
Exponential	394.12	**201.84**	192.53	192.00	595.96	586.65	586.12
Loglogistic	**391.08**	204.83	**188.99**	**187.78**	**595.92**	**580.08**	**578.86**
Weibull	394.93	203.80	193.89	193.32	598.73	588.82	588.25
Lognormal	395.36	206.53	190.64	189.48	601.89	586.00	584.84
Gompertz	396.12	203.80	194.21	193.60	599.92	590.33	589.72

Table 5. BIC for different parametric models for OS extrapolation

Parametric Model	Regorafenib + BSC	Placebo + BSC			Sum AIC (placebo + regorafenib)		
		Un-adjusted	RPSFT	IPE	Un-adjusted	RPSFT	IPE
Exponential	397.01	**204.03**	194.72	194.19	**601.04**	591.73	591.20
Loglogistic	**396.87**	209.21	**193.37**	**192.16**	606.08	**590.24**	**589.02**
Weibull	400.71	208.18	198.27	197.70	608.89	598.98	598.41
Lognormal	401.14	210.91	195.02	193.86	612.05	596.16	595.00
Gompertz	401.90	208.18	198.59	197.98	610.08	600.49	599.88

Following visual inspection of the parametric functions applied to the Kaplan-Maier curves for the two study arms and analysis of the AIC and BIC, log-logistic was selected as best fitting model.

Table **6** and Table 7 display the base case results without and with PAS based on the same inputs and model settings reported in chapter 5 of the NICE submission.

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Table 6. Base-case results (without PAS) based on 2017 data cut off

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (LYs)	ICER (£) incremental (QALYs)
Placebo + BSC	10,395	1.154	0.761					
Regorafenib	[redacted]	2.546	1.733					
				[redacted]	1.393	0.971	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 7. Base-case results (with PAS) based on 2017 data cut off

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (LYs)	ICER (£) incremental (QALYs)
Placebo + BSC	10,395	1.154	0.761					
Regorafenib	36,478	2.546	1.733					
				26,082	1.393	0.971	18,730	26,852
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

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The cost breakdown for the base case results is presented in Table 8.

Table 8. Base case results – cost breakdown (2017 data cut-off)

	Component	Regorafenib + BSC	Placebo + BSC	Incremental
List price	Drug costs - progression-free	£[redacted]	£0	£[redacted]
	Drug costs - post-progression	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£3	£[redacted]
	Monitoring costs	£[redacted]	£1,418	£[redacted]
	End-of-life costs	£[redacted]	£8,503	-£[redacted]
	Total cost	**£[redacted]**	**£10,395**	**£[redacted]**
PAS price	Drug costs - progression-free	£[redacted]	£0	£[redacted]
	Drug costs - post-progression	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£3	£[redacted]
	Monitoring costs	£[redacted]	£1,418	£[redacted]
	End-of-life costs	£[redacted]	£8,503	-£[redacted]
	Total cost breakdown	**£36,478**	**£10,395**	**£26,082**

One-way sensitivity analysis (OWSA) and probabilistic sensitivity analysis (PSA) were conducted to explore the effect of parameter uncertainty.

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Probabilistic sensitivity analysis

Simulations with 3,000 iterations were produced and the average results are shown in Table 9 below.

Table 9. Average results from PSA (with and without PAS) – based on 2017 data cut-off

	Regorafenib + BSC			Placebo + BSC			Incremental			ICER (£/QALY)
	LYs	QALYs	Costs	LYs	QALYs	Costs	LYs	QALYs	Costs	
List Price	2.560	1.745	£[redacted]	1.179	0.778	£11,018	1.381	0.966	£[redacted]	£[redacted]
PAS price	2.561	1.745	£37,904	1.179	0.778	£11,011	1.382	0.966	£26,894	£27,831

Figure 5 and Figure 6 show the cost-effectiveness plane without and with the PAS price.

Figure **7** and Figure 8 show the cost-effectiveness acceptability curve (CEAC) without and with the PAS price. At a willingness to pay of £50,000 per QALY gained regorafenib was [redacted]% likely to be cost-effective at its list price and 98% likely at its PAS price.

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Figure 5. Cost-effectiveness plane showing per patient incremental cost and QALYs (without PAS)

Figure 6. CEAC based on willingness-to-pay per QALY (without PAS)

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Figure 7. Cost-effectiveness plane showing per patient incremental cost and QALYs (with PAS)

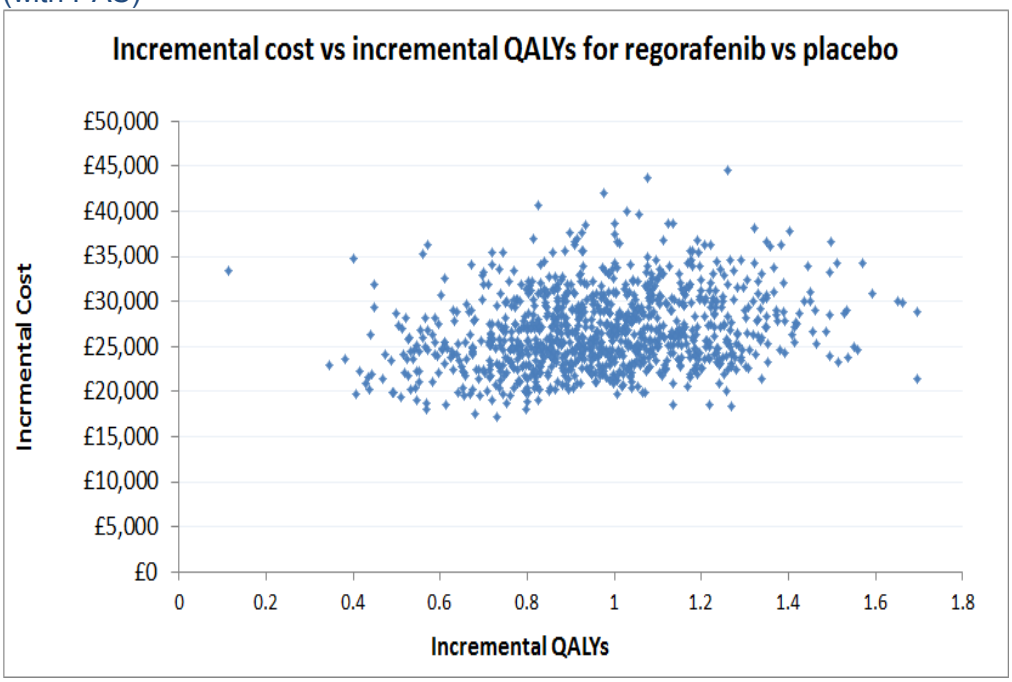
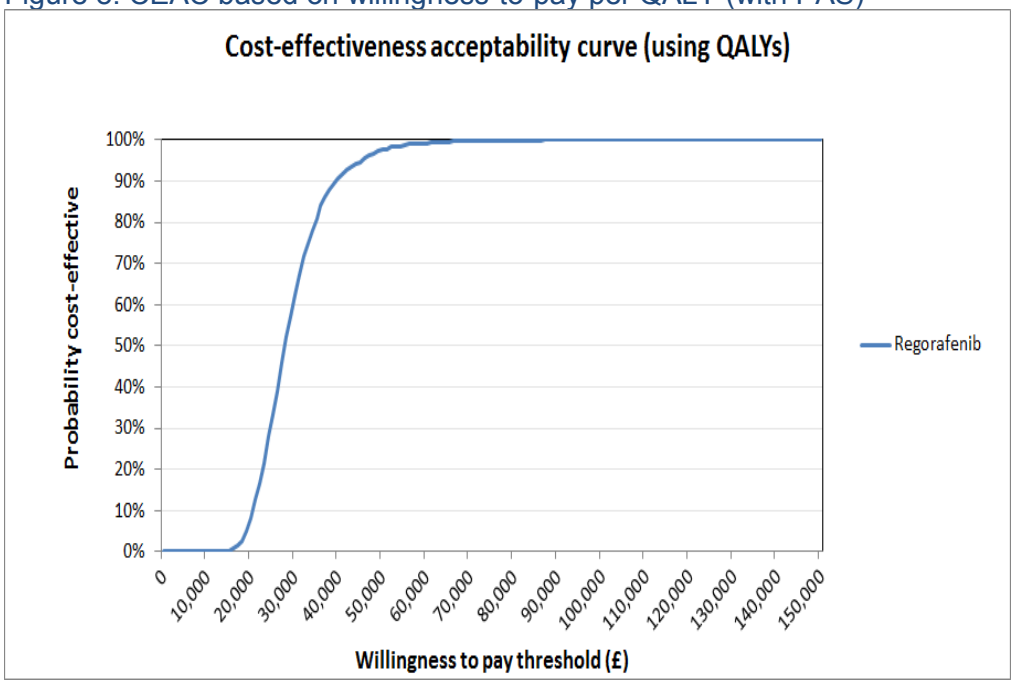


Figure 8. CEAC based on willingness-to-pay per QALY (with PAS)



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Incremental cost effectiveness analysis results estimated from the probabilistic sensitivity analysis are consistent with those found in the base-case analysis

Deterministic sensitivity analysis

The values used for the lower and upper OWSA analysis are the same presented in the NICE submission.

Results of the deterministic sensitivity analysis are presented in Table 10 and Table 11.

The top 15 model drivers are shown in the tornado diagram in Figure 9 in terms of incremental cost per QALY (at the list price for regorafenib), the tornado diagram using the PAS price is shown in Figure 10. For both, the highest impact was observed when the drug acquisition cost for regorafenib was varied. This provided an ICER varying between £[redacted] and £[redacted] per QALY gained when applying the list price and between £21,788 and £31,916 per QALY gained when using the PAS price. Variation of the discount rate for the utilities and costs were also important in determining the ICER.

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Table 10. Full OWSA results (without PAS) based on 2017 data cut-off

	Low variation			High variation		
Variable	**Inc Cost (£)**	**Inc QALYs**	**ICER (£/QALY)**	**Inc Cost (£)**	**Inc QALYs**	**ICER (£/QALY)**
Regorafenib drug cost (2616.87, 3925.3)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
Discount rate utilities (0, 0.06)	[redacted]	1.1798	[redacted]	[redacted]	0.8753	[redacted]
Discount rate costs (0, 0.06)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
Utility of progressed health state (0.57, 0.72)	[redacted]	0.9097	[redacted]	[redacted]	1.0330	[redacted]
Utility of progression-free health state - Regorafenib (0.72, 0.82)	[redacted]	0.9365	[redacted]	[redacted]	1.0061	[redacted]
Utility of progression-free health state - Placebo (0.72, 0.82)	[redacted]	0.9774	[redacted]	[redacted]	0.9653	[redacted]
Regorafenib + BSC management costs while progression-free (99.37, 149.05)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
BSC management costs post-progression (71.18, 106.78)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
BSC management costs while progression-free (64.05, 96.08)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
End of life costs (8052.12, 9422)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
Additional start-up costs regorafenib (44.58, 66.86)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
Hypertension probability on regorafenib (0.16, 0.31)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
Hypertension cost (9.48, 14.23)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
Diarrhoea probability on regorafenib (0.01, 0.09)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
Hypertension probability on placebo (0, 0.06)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
Diarrhoea cost (5.62, 8.43)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
HFSR cost (0, 0)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
HFSR probability on regorafenib (0.13, 0.26)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
HFSR probability on placebo (0, 0)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
Diarrhoea probability on placebo (0, 0)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]

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Variable	Low variation			High variation		
	Inc Cost (£)	Inc QALYs	ICER (£/QALY)	Inc Cost (£)	Inc QALYs	ICER (£/QALY)
Death utility (0, 0)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
OS regorafenib vs placebo unadjusted HR (0.79, 1.53)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
OS regorafenib vs placebo RPSFT HR (1.2, 2.37)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
OS regorafenib vs placebo IPE HR (1.28, 2.53)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]

Table 11. Full OWSA results (with PAS) based on 2017 data cut-off

Variable	Low variation			High variation		
	Inc Cost (£)	Inc QALYs	ICER (£/QALY)	Inc Cost (£)	Inc QALYs	ICER (£/QALY)
Regorafenib drug cost (2616.87, 3925.3)	21,164.03	0.9713	21,788.42	31,000.90	0.9713	31,915.51
Discount rate utilities (0, 0.06)	26,082.47	1.1798	22,108.14	26,082.47	0.8753	29,797.40
Discount rate costs (0, 0.06)	27,696.84	0.9713	28,513.97	25,211.22	0.9713	25,955.02
Utility of progressed health state (0.57, 0.72)	26,082.47	0.9365	27,849.92	26,082.47	1.0061	25,923.06
Utility of progression-free health state - Regorafenib (0.72, 0.82)	26,082.47	0.9774	26,685.11	26,082.47	0.9653	27,020.92
Utility of progression-free health state - Placebo (0.72, 0.82)	26,082.47	0.9097	28,670.88	26,082.47	1.0330	25,250.07
Regorafenib + BSC management costs while progression-free (99.37, 149.05)	25,857.58	0.9713	26,620.44	26,307.35	0.9713	27,083.49
BSC management costs post-progression (71.18, 106.78)	25,895.45	0.9713	26,659.43	26,269.48	0.9713	27,044.50
BSC management costs while progression-free (64.05, 96.08)	26,121.04	0.9713	26,891.68	26,043.89	0.9713	26,812.25
End of life costs (8052.12, 9422)	26,115.36	0.9713	26,885.83	26,049.52	0.9713	26,818.05
Additional start-up costs regorafenib (44.58, 66.86)	26,071.32	0.9713	26,840.49	26,093.61	0.9713	26,863.44
Hypertension probability on regorafenib (0.16, 0.31)	26,080.43	0.9713	26,849.87	26,084.66	0.9713	26,854.23

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Variable	Low variation			High variation		
	Inc Cost (£)	Inc QALYs	ICER (£/QALY)	Inc Cost (£)	Inc QALYs	ICER (£/QALY)
Hypertension cost (9.48, 14.23)	26,080.98	0.9713	26,850.43	26,083.95	0.9713	26,853.50
Diarrhoea probability on regorafenib (0.01, 0.09)	26,081.92	0.9713	26,851.40	26,083.03	0.9713	26,852.55
Hypertension probability on placebo (0, 0.06)	26,081.22	0.9713	26,850.68	26,083.74	0.9713	26,853.27
Diarrhoea cost (5.62, 8.43)	26,082.31	0.9713	26,851.81	26,082.62	0.9713	26,852.12
HFSR cost (0, 0)	26,082.47	0.9713	26,851.96	26,082.47	0.9713	26,851.96
HFSR probability on regorafenib (0.13, 0.26)	26,082.47	0.9713	26,851.96	26,082.47	0.9713	26,851.96
HFSR probability on placebo (0, 0)	26,082.47	0.9713	26,851.96	26,082.47	0.9713	26,851.96
Diarrhoea probability on placebo (0, 0)	26,082.47	0.9713	26,851.96	26,082.47	0.9713	26,851.96
Death utility (0, 0)	26,082.47	0.9713	26,851.96	26,082.47	0.9713	26,851.96
OS regorafenib vs placebo unadjusted HR (0.79, 1.53)	26,082.47	0.9713	26,851.96	26,082.47	0.9713	26,851.96
OS regorafenib vs placebo RPSFT HR (1.2, 2.37)	26,082.47	0.9713	26,851.96	26,082.47	0.9713	26,851.96
OS regorafenib vs placebo IPE HR (1.28, 2.53)	26,082.47	0.9713	26,851.96	26,082.47	0.9713	26,851.96

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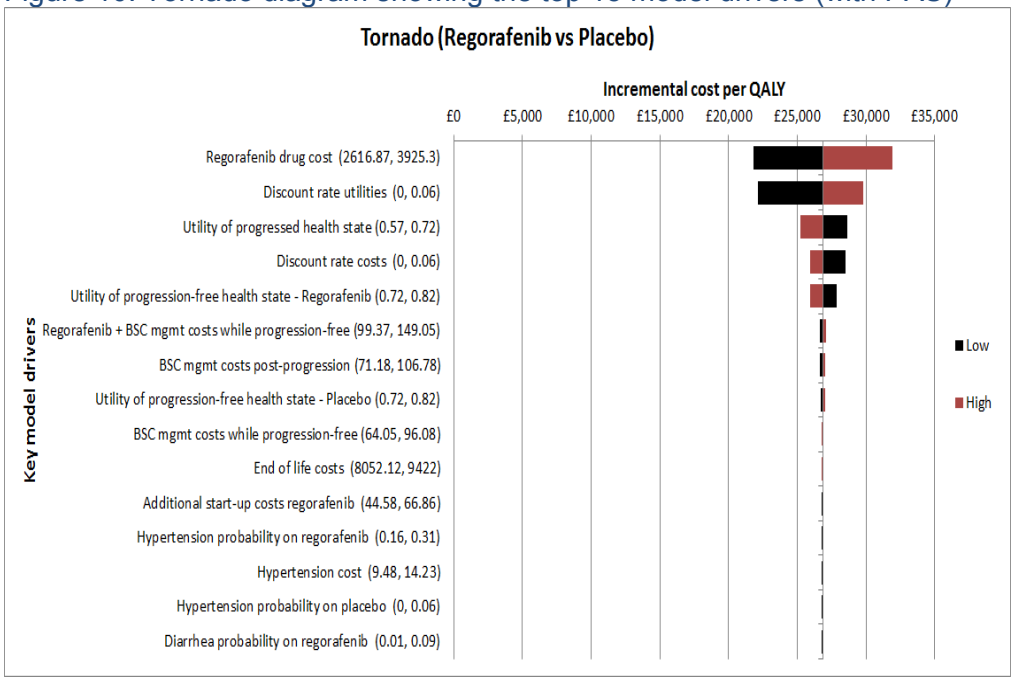
Figure 9. Tornado diagram showing the top 15 model drivers (without PAS)

Figure 10. Tornado diagram showing the top 15 model drivers (with PAS)



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Scenario analysis

Scenario analysis was performed on key areas of uncertainty in the model, these included areas where assumptions could be challenged.

Scenario analysis 1 – Overall survival extrapolation using the Weibull and Gompertz parametric model

When the Weibull parametric model was selected for overall survival extrapolation both the incremental costs and the incremental QALYs decreased. Because of the large impact on incremental QALYs, the net effect was an increase in the ICER to £[redacted] using regorafenib list price and £31,974 using the PAS price. The results for this scenario are summarised in Table 12, and the cost breakdown is shown in Table 13.

Table 12. Scenario analysis 1a - Overall survival extrapolation with Weibull

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.092	0.956	1.137
	PFLYs	0.706	0.124	0.582
	QALYs	1.439	0.633	0.805
	Costs	£[redacted]	£10,223	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.092	0.956	1.137
	PFLYs	0.706	0.124	0.582
	QALYs	1.439	0.633	0.805
	Costs	£35,977	£10,223.42	£25,753
	Incremental cost per QALY			**£31,974**

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Table 13. Scenario analysis 1a - Cost breakdown for overall survival with Weibull extrapolation

	Component	Regorafenib + BSC	Placebo + BSC	Incremental
List price	Drug costs - progression-free	£[redacted]	£0	£[redacted]
	Drug costs - post-progression	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£2	£[redacted]
	Monitoring costs	£[redacted]	£1,188	£[redacted]
	End-of-life costs	£[redacted]	£8,561	-£[redacted]
	Total cost	**£[redacted]**	**£10,223**	**£[redacted]**
PAS price	Drug costs - progression-free	£[redacted]	£0	£[redacted]
	Drug costs - post-progression	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£2	£[redacted]
	Monitoring costs	£[redacted]	£1,188	£[redacted]
	End-of-life costs	£[redacted]	£8,561	-£[redacted]
	Total cost breakdown	**£35,977**	**£10,223**	**£25,753**

When the Gompertz parametric model was selected for overall survival extrapolation both the incremental costs and the incremental QALYs decreased. Because of the large impact on incremental QALYs, the net effect was an increase in the ICER to £[redacted] using regorafenib list price and £33,157 using the PAS price. The results for this scenario are summarised in Table 14, and the cost breakdown is shown in Table 15.

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Table 14. Scenario analysis 1b - Overall survival extrapolation with Gompertz extrapolation

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.136	1.042	1.094
	PFLYs	0.709	0.124	0.585
	QALYs	1.467	0.689	0.778
	Costs	£[redacted]	£10,293	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.136	1.042	1.094
	PFLYs	0.709	0.124	0.585
	QALYs	1.467	0.689	0.778
	Costs	£36,085	£10,293	£25,792
	Incremental cost per QALY			**£33,157**

Table 15. Scenario analysis 1b - Cost breakdown for overall survival with Gompertz extrapolation

	Component	Regorafenib + BSC	Placebo + BSC	Incremental
List price	Drug costs - progression-free	£[redacted]	£0	£[redacted]
	Drug costs - post-progression	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£2	£[redacted]
	Monitoring costs	£[redacted]	£1,289	£[redacted]
	End-of-life costs	£[redacted]	£8,530	-£[redacted]
	Total cost	**£[redacted]**	**£10,293**	**£[redacted]**
PAS price	Drug costs - progression-free	£[redacted]	£0	£[redacted]
	Drug costs - post-progression	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£2	£[redacted]
	Monitoring costs	£[redacted]	£1,289	£[redacted]
	End-of-life costs	£[redacted]	£8,530	-£[redacted]
	Total cost	**£36,085**	**£10,293**	**£25,792**

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Scenario analysis 2 – RPSFT crossover correction methods

In this scenario analysis the RPSFT method (with recensoring) was explored, and three different OS survival models were fitted:

2a: Log-logistic

2b: Weibull

2c: Gompertz

The log-logistic model provided the best statistical fit according to the AIC (see Table **4** and Table 5).

We report the results for both Weibull and Gompertz parametric functions, in addition to the best fitting log-logistic function to maintain consistency with the analysis performed in the above scenario.

Table 16 to Table 21 below show the results when the crossover adjustment method was changed with each OS parametric function. RPSFT with the log-logistic function increased the ICER to £[redacted] per QALY gained with the list price and £27,934 with the PAS price. Changing the OS parametric function to Weibull increased the ICER further to £[redacted] with the list price and £33,013 with the PAS price. This increased to £[redacted] with the list price and £34,056 with the PAS price when the OS parametric function was changed to Gompertz.

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Table 16. Scenario analysis 2a - RPSFT with OS extrapolation using Log-logistic extrapolation

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.546	1.215	1.331
	PFLYs	0.710	0.124	0.586
	QALYs	1.733	0.801	0.932
	Costs	£[redacted]	£10,448	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.546	1.215	1.331
	PFLYs	0.710	0.124	0.586
	QALYs	1.733	0.801	0.932
	Costs	£36,478	£10,448	£26,030
	Incremental cost per QALY			**£27,934**

Table 17. Scenario analysis 2a - Cost breakdown for RPSFT and OS using Log-logistic extrapolation

	Component	Regorafenib + BSC	Placebo + BSC	Incremental
List price	Drug costs - progression-free	£[redacted]	£0	£[redacted]
	Drug costs - post-progression	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£3	£[redacted]
	Monitoring costs	£[redacted]	£1,489	£[redacted]
	End-of-life costs	£[redacted]	£8,485	-£[redacted]
	Total cost	**£[redacted]**	**£10,448**	**£[redacted]**
PAS price	Drug costs - progression-free	£[redacted]	£0	£[redacted]
	Drug costs - post-progression	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£3	£[redacted]
	Monitoring costs	£[redacted]	£1,489	£[redacted]
	End-of-life costs	£[redacted]	£8,485	-£[redacted]
	Total cost	**£36,478**	**£10,448**	**£26,030**

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Table 18. Scenario analysis 2b - RPSFT with OS extrapolation using Weibull extrapolation

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.092	0.996	1.096
	PFLYs	0.706	0.124	0.582
	QALYs	1.439	0.660	0.779
	Costs	£[redacted]	£10,259	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.092	0.996	1.096
	PFLYs	0.706	0.124	0.582
	QALYs	1.439	0.660	0.779
	Costs	£35,977	£10,259	£25,717
	Incremental cost per QALY			**£33,013**

Table 19. Scenario analysis 2b - Cost breakdown for RPSFT and OS using Weibull extrapolation

	Component	Regorafenib + BSC	Placebo + BSC	Incremental
List price	Drug costs - progression-free	£[redacted]	£0	£[redacted]
	Drug costs - post-progression	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£2	£[redacted]
	Monitoring costs	£[redacted]	£1,235	£[redacted]
	End-of-life costs	£[redacted]	£8,550	-£[redacted]
	Total cost	**£[redacted]**	**£10,259**	**£[redacted]**
PAS price	Drug costs - progression-free	£[redacted]	£0	£[redacted]
	Drug costs - post-progression	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£2	£[redacted]
	Monitoring costs	£[redacted]	£1,235	£[redacted]
	End-of-life costs	£[redacted]	£8,550	-£[redacted]
	Total cost	**£35,977**	**£10,259**	**£25,717**

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Table 20. Scenario analysis 2c - RPSFT with OS extrapolation using Gompertz extrapolation

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.136	1.075	1.061
	PFLYs	0.709	0.124	0.585
	QALYs	1.467	0.711	0.756
	Costs	£[redacted]	£10,323	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.136	1.075	1.061
	PFLYs	0.709	0.124	0.585
	QALYs	1.467	0.711	0.756
	Costs	£36,085	£10,323	£25,762
	Incremental cost per QALY			**£34,056**

Table 21. Scenario analysis 2c - Cost breakdown for RPSFT and OS using Gompertz extrapolation

	Component	Regorafenib + BSC	Placebo + BSC	Incremental
List price	Drug costs - progression-free	£[redacted]	£0	£[redacted]
	Drug costs - post-progression	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£2	£[redacted]
	Monitoring costs	£[redacted]	£1,327	£[redacted]
	End-of-life costs	£[redacted]	£8,522	-£[redacted]
	Total cost	**£[redacted]**	**£10,323**	**£[redacted]**
PAS price	Drug costs - progression-free	£[redacted]	£0	£[redacted]
	Drug costs - post-progression	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£2	£[redacted]
	Monitoring costs	£[redacted]	£1,327	£[redacted]
	End-of-life costs	£[redacted]	£8,522	-£[redacted]
	Total cost	**£36,085**	**£10,323**	**£25,762**

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Scenario analysis 3 – Resource use according to clinical expert opinion

Resource use inputs according to clinical experts' opinion presented in Table 87 to Table 90 of the NICE submission were used in this scenario analysis.

Table 22 and Table 23 show the results when all the resource use assumptions are applied as per the clinical experts' opinion.

Table 22. Scenario analysis 3 – Results using all clinical expert resource use assumptions

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.546	1.154	1.393
	PFLYs	0.710	0.124	0.586
	QALYs	1.733	0.761	0.971
	Costs	£[redacted]	£10,044	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.546	1.154	1.393
	PFLYs	0.710	0.124	0.586
	QALYs	1.733	0.761	0.971
	Costs	£35,995	£10,044	£25,951
	Incremental cost per QALY			**£26,717**

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Table 23. Scenario analysis 3 - Clinical expert resource use assumptions comparison cost breakdown

	Component	Regorafenib + BSC	Placebo + BSC	Incremental
List price	Drug costs progression-free	£[redacted]	£0.00	£[redacted]
	Drug costs post-progression	£[redacted]	£0.00	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£205	-£[redacted]
	Adverse Event costs	£[redacted]	£3	£[redacted]
	Monitoring costs	£[redacted]	£1,333	£[redacted]
	End-of-life costs	£[redacted]	£8,503	-£[redacted]
	Total cost	**£[redacted]**	**£10,044**	**£[redacted]**
PAS price	Drug costs progression-free	£[redacted]	£0.00	£[redacted]
	Drug costs post-progression	£[redacted]	£0.00	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£205	-£[redacted]
	Adverse Event costs	£[redacted]	£3	£[redacted]
	Monitoring costs	£[redacted]	£1,333	£[redacted]
	End-of-life costs	£[redacted]	£8,503	-£[redacted]
	Total cost	**£35,995**	**£10,044**	**£25,951**

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Scenario analysis 4 – Cost of post-progression treatment in the regorafenib + BSC arm

Three scenarios were explored with treatment post-progression in the regorafenib arm continued for:

- [redacted] days (overall SAF population in the GRID study) for all the patients who progressed
- [redacted] days (UK SAF population in the GRID study) for all the patients who progressed
- 56 days (8 weeks) only in 25.3% of the patients who progressed as resulted from the 2013 and 2016 physician surveys for England and Wales

The results are shown in the tables below.

Inclusion of the cost of post-progression treatment for [redacted] days yielded the ICER at £[redacted] without the PAS and £43,049 with the PAS. Inclusion of the cost of post-progression treatment for [redacted] days when considering the UK patient population yielded the ICER at £[redacted] without the PAS and £30,271 with the PAS. When considering the inputs from the standard clinical practice in England and Wales – e.g. 25.3% of patients continuing treatment with regorafenib for 8 weeks on average after disease progression - the ICER resulted at £[redacted] without PAS and £27,107 with PAS.

Table 24. Scenario analysis 4a - Cost of post-progression treatment ([redacted] days)

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.546	1.154	1.393
	PFLYs	0.710	0.124	0.586
	QALYs	1.733	0.761	0.971
	Costs	£[redacted]	£10,395	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.546	1.154	1.393
	PFLYs	0.710	0.124	0.586
	QALYs	1.733	0.761	0.971
	Costs	£52,210	£10,395	£41,815
	Incremental cost per QALY			**£43,049**

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Table 25. Scenario analysis 4a - Cost of post-progression treatment cost breakdown ([redacted] days)

	Component	Regorafenib + BSC	Placebo + BSC	Incremental
List price	Drug costs - progression-free	£[redacted]	£0.00	£[redacted]
	Drug costs - post-progression	£[redacted]	£0.00	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£3	£[redacted]
	Monitoring costs	£[redacted]	£1,418	£[redacted]
	End-of-life costs	£[redacted]	£8,503	-£[redacted]
	Total cost	**£[redacted]**	**£10,395**	**£[redacted]**
PAS price	Drug costs - progression-free	£[redacted]	£0.00	£[redacted]
	Drug costs - post-progression	£[redacted]	£0.00	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£3	£[redacted]
	Monitoring costs	£[redacted]	£1,418	£[redacted]
	End-of-life costs	£[redacted]	£8,503	-£[redacted]
	Total cost	**£52,210**	**£10,395**	**£41,815**

Table 26. Scenario analysis 4b - Cost of post-progression treatment for the UK subpopulation ([redacted] days)

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.546	1.154	1.393
	PFLYs	0.710	0.124	0.586
	QALYs	1.733	0.761	0.971
	Costs	£[redacted]	£10,395	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.546	1.154	1.393
	PFLYs	0.710	0.124	0.586
	QALYs	1.733	0.761	0.971
	Costs	£39,799	£10,395	£29,403
	Incremental cost per QALY			**£30,271**

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Table 27. Scenario analysis 4b - Cost of post-progression treatment for the UK subpopulation cost breakdown ([redacted] days)

	Component	Regorafenib + BSC	Placebo + BSC	Incremental
List price	Drug costs - progression-free	£[redacted]	£0	£[redacted]
	Drug costs - post-progression	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£3	£[redacted]
	Monitoring costs	£[redacted]	£1,418	£[redacted]
	End-of-life costs	£[redacted]	£8,503	-£[redacted]
	Total cost	**£[redacted]**	**£10,395**	**£[redacted]**
PAS price	Drug costs - progression-free	£[redacted]	£0	£[redacted]
	Drug costs - post-progression	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£3	£[redacted]
	Monitoring costs	£[redacted]	£1,418	£[redacted]
	End-of-life costs	£[redacted]	£8,503	-£[redacted]
	Total cost	**£39,799**	**£10,395**	**£29,403**

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Table 28. Scenario analysis 4c - Cost of post-progression treatment based on physician survey inputs (25.3% of patients treated for 8 weeks with TKI treatment after disease progression)

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.546	1.154	1.393
	PFLYs	0.710	0.124	0.586
	QALYs	1.733	0.761	0.971
	Costs	£[redacted]	£10,395	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.546	1.154	1.393
	PFLYs	0.710	0.124	0.586
	QALYs	1.733	0.761	0.971
	Costs	£36,725	£10,395	£26,330
	Incremental cost per QALY			**£27,107**

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Table 29. Scenario analysis 4c - Cost of post-progression treatment based on physician survey inputs (25.3% of patients treated for 8 weeks with TKI treatment after disease progression)

	Component	Regorafenib + BSC	Placebo + BSC	Incremental
List price	Drug costs - progression-free	£[redacted]	£0.00	£[redacted]
	Drug costs - post-progression	£[redacted]	£0.00	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£3	£[redacted]
	Monitoring costs	£[redacted]	£1,418	£[redacted]
	End-of-life costs	£[redacted]	£8,503	-£[redacted]
	Total cost	**£[redacted]**	**£10,395**	**£[redacted]**
PAS price	Drug costs - progression-free	£[redacted]	£0.00	£[redacted]
	Drug costs - post-progression	£[redacted]	£0.00	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£3	£[redacted]
	Monitoring costs	£[redacted]	£1,418	£[redacted]
	End-of-life costs	£[redacted]	£8,503	-£[redacted]
	Total cost	**£36,725**	**£10,395**	**£26,330**

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Scenario analysis 5 – EQ-5D utilities from the repeated measures comparison

Table 30 shows the results using health state utility values from the EQ-5D repeated measures comparison (see Table 38 of the NICE submission) instead of the paired-sampled analyses used in the base case.

The ICER slightly decreased to £[redacted] per QALY with the list price and £26,020 per QALY with the PAS price. The cost breakdown is not shown because it is identical to the base case.

Table 30. Scenario analysis 5a - Results using the repeated measured EQ-5D utilities

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.546	1.154	1.393
	PFLYs	0.710	0.124	0.586
	QALYs	1.818	0.816	1.002
	Costs	£[redacted]	£10,395	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.546	1.154	1.393
	PFLYs	0.710	0.124	0.586
	QALYs	1.818	0.816	1.002
	Costs	£36,478	£10,395	£26,082
	Incremental cost per QALY			**£26,020**

Despite adverse events such as HFSR, diarrhoea and fatigue are easily manageable and their effect on the patient's HRQL can be deemed negligible, a scenario analysis was conducted using lower utility values for regorafenib in the progression-free health state compared to placebo. Utility values from the EQ-5D repeated measures analysis based on the splitting of the progression-free state into regorafenib and placebo arms (see Table 39 of the NICE submission) were used. Table 31 displays the results of this scenario analysis.

The ICER resulting from this analysis decreased slightly at £[redacted] without the PAS and £26,550 with the PAS. The improvement in cost-effectiveness, as compared to the same analysis based on the 2015 data, is due to the longer time spent in the progressed state which is reflected into a total progressed utility outweighing the decrease in progression-free utility.

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Table 31. Scenario analysis 5b - Results using the repeated measured EQ-5D utilities based on the splitting of the progression-free health state into treatment arms

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.546	1.154	1.393
	PFLYs	0.710	0.124	0.586
	QALYs	1.777	0.794	0.982
	Costs	£[redacted]	£10,395	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.546	1.154	1.393
	PFLYs	0.710	0.124	0.586
	QALYs	1.777	0.794	0.982
	Costs	£36,478	£10,395	£26,082
	Incremental cost per QALY			**£26,550**

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Scenario analysis 6 – Using EORTC from GRID as the utility data source

Table 32 shows the results using health state utility values from the EORTC repeated measures analysis instead of the EQ-5D paired-sampled analysis. The utilities used for this analysis are those reported in Table 41 of the NICE submission.

Another scenario analysis was performed using the EORTC-derived utilities from the paired-samples comparison method. The utilities used for this analysis can be found in Table 40 of the NICE submission. The results for this scenario analysis can be found in Table 33 below.

The ICER reduced from £[redacted] using regorafenib list price to £24,262 using the PAS price. The cost breakdown is not shown because it is identical to the base case.

Table 32. Scenario analysis 6a - Results from using repeated measures EORTC utilities from the GRID trial

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.546	1.154	1.393
	PFLYs	0.710	0.124	0.586
	QALYs	1.952	0.877	1.075
	Costs	£[redacted]	£10,395	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.546	1.154	1.393
	PFLYs	0.710	0.124	0.586
	QALYs	1.952	0.877	1.075
	Costs	£36,478	£10,395	£26,082
	Incremental cost per QALY			**£24,262**

When using paired-samples comparison of EORTC-derived utilities, the ICER reduced from £[redacted] using regorafenib list price to £24,037 using the PAS price.

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Table 33. Scenario analysis 6b - Results using paired-samples comparison of EORTC-derived utilities

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.546	1.154	1.393
	PFLYs	0.710	0.124	0.586
	QALYs	1.960	0.875	1.085
	Costs	£[redacted]	£10,395	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.546	1.154	1.393
	PFLYs	0.710	0.124	0.586
	QALYs	1.960	0.875	1.085
	Costs	£36,478	£10,395	£26,082
	Incremental cost per QALY			**£24,037**

B6. On p147, please provide further details on why the Spanish study (Sanz-Granda et al. 2015) was considered not relevant to the UK for the cost-effectiveness searches?

Overall survival data used in this study were taken from the GRID dataset dated 31st January 2014 (112). At the time of the NICE submission (ID1056), a more recent dataset, dated 8th June 2015, was available. Crossover corrections necessary for the adjustment of the OS data used in the cost-utility analysis by Sanz-Granda et al (2015) were not recensored as recommended by NICE Decision Support Unit (113).

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2. REQUEST FOR CLARIFICATION # 2 – Date: 02/05/2017

Dear [redacted],

Further to your email of 27 April 2017, please could we ask you to provide the hazard ratios (and associated 95% confidence intervals) for overall survival using the April 2017 data cut off. Specifically please ensure all the following results are provided:

- Unadjusted
- Adjusted IPE
- Adjusted RPSFT

We would be grateful to receive these as soon as possible but no later than close of business on Thursday 4 May 2017. Please use the following NICE Docs link to upload your response: https://appraisals.nice.org.uk/request/23685

Thank you.

Kind regards,

[redacted]
Technology Appraisals Project Manager - Committee D
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Table 34 displays the hazard ratios (HRs) and associated confidence intervals for the 2017 OS data cut off when considering patients' stratification by prior anti-cancer drug group and region.

Table 34. Hazard ratios for overall survival (2017 data cut off) with stratification by prior anti-cancer drug group and region

Adjustment	HR	95% CI		p-value
		Lower	Upper	
Unadjusted	0.8983228	0.6455495	1.250073	0.2621241
IPE-adjusted	0.4535286	0.320965	0.6408432	0.0000022
RPSFT-adjusted	0.4826214	0.3422664	0.6805324	0.000011

Table 35 presents the results for the analysis of the 2017 OS data cut off when no patients' stratification is considered.

Table 35. Hazard ratios for overall survival (2017 data cut off) without stratification

Adjustment	HR	95% CI		p-value
		Lower	Upper	
Unadjusted	0.8842283	0.6378846	1.225707	0.2298251
IPE-adjusted	0.4557933	0.3235592	0.6420696	0.0000021
RPSFT-adjusted	0.477118	0.3391964	0.6711204	0.0000071

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3. REQUEST FOR CLARIFICATION # 3 – Date: 11/05/2017

Dear [redacted],

Thank you for providing data using a more recent 2017 data cut off. The evidence review group would like clarification on whether the treatment durations in both treatment arms were also updated in the 2017 analyses. Please confirm the treatment durations that were used in the model for each treatment arm and if these were updated please provide the new values that were used in the 2017 analyses.

Please could we also request that you include all data relating to the 2017 analyses in an updated response to clarification and submit this through NICE docs by 5pm on Monday 15 May 2017? This includes the 2017 hazard ratios that have been provided in a separate document and details of treatment durations. Your help with this is much appreciated and will help to reduce the number of documents for the committee meeting.

You can upload your response through NICE Docs:
https://appraisals.nice.org.uk/request/26945

Best wishes,
[redacted]

[redacted] [redacted]
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Response to question B5 reported in section 1 only included the 2017 update for the overall survival data. Because of time constraints, the 2017 data update for time to regorafenib discontinuation and mean observed dose of regorafenib by cycle was not included in those analyses. The full set of analyses including the complete 2017 data update for overall survival, time to regorafenib discontinuation and mean observed dose of regorafenib by cycle is presented in this section. Bayer's new base case is formed by the cost effectiveness analysis presented in this section.

Cost effectiveness analysis based on the 2017 data update for overall survival, time to regorafenib discontinuation and mean observed dose of regorafenib by cycle (Bayer's new base case)

An additional analysis has been carried out to apply time to discontinuation of regorafenib data directly. In this analysis the calculation of treatment costs is independent of patient progression. For this analysis the proportion of regorafenib patients on treatment by cycle was obtained directly from the Kaplan-Meier time to discontinuation curve. The mean observed dose of regorafenib (excluding those with a dose of 0mg) by cycle was then applied to the proportion on treatment in order to calculate treatment costs by cycle. This analysis only impacts the drug costing component of the model, all other aspects of the model, including the use of updated overall survival data, remain unchanged.

The time to treatment discontinuation curve for regorafenib used for this analysis is Figure 11. Note that no extrapolation of the curve was performed as only 2% of patients remained on treatment by end of follow-up.

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Figure 11. GRID Kaplan Meier time to treatment discontinuation (regorafenib)

Table 36 and Table 37 display the base case results without and with PAS. The cost of regorafenib is based on discontinuation curve and mean observed dose of regorafenib. All other inputs and model remained unchanged compared to the response submitted on April 24th (see response to question B5 in section 1) using the updated overall survival data and chapter 5 of the NICE submission.

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Table 36. Base-case results (without PAS) based on 2017 data cut off and time to discontinuation curve

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (LYs)	ICER (£) incremental (QALYs)
Placebo + BSC	10,395	1.154	0.761					
Regorafenib	[redacted]	2.546	1.733					
				[redacted]	1.393	0.971	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 37. Base-case results (with PAS) based on 2017 data cut off and time to discontinuation curve

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (LYs)	ICER (£) incremental (QALYs)
Placebo + BSC	10,395	1.154	0.761					
Regorafenib	47,249	2.546	1.733					
				36,854	1.393	0.971	26,465	37,941
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

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The cost breakdown for the base case results is presented in Table 38.

Table 38. Base case results – cost breakdown

	Component	Regorafenib + BSC	Placebo + BSC	Incremental
List price	Drug costs	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£3	£[redacted]
	Monitoring costs	£[redacted]	£1,418	£[redacted]
	End-of-life costs	£[redacted]	£8,503	-£[redacted]
	Total cost	**£[redacted]**	£10,395	**£[redacted]**
PAS price	Drug costs	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£3	£[redacted]
	Monitoring costs	£[redacted]	£1,418	£[redacted]
	End-of-life costs	£[redacted]	£8,503	-£[redacted]
	Total cost breakdown	**£47,249**	**£10,395**	**£36,854**

One-way sensitivity analysis (OWSA) and probabilistic sensitivity analysis (PSA) were conducted to explore the effect of parameter uncertainty.

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Probabilistic sensitivity analysis

Simulations with 3,000 iterations were produced and the average results are shown in Table 39 below.

Table 39. Average results from PSA (with and without PAS)

	Regorafenib + BSC			Placebo + BSC			Incremental			ICER (£/QALY)
	LYs	QALYs	Costs	LYs	QALYs	Costs	LYs	QALYs	Costs	
List Price	2.560	1.741	£[redacted]	1.178	0.776	£11,016	1.382	0.965	£[redacted]	£[redacted]
PAS price	2.563	1.745	£48,152	1.183	0.780	£11,021	1.380	0.965	£37,130	£38,494

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Figure 12 and Figure 13 show the cost-effectiveness plane without and with the PAS price. Figure 14 and Figure 15 show the cost-effectiveness acceptability curve (CEAC) without and with the PAS price. At a willingness to pay of £50,000 per QALY gained regorafenib was [redacted]% likely to be cost-effective at its list price and 82% likely at its PAS price.

Figure 12. Cost-effectiveness plane showing per patient incremental cost and QALYs (without PAS)

Figure 13. CEAC based on willingness-to-pay per QALY (without PAS)

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Figure 14. Cost-effectiveness plane showing per patient incremental cost and QALYs (with PAS)

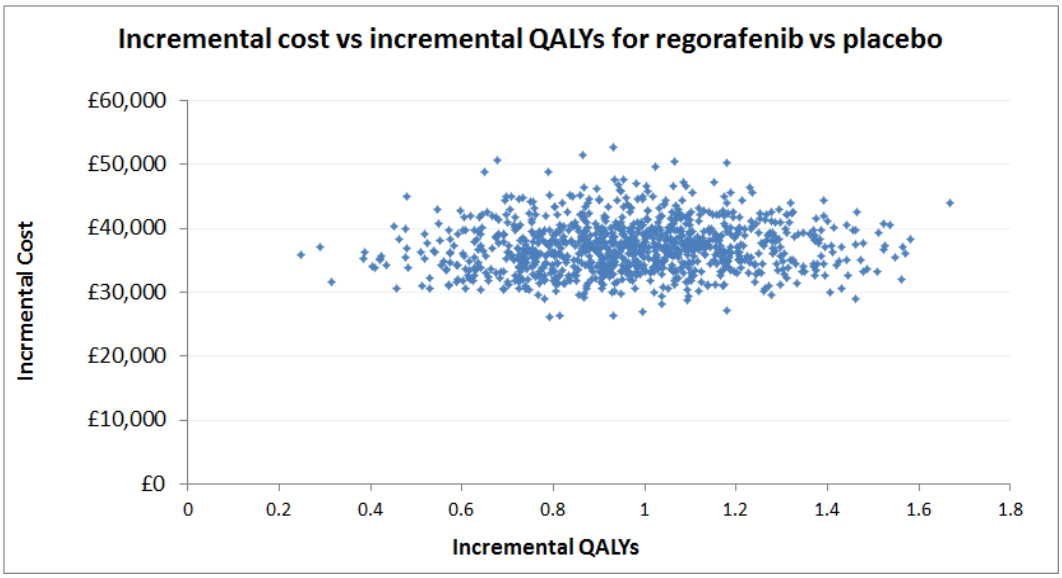
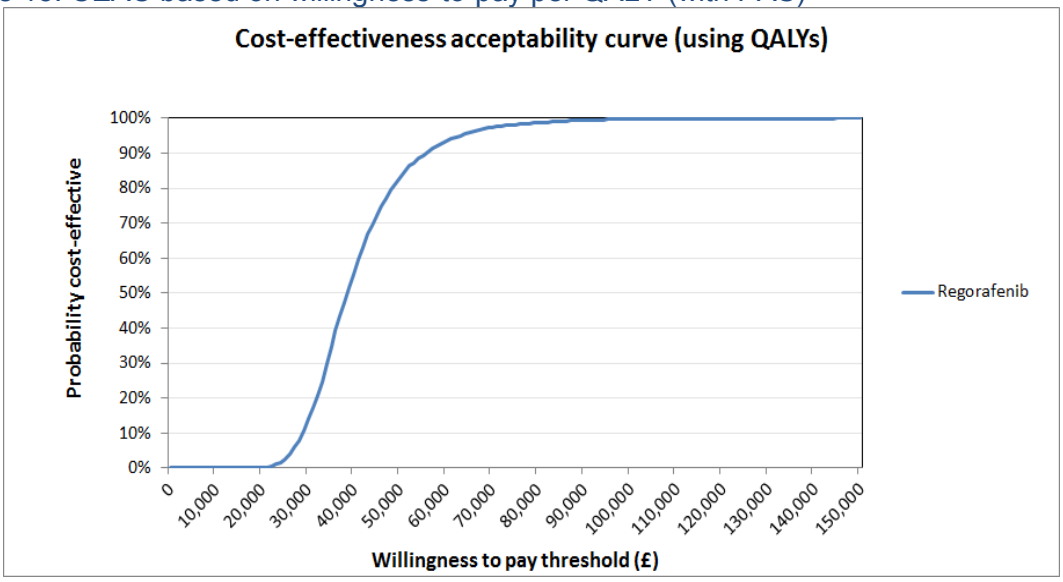


Figure 15. CEAC based on willingness-to-pay per QALY (with PAS)



Incremental cost effectiveness analysis results estimated from the probabilistic sensitivity analysis are consistent with those found in the base-case analysis.

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Deterministic sensitivity analysis

The values used for the lower and upper OWSA analysis are the same presented in the submission.

Results of the deterministic sensitivity analysis are presented in Table 40 and Table 41.

The top 15 model drivers are shown in the tornado diagram in Figure 16 in terms of incremental cost per QALY (at the list price for regorafenib). The tornado diagram using the PAS price is shown in
Figure **17**. For both, the highest impact was observed when the drug acquisition cost for regorafenib was varied. This provided an ICER varying between £[redacted] and £[redacted] per QALY gained when applying the list price and between £30,660 and £45,222 per QALY gained when using the PAS price. Variation of the discount rate for the utilities and costs were also important in determining the ICER.

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Table 40. Full OWSA results (without PAS)

	Low variation			High variation		
Variable	**Inc Cost (£)**	**Inc QALYs**	**ICER (£/QALY)**	**Inc Cost (£)**	**Inc QALYs**	**ICER (£/QALY)**
Regorafenib drug cost (2995.2, 4492.8)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
Discount rate utilities (0, 0.06)	[redacted]	1.1798	[redacted]	[redacted]	0.8753	[redacted]
Utility of progressed health state (0.57, 0.72)	[redacted]	0.9097	[redacted]	[redacted]	1.0330	[redacted]
Discount rate costs (0, 0.06)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
Utility of progression-free health state - Regorafenib (0.72, 0.82)	[redacted]	0.9365	[redacted]	[redacted]	1.0061	[redacted]
Utility of progression-free health state - Placebo (0.72, 0.82)	[redacted]	0.9774	[redacted]	[redacted]	0.9653	[redacted]
Regorafenib + BSC management costs while progression-free (99.37, 149.05)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
BSC management costs post-progression (71.18, 106.78)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
BSC management costs while progression-free (64.05, 96.08)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
End of life costs (8052.12, 9422)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
Additional start-up costs regorafenib (44.58, 66.86)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
Hypertension probability on regorafenib (0.16, 0.31)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
Hypertension cost (9.48, 14.23)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
Hypertension probability on placebo (0, 0.06)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
Diarrhoea probability on regorafenib (0.01, 0.09)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
Diarrhoea cost (5.62, 8.43)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
HFSR cost (0, 0)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
HFSR probability on regorafenib (0.13, 0.26)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
HFSR probability on placebo (0, 0)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
Diarrhoea probability on placebo (0, 0)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]

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Variable	Low variation			High variation		
	Inc Cost (£)	Inc QALYs	ICER (£/QALY)	Inc Cost (£)	Inc QALYs	ICER (£/QALY)
Death utility (0, 0)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
OS regorafenib vs placebo unadjusted HR (0.8, 1.55)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
OS regorafenib vs placebo RPSFT HR (1.47, 2.92)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]
OS regorafenib vs placebo IPE HR (1.56, 3.12)	[redacted]	0.9713	[redacted]	[redacted]	0.9713	[redacted]

Table 41. Full OWSA results (with PAS)

Variable	Low variation			High variation		
	Inc Cost (£)	Inc QALYs	ICER (£/QALY)	Inc Cost (£)	Inc QALYs	ICER (£/QALY)
Regorafenib drug cost (2995.2, 4492.8)	29,780.97	0.9713	30,659.58	43,926.32	0.9713	45,222.26
Discount rate utilities (0, 0.06)	36,853.64	1.1798	31,238.06	36,853.64	0.8753	42,102.72
Utility of progressed health state (0.57, 0.72)	36,853.64	0.9097	40,510.98	36,853.64	1.0330	35,677.50
Discount rate costs (0, 0.06)	38,493.59	0.9713	39,629.25	35,902.12	0.9713	36,961.32
Utility of progression-free health state - Regorafenib (0.72, 0.82)	36,853.64	0.9365	39,350.99	36,853.64	1.0061	36,628.41
Utility of progression-free health state - Placebo (0.72, 0.82)	36,853.64	0.9774	37,705.16	36,853.64	0.9653	38,179.65
Regorafenib + BSC management costs while progression-free (99.37, 149.05)	36,628.76	0.9713	37,709.40	37,078.53	0.9713	38,172.44
BSC management costs post-progression (71.18, 106.78)	36,666.63	0.9713	37,748.39	37,040.66	0.9713	38,133.45
BSC management costs while progression-free (64.05, 96.08)	36,892.22	0.9713	37,980.63	36,815.07	0.9713	37,901.21
End of life costs (8052.12, 9422)	36,886.54	0.9713	37,974.79	36,820.70	0.9713	37,907.00
Additional start-up costs regorafenib (44.58, 66.86)	36,842.50	0.9713	37,929.45	36,864.79	0.9713	37,952.39
Hypertension probability on regorafenib (0.16, 0.31)	36,851.61	0.9713	37,938.82	36,855.84	0.9713	37,943.18

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Variable	Low variation			High variation		
	Inc Cost (£)	Inc QALYs	ICER (£/QALY)	Inc Cost (£)	Inc QALYs	ICER (£/QALY)
Hypertension cost (9.48, 14.23)	36,852.16	0.9713	37,939.39	36,855.13	0.9713	37,942.45
Hypertension probability on placebo (0, 0.06)	36,852.40	0.9713	37,939.63	36,854.91	0.9713	37,942.23
Diarrhoea probability on regorafenib (0.01, 0.09)	36,853.10	0.9713	37,940.35	36,854.21	0.9713	37,941.50
Diarrhoea cost (5.62, 8.43)	36,853.49	0.9713	37,940.76	36,853.80	0.9713	37,941.08
HFSR cost (0, 0)	36,853.64	0.9713	37,940.92	36,853.64	0.9713	37,940.92
HFSR probability on regorafenib (0.13, 0.26)	36,853.64	0.9713	37,940.92	36,853.64	0.9713	37,940.92
HFSR probability on placebo (0, 0)	36,853.64	0.9713	37,940.92	36,853.64	0.9713	37,940.92
Diarrhoea probability on placebo (0, 0)	36,853.64	0.9713	37,940.92	36,853.64	0.9713	37,940.92
Death utility (0, 0)	36,853.64	0.9713	37,940.92	36,853.64	0.9713	37,940.92
OS regorafenib vs placebo unadjusted HR (0.8, 1.55)	36,853.64	0.9713	37,940.92	36,853.64	0.9713	37,940.92
OS regorafenib vs placebo RPSFT HR (1.47, 2.92)	36,853.64	0.9713	37,940.92	36,853.64	0.9713	37,940.92
OS regorafenib vs placebo IPE HR (1.56, 3.12)	36,853.64	0.9713	37,940.92	36,853.64	0.9713	37,940.92

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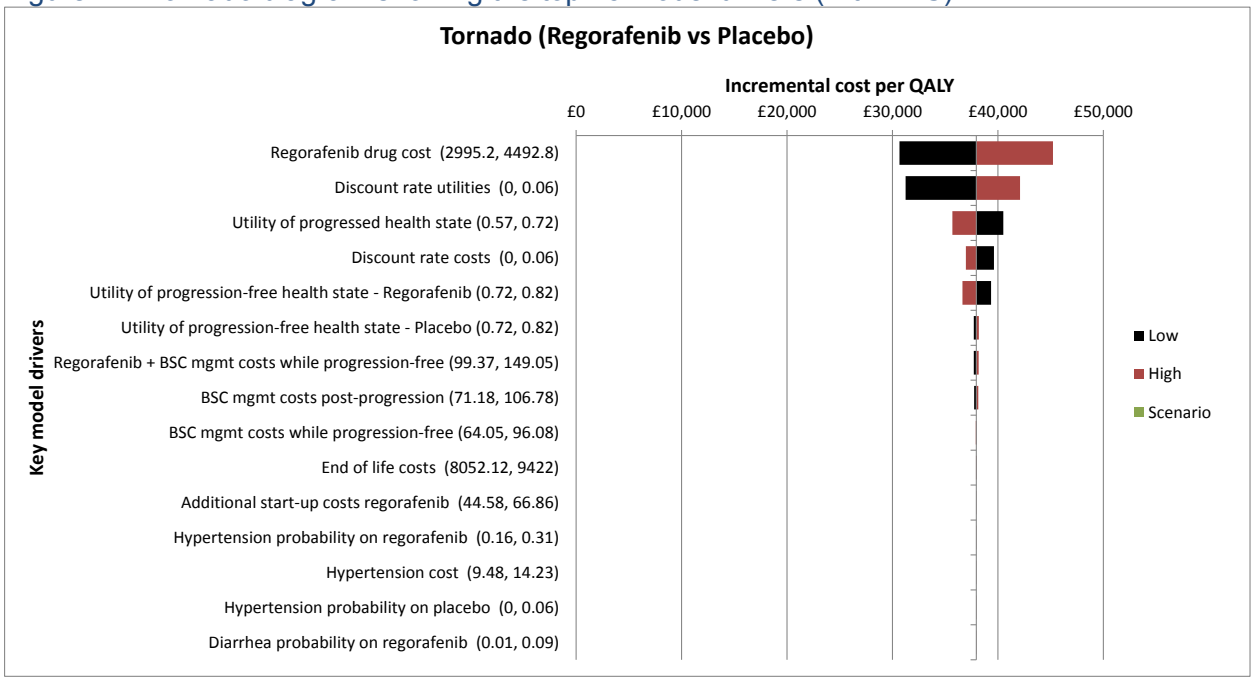
Figure 16. Tornado diagram showing the top 15 model drivers (without PAS)

Figure 17. Tornado diagram showing the top 15 model drivers (with PAS)



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Scenario analysis

Scenario analysis was performed on key areas of uncertainty in the model, these included areas where assumptions could be challenged.

Scenario analysis 1 – Overall survival extrapolation using the Weibull and Gompertz parametric model

When the Weibull parametric model was selected for overall survival extrapolation both the incremental costs and the incremental QALYs decreased. Because of the large impact on incremental QALYs, the net effect was an increase in the ICER to £[redacted] using regorafenib list price and £45,498 using the PAS price. The results for this scenario are summarised in Table 42, and the cost breakdown is shown in Table 43.

Table 42. Scenario analysis 1a - Overall survival extrapolation with Weibull

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.092	0.956	1.137
	PFLYs	0.706	0.124	0.582
	QALYs	1.439	0.633	0.805
	Costs	£[redacted]	£10,223	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.092	0.956	1.137
	PFLYs	0.706	0.124	0.582
	QALYs	1.439	0.633	0.805
	Costs	£46,869	£10,223	£36,646
	Incremental cost per QALY			**£45,498**

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Table 43. Scenario analysis 1a - Cost breakdown for overall survival with Weibull extrapolation

	Component	Regorafenib + BSC	Placebo + BSC	Incremental
List price	Drug costs	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£2	£[redacted]
	Monitoring costs	£[redacted]	£1,188	£[redacted]
	End-of-life costs	£[redacted]	£8,561	-£[redacted]
	Total cost	**£[redacted]**	**£10,223**	**£[redacted]**
PAS price	Drug costs	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£2	£[redacted]
	Monitoring costs	£[redacted]	£1,188	£[redacted]
	End-of-life costs	£[redacted]	£8,561	-£[redacted]
	Total cost breakdown	**£46,869**	**£10,223**	**£36,646**

When the Gompertz parametric model was selected for overall survival extrapolation both the incremental costs and the incremental QALYs decreased. Because of the large impact on incremental QALYs, the net effect was an increase in the ICER to £[redacted] using regorafenib list price and £47,068 using the PAS price. The results for this scenario are summarised in Table 44, and the cost breakdown is shown in Table 45.

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Table 44. Scenario analysis 1b - Overall survival extrapolation with Gompertz extrapolation

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.136	1.042	1.094
	PFLYs	0.709	0.124	0.585
	QALYs	1.467	0.689	0.778
	Costs	£[redacted]	£10,293	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.136	1.042	1.094
	PFLYs	0.709	0.124	0.585
	QALYs	1.467	0.689	0.778
	Costs	£46,906	£10,293	£36,612
	Incremental cost per QALY			**£47,068**

Table 45. Scenario analysis 1b - Cost breakdown for overall survival with Gompertz extrapolation

	Component	Regorafenib + BSC	Placebo + BSC	Incremental
List price	Drug costs	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£2	£[redacted]
	Monitoring costs	£[redacted]	£1,289	£[redacted]
	End-of-life costs	£[redacted]	£8,530	-£[redacted]
	Total cost	**£[redacted]**	**£10,293**	**£[redacted]**
PAS price	Drug costs	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£2	£[redacted]
	Monitoring costs	£[redacted]	£1,289	£[redacted]
	End-of-life costs	£[redacted]	£8,530	-£[redacted]
	Total cost	**£46,906**	**£10,293**	**£36,612**

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Scenario analysis 2 – RPSFT crossover correction methods

In this scenario analysis the RPSFT method (with recensoring) was explored, and three different OS survival models were fitted:

2a: Log-logistic

2b: Weibull

2c: Gompertz

The log-logistic model provided the best statistical fit according to the AIC.

We report the results for both Weibull and Gompertz parametric functions, in addition to the best fitting log-logistic function to maintain consistency with the analysis performed in the above scenario.

Table 46 to Table 51 below show the results when the crossover adjustment method was changed with each OS parametric function. RPSFT with the log-logistic function increased the ICER to £[redacted] per QALY gained with the list price and £39,493 with the PAS price. Changing the OS parametric function to Weibull increased the ICER further to £[redacted] with the list price and £46,996 with the PAS price. This increased to £[redacted] with the list price and £48,360 with the PAS price when the OS parametric function was changed to Gompertz.

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Table 46. Scenario analysis 2a - RPSFT with OS extrapolation using Log-logistic extrapolation

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.546	1.215	1.331
	PFLYs	0.710	0.124	0.586
	QALYs	1.733	0.801	0.932
	Costs	£[redacted]	£10,448	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.546	1.215	1.331
	PFLYs	0.710	0.124	0.586
	QALYs	1.733	0.801	0.932
	Costs	£47,249	£10,448	£36,801
	Incremental cost per QALY			**£39,493**

Table 47. Scenario analysis 2a - Cost breakdown for RPSFT and OS using Log-logistic extrapolation

	Component	Regorafenib + BSC	Placebo + BSC	Incremental
List price	Drug costs	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£3	£[redacted]
	Monitoring costs	£[redacted]	£1,489	£[redacted]
	End-of-life costs	£[redacted]	£8,485	-£[redacted]
	Total cost	**£[redacted]**	**£10,448**	**£[redacted]**
PAS price	Drug costs	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£3	£[redacted]
	Monitoring costs	£[redacted]	£1,489	£[redacted]
	End-of-life costs	£[redacted]	£8,485	-£[redacted]
	Total cost	**£47,249**	**£10,448**	**£36,801**

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Table 48. Scenario analysis 2b - RPSFT with OS extrapolation using Weibull extrapolation

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.092	0.996	1.096
	PFLYs	0.706	0.124	0.582
	QALYs	1.439	0.660	0.779
	Costs	£[redacted]	£10,259	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.092	0.996	1.096
	PFLYs	0.706	0.124	0.582
	QALYs	1.439	0.660	0.779
	Costs	£46,869	£10,259	£36,610
	Incremental cost per QALY			**£46,996**

Table 49. Scenario analysis 2b - Cost breakdown for RPSFT and OS using Weibull extrapolation

	Component	Regorafenib + BSC	Placebo + BSC	Incremental
List price	Drug costs	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£2	£[redacted]
	Monitoring costs	£[redacted]	£1,235	£[redacted]
	End-of-life costs	£[redacted]	£8,550	-£[redacted]
	Total cost	**£[redacted]**	**£10,259**	**£[redacted]**
PAS price	Drug costs	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£2	£[redacted]
	Monitoring costs	£[redacted]	£1,235	£[redacted]
	End-of-life costs	£[redacted]	£8,550	-£[redacted]
	Total cost	**£46,869**	**£10,259**	**£36,610**

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Table 50. Scenario analysis 2c - RPSFT with OS extrapolation using Gompertz extrapolation

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.136	1.075	1.061
	PFLYs	0.709	0.124	0.585
	QALYs	1.467	0.711	0.756
	Costs	£[redacted]	£10,323	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.136	1.075	1.061
	PFLYs	0.709	0.124	0.585
	QALYs	1.467	0.711	0.756
	Costs	£46,906	£10,323	£36,582
	Incremental cost per QALY			**£48,360**

Table 51. Scenario analysis 2c - Cost breakdown for RPSFT and OS using Gompertz extrapolation

	Component	Regorafenib + BSC	Placebo + BSC	Incremental
List price	Drug costs	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£2	£[redacted]
	Monitoring costs	£[redacted]	£1,327	£[redacted]
	End-of-life costs	£[redacted]	£8,522	-£[redacted]
	Total cost	**£[redacted]**	**£10,323**	**£[redacted]**
PAS price	Drug costs	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£2	£[redacted]
	Monitoring costs	£[redacted]	£1,327	£[redacted]
	End-of-life costs	£[redacted]	£8,522	-£[redacted]
	Total cost	**£46,906**	**£10,323**	**£36,582**

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Scenario analysis 3 – Resource use according to clinical expert opinion

Resource use inputs according to clinical experts' opinion presented in Table 87 to Table 90 of the NICE submission were used in this scenario analysis.

Table 52 and Table 53 show the results when all the resource use assumptions are applied as per the clinical experts' opinion.

Table 52. Scenario analysis 3 – Results using all clinical expert resource use assumptions

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.546	1.154	1.393
	PFLYs	0.710	0.124	0.586
	QALYs	1.733	0.761	0.971
	Costs	£[redacted]	£10,044	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.546	1.154	1.393
	PFLYs	0.710	0.124	0.586
	QALYs	1.733	0.761	0.971
	Costs	£46,766	£10,044	£36,722
	Incremental cost per QALY			**£37,806**

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Table 53. Scenario analysis 3 - Clinical expert resource use assumptions comparison cost breakdown

	Component	Regorafenib + BSC	Placebo + BSC	Incremental
List price	Drug costs	£[redacted]	£0.00	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£205	-£[redacted]
	Adverse Event costs	£[redacted]	£3	£[redacted]
	Monitoring costs	£[redacted]	£1,333	£[redacted]
	End-of-life costs	£[redacted]	£8,503	-£[redacted]
	Total cost	**£[redacted]**	**£10,044**	**£[redacted]**
PAS price	Drug costs	£[redacted]	£0.00	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£205	-£[redacted]
	Adverse Event costs	£[redacted]	£3	£[redacted]
	Monitoring costs	£[redacted]	£1,333	£[redacted]
	End-of-life costs	£[redacted]	£8,503	-£[redacted]
	Total cost	**£46,766**	**£10,044**	**£36,722**

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Scenario analysis 4 – Cost of post-progression treatment in the regorafenib + BSC arm

Exploration of the cost of post-progression treatment is not relevant in this analysis as treatment duration is directly derived from the Kaplan-Meier time to discontinuation data.

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Scenario analysis 5 – EQ-5D utilities from the repeated measures comparison

Table 54 shows the results using health state utility values from the EQ-5D repeated measures comparison (see Table 38 of the NICE submission) instead of the paired-sampled analyses used in the base case.

The ICER slightly decreased to £[redacted] per QALY with the list price and £36,765 per QALY with the PAS price. The cost breakdown is not shown because it is identical to the base case.

Table 54. Scenario analysis 5a - Results using the repeated measured EQ-5D utilities

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.546	1.154	1.393
	PFLYs	0.710	0.124	0.586
	QALYs	1.818	0.816	1.002
	Costs	£[redacted]	£10,395	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.546	1.154	1.393
	PFLYs	0.710	0.124	0.586
	QALYs	1.818	0.816	1.002
	Costs	£47,249	£10,395	£36,854
	Incremental cost per QALY			**£36,765**

Despite adverse events such as HFSR, diarrhoea and fatigue are easily manageable and their effect on the patient's HRQL can be deemed negligible, a scenario analysis was conducted using lower utility values for regorafenib in the progression-free health state compared to placebo. Utility values from the EQ-5D repeated measures analysis based on the splitting of the progression-free state into regorafenib and placebo arms (see Table 39 of the NICE submission) were used. Table 55 displays the results of this scenario analysis.

The ICER resulting from this analysis decreased slightly at £[redacted] without the PAS and £37,514 with the PAS. The improvement in cost-effectiveness, as compared to the same analysis based on the 2015 data, is due to the longer time spent in the progressed state which is reflected into a total progressed utility outweighing the decrease in progression-free utility.

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Table 55. Scenario analysis 5b - Results using the repeated measured EQ-5D utilities based on the splitting of the progression-free health state into treatment arms

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.546	1.154	1.393
	PFLYs	0.710	0.124	0.586
	QALYs	1.777	0.794	0.982
	Costs	£[redacted]	£10,395	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.546	1.154	1.393
	PFLYs	0.710	0.124	0.586
	QALYs	1.777	0.794	0.982
	Costs	£47,249	£10,395	£36,854
	Incremental cost per QALY			**£37,514**

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Scenario analysis 6 – Using EORTC from GRID as the utility data source

Table 56 shows the results using health state utility values from the EORTC repeated measures analysis instead of the EQ-5D paired-sampled analysis. The utilities used for this analysis are those reported in Table 41 of the NICE submission.

Another scenario analysis was performed using the EORTC-derived utilities from the paired-samples comparison method. The utilities used for this analysis can be found in Table 40 of the NICE submission. The results for this scenario analysis can be found in Table 57 below.

The ICER reduced from £[redacted] using regorafenib list price to £34,281 using the PAS price. The cost breakdown is not shown because it is identical to the base case.

Table 56. Scenario analysis 6a - Results from using repeated measures EORTC utilities from the GRID trial

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.546	1.154	1.393
	PFLYs	0.710	0.124	0.586
	QALYs	1.952	0.877	1.075
	Costs	£[redacted]	£10,395	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.546	1.154	1.393
	PFLYs	0.710	0.124	0.586
	QALYs	1.952	0.877	1.075
	Costs	£47,249	£10,395	£36,854
	Incremental cost per QALY			**£34,281**

When using paired-samples comparison of EORTC-derived utilities, the ICER reduced from £[redacted] using regorafenib list price to £33,964 using the PAS price.

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Table 57. Scenario analysis 6b - Results using paired-samples comparison of EORTC-derived utilities

	Outcome	Regorafenib + BSC	Placebo + BSC	Incremental
List price	LYs	2.546	1.154	1.393
	PFLYs	0.710	0.124	0.586
	QALYs	1.960	0.875	1.085
	Costs	£[redacted]	£10,395	£[redacted]
	Incremental cost per QALY			**£[redacted]**
PAS price	LYs	2.546	1.154	1.393
	PFLYs	0.710	0.124	0.586
	QALYs	1.960	0.875	1.085
	Costs	£47,249	£10,395	£36,854
	Incremental cost per QALY			**£33,964**

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Patient/carer organisation submission (STA)

Regorafenib for previously treated unresectable or metastatic gastrointestinal stromal tumours [ID1056]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. *About you and your organisation*

Your name: [redacted]

Name of your organisation: GIST Support UK

Your position in the organisation: [redacted]

Brief description of the organisation:

GIST Support UK is the only Charity devoted solely to the support of GIST cancer patients in the UK. By raising awareness and being accessible to patients and clinicians around the country, we are helping them to manage this devastating diagnosis more effectively.

Our charity is run entirely by volunteers – who are in the main GIST patients and carers. We rely primarily on donations from members of the public and those directly affected by this terrible cancer. The stated objectives of GSUK are:

1. to promote and protect the physical and mental health of patients with Gastro-Intestinal Stromal Tumours (GIST) in the United Kingdom through the provision of information, support, education and practical advice to them and their carers;
2. the relief of sickness and the preservation of health in particular by promoting and supporting research with the publication of the useful results thereof and the development of more effective treatment and care for patients with GIST;
3. to advance the education of the general public and health professionals in all areas relating to GIST

Because GSUK is a charitable trust and not a membership organisation, it does not have a "membership" in the legal sense. However we do maintain a database of patients and carers who have contacted us for help and support.

There are over 150 different sarcomas, all very rare but GIST happens to be the most common (incidence 15 per million, so around 800 new occurrences in the UK each year). There is no known cause and currently no known cure for metastatic or inoperable disease, although there are targeted therapies (tyrosine kinase inhibitors, or TKIs) for some varieties of GIST which maintain remission or stability. Most people are diagnosed in their 50-60s, but there is an exceedingly rare form which arises in younger people - usually late teenage girls. The younger adults and children usually have what is called Wild-type GIST and we have set up an initiative called PAWS GIST to focus on improving treatments and finding a cure for this group.

Patients often feel isolated as the public and most doctors have not heard of GIST. It is difficult to get accurate diagnosis and inappropriate treatment sometimes occurs. There are few treatments available, few or no clinical trials and limited research happening in the UK.

GSUK exists to support patients and provide information about the disease and treatments. GSUK has a telephone helpline, a website (www.gistsupportuk.com) and an active private email group where patients share information on subjects such as surgery, TKI treatment and management. We hold three patient meetings in different locations around the UK each year and have active Facebook and Twitter communities. We participate and network with relevant patient, medical, industry and regulatory groups and bodies to raise awareness of our patients needs and to learn about any new advances. Our Medical advisory Board includes leading UK GIST specialists who advise and help us to support GIST patients and our efforts to stimulate research.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

We have no direct or indirect links to the tobacco industry.

2. *Living with the condition*

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

GISTs often show no symptoms for a long time. The first symptoms are often caused by the tumour pressing on some other organ. Sometimes the GIST may bleed into the abdominal cavity or the gut. This causes anaemia. If the GIST is large, the doctor may be able to feel a swelling in the abdomen. GISTs, particularly in the liver, can also cause night-sweats.

GIST in the oesophagus can cause difficulty with swallowing (dysphagia).

GIST In the stomach can cause pain or discomfort, indigestion, nausea, vomiting, feeling of fullness, bleeding into the gastrointestinal tract causing black coloured stools, or any combination of these.

GIST in the intestine can cause bleeding, pain, constipation, diarrhea, pain, or just vague abdominal discomfort.

All of the above can make daily life extremely difficult and trying to cope with this condition can put a huge strain on patients and their families.

Hearing the news that you have a rare cancer, and having to face up to all the treatments and hospital appointments can put a huge strain on the life of a GIST patient and their family. This is further compounded by the fact that most people, including doctors, have not heard of GIST. There are few treatments available, few or no clinical trials and limited research happening in the UK.

Feelings of panic and fear are almost inevitable for the patient; Family and friends will be scared too. There may well be times of depression, since it often takes years before a GIST is finally discovered and there have often been long periods of unexplained symptoms and the lonely feeling of not being understood.

Most of us who have become part of GIST Support UK, were at one time in that terrible place where a GIST diagnosis for us or a loved one shattered our lives. As with any cancer diagnosis your life is turned upside down and life becomes full of hospital visits and the possibility of treatments many of which are very unpleasant e.g. partial or total gastrectomy, significant liver surgery etc.

GIST treatment has been revolutionised by the introduction of tyrosine kinase inhibitors which has led to patients living several years with advanced disease. However advanced GIST is life-threatening if uncontrolled. Hence patients experiencing progression after treatment with, or who are intolerant of imatinib and sunitinib tend to have very limited life expectancy without regorafenib. The prognosis for these patients is generally less than 12 months. This is particularly difficult for patients and their families as they are often young, relatively well and working or in education when first diagnosed.

The psychological impact of knowing their prognosis combined with the physical symptoms, especially pain and extreme tiredness has a devastating effect on the quality of life of the patient and their family.

3. *Current practice in treating the condition*

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Ideally patients are seeking curative treatments, e.g. surgery. In the absence of this option, GIST patients are seeking treatments that will control their disease allowing them to live life "normally" and give time until a curative treatment can be found. Some patients achieve longer term remission on regorafenib. This high quality time is incredibly meaningful for patients and their families.

The important features of treatment are:

1. **The ability to continue work or education**

As our patient experts and others in our network demonstrate, the ability to continue work and education is of utmost importance for them and their families. The treatment burden of regorafenib is minimal and, in patients who respond, it can make the difference between being housebound and being able to return to full-time work/education.

2. **The management of symptoms such as pain and extreme tiredness.**

Some patients experience a decrease in tumour volume for extended periods when taking regorafenib, which in turn decreases symptoms such as pain, tiredness and shortness of breath and so makes life tolerable. Patients who respond to regorafenib can maintain a relatively normal life and can even continue to work full-time as side effects are relatively manageable.

3. **Helping relieve psychological distress.**

For patients who do not respond to either of imatinib or sunitinib, or once those two drugs become ineffective the existence and responsiveness of regorafenib (both in terms of effectiveness of the drug and reduction in side effects) greatly relieves the deep anxiety many patients feel.

Regorafenib is potentially all that stands between a GIST patient and death as there are no further drug options at present that are either definitely available in England and / or which have a proven positive effect for GIST.

Regorafenib provides patients with hope that their disease can be managed giving an invaluable psychological boost to them and their families. They hope that in this extra time new improved and even curative treatments can be found. It can help them to retain their place in wider society and is hugely important to their sense of well-being and that of their family and carers.

4. Convenience of how and where the treatment is received.

The reassurance and convenience of being treated as an outpatient is huge.

Regorafenib is prescribed in tablet form which makes outpatient treatment practical. It is easy to take and not too disruptive to daily life. Patients generally attend outpatient appointments every 4-6 weeks and require scans every 2-3 months to assess their tumour(s). Thus the treatment burden for patients and families is limited. Patients are monitored for potential toxicity / side effects and often report very markedly less severe side effects than sunitinib and feeling in very much better health overall with dose management:

To quote one of our patients:

"Regorafenib is much better for me than previous treatments where a very sore mouth made eating difficult and excess bile meant I could only sleep sitting up. As a keen hill walker I continue to walk considerable distances over rough terrain and am a lot "weller" on regorafenib than a lot of well people of my age".

5. The ability to self-care or maintain independence and dignity.

Regorafenib itself and the treatment that patients receive enables them to self-care and maintain independence and dignity in a way that would not be possible otherwise. It does not rely on being in an urban setting or geographically near to a centre of GIST expertise, but rather that the combination of:

a) patient-focused, intelligent and skilled local GIST oncological and surgical input,

b) specialised GIST input an hour or so away, and

c) methodological and timely GP input locally, provides patients with a timely and reassuring path leading firstly to the prescription of regorafenib, then followed up and monitored closely and regularly.

Patients who have failed other TKIs describe having access to regorafenib as "the difference between life and death" as the only other option available would be best supportive care.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

The standard treatments available to GIST patients are as follows:

1. **Surgery -** If the tumour is small and easy to get at, and has not spread, surgery is the usual treatment. This may be possible laparoscopically, (by key-hole surgery), but open surgery may be needed.
2. **Adjuvant treatment with imatinib (Glivec®) after surgery** if the tumour has a high risk of recurrence, trial data shows that taking imatinib after surgery statistically increases the time to recurrence. It also increases overall survival, and more data is being collected to confirm these findings. Imatinib has now been approved in the UK as a standard treatment for GIST following surgery.
3. **Treatment with imatinib before surgery**. This is the usual first-line treatment in the UK if hospital team decide that the tumour or tumours are too difficult to remove surgically or that immediate surgery will cause excessive morbidity, e.g. total removal of the stomach or the need for a bowel stoma. Imatinib stops most GIST tumours growing. It may also cause tumours to shrink, meaning that after a period of treatment with imatinib, for up to a year, an operation becomes possible or can be done with much less morbidity.
4. **Treatment of advanced disease.** The first line treatment for inoperable disease or widespread metastatic disease is imatinib, which is effective in about 85% of patients. If imatinib does not work or stops working the next stage of treatment is most often a change to **sunitinib (Sutent®).** This drug binds to the target molecule (KIT or PDGFRA) in a different place from imatinib, and it also helps to stop new blood vessels from growing. Sunitinib can cause more side effects than imatinib. If the normal regime doesn't suit a patient it may be possible to change the dose or the pattern of the way the drug is taken to manage the side effects.
5. **If a patient has an exon 9 mutation,** increasing the dose of imatinib to 800 mgs a day, is the best course to take. It has been proved to work better than 400 mgs for exon 9 mutation GISTs and recent data demonstrates a survival benefit (Casali et al in press). Funding for this is not generally available under the NHS, but some NHS Clinical Commissioning Groups will fund it from the Cancer Drug Fund.
6. **Regorafenib (Stivarga®)** This drug is available for oncologists to prescribe after patients have progressed or are intolerant to imatinib and/or sunitinib via the Cancer Drugs Fund based on the data from a large international randomised controlled trial. Feedback from patients indicates that it is well tolerated and effective.
7. **Enter a clinical trial -** Trials usually have very strict entry criteria which depend on what treatments you have already had, so eligibility will not be a foregone conclusion.

The above treatments are all that are currently available to GIST patients under the NHS and all are very welcome.

4. *What do patients or carers consider to be the advantages of the treatment being appraised?*

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

There are currently no other licensed treatments available for patients with GIST who have progressed on, or are intolerant of, imatinib and sunitinib. Regorafenib has been shown to improve progression free survival and delay the time until patients have further symptoms. Patients who have failed other TKIs describe having access to regorafenib as "the difference between life and death".

The important features of treatment are that it offers:

Hope - of a future by managing their GIST cancer

Time - to find improved treatments

Life – which can be lived to the full.

Regorafenib benefits patients by:

- **Being well tolerated**
- **Improving progression free survival**
- **Being easy to take**
- **Reducing psychological distress**
- **Being administered as an outpatient**
- **Enabling a normal life-style**

GIST patients and their families have been awaiting an effective treatment like regorafenib for years and are hugely grateful to have it as a third line treatment.

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

- Regorafenib (Stivarga®) is the 3rd line treatment for patients with advanced GIST when the only 2 other available treatments are ineffective.
- It has shown **SIGNIFICANT CLINICAL BENEFIT** – stopping or significantly slowing tumour growth and in some cases shrinking the tumour.
- **It works against a wider spectrum of secondary mutations** and is better tolerated. GIST patients deserve to be allowed access.
- It offers **Hope** of a future by managing GIST cancer
- **Time** - to find improved treatments
- **Life** – which can be lived to the full

Regorafenib benefits patients by:

- Being well tolerated
- Improving progression free survival
- Being easy to take
- Reducing psychological distress
- Being administered as an outpatient
- Enabling a normal life-style

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

GIST patients have very limited treatment options. 40% of GIST patients have advanced disease at diagnosis. These 40% generally find that:

- Imatinib either does not work or becomes ineffective after about 2 years
- They are not able to tolerate sunitinib or the disease progresses on this drug
- Regorafenib is the only third line agent to have activity after imatinib and sunitinib, so there are no comparators and in a few patients it can be the first drug that stabilises their disease.

Regorafenib has been rigorously reviewed and is now fully approved as the third line treatment for GIST patients both in Scotland and Wales. We would like to see equality of access for GIST patients who live in England and avoid a "National post-code lottery" situation. This treatment makes a substantial impact for patients, their families and treating clinicians, representing a huge step change in the way that GIST is managed. **Without this drug GIST patients have NO ALTERNATIVE TREATMENT AVAILABLE.**

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

Patients and carers all agree that they want to benefit by having access to Regorafenib should their GIST progress beyond the control of Imatinib & Sutent.

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Notwithstanding the side effects of regorafenib there are no disadvantages to having this effective third line treatment available

Please list any concerns patients or carers have about current NHS treatments in England.

Patients and carers concerns relate to the prospect of not having access to this life saving treatment when they need it.

Please list any concerns patients or carers have about the treatment being appraised.

Patients and carers concerns relate to the prospect of not having access to this life saving treatment when they need it.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

N/A

6. *Patient population*

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Regorafenib is for all types of GIST cancer patients including those who have metastatic disease at diagnosis may have had surgery but are not free of disease and those who develop secondary mutations causing resistance to imatinib and sunitinib. The population that particularly benefits is the group with secondary mutations causing resistance both to sunitinib and imatinib who do respond to reogarefinib.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

No

7. *Research evidence on patient or carer views of the treatment*

Is your organisation familiar with the published research literature for the treatment?

☑ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

We believe that experience with regorafenib since licensing confirms the reports from the clinical trials

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

Yes, no limitations have become apparent

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

No, no additional problems with regorafenib have emerged with longer follow-up or wider experience in routine NHS care.

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☑ Yes ☐ No

If yes, please provide references to the relevant studies.

Poole CD et al Gastric Cancer 2015;18(3):627-34

8. *Equality*

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having 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 treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Regorafenib has been rigorously reviewed and is now fully approved as the third line treatment for GIST patients both in Scotland and Wales. We would like to see equality of access for GIST patients who live in England and avoid a "National post-code lottery" situation.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

Anecdotal evidence in patients unable to tolerate the full dose suggests that dose modification is possible whilst maintaining clinical benefit.

9. *Other issues*

Do you consider the treatment to be innovative?

☑ **Yes** ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

For those GIST patients who progress onto regorafenib it is for some the first time their disease becomes stable and for some the first time that their tumours have shown shrinkage. The side effects are also, for most, more tolerable than previous treatments.

Are there any other issues that you would like the Appraisal Committee to consider?

No

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Regorafenib is the only third line treatment for GIST cancer – there is nothing in the pipeline.
- Regorafenib is for some the first ever and only effective treatment
- Regorafenib offers hope of a future, by managing GIST
- Regorafenib offers patients extra time to benefit from new and improved treatments
- Regorafenib enables GIST patients to live life to the full – the alternative is death.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Regorafenib for previously treated unresectable or metastatic gastrointestinal stromal tumours [ID1056]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]
Name of your organisation: Sarcoma UK
Your position in the organisation: [redacted]
Brief description of the organisation:

Sarcoma UK is the only cancer charity in the UK focusing on all types of Sarcoma. We work with patients, carers, supporters, health professionals and researchers to drive awareness of sarcoma, promote early diagnosis and improve patient experience. The charity is funded by voluntary donations from supporters who predominantly have a personal connection with the cause.

Sarcoma UK is not a membership organisation but has a database of over 7000 active and engaged supporters. In 2015/16, we received £25,500 from four individual pharmaceutical companies (representing 2% of the charity's overall income) to support specific pieces of work including a research-focused event. We receive no funding from government or other statutory sources.

Sarcoma UK runs a national specialist nurse-led Support Line for sarcoma patients and their families. This provides expert information and support by email and telephone across all sarcoma sub-types. Regular audit of the service provides Sarcoma UK with invaluable information about patient experience and concerns, which has informed this submission.

We have worked with GIST Support UK in the preparation of this submission. Both charities have agreed to submit individual responses to NICE but are supportive of each other's position.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: none

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

There are about 800 new cases of GIST a year in the UK and whilst it is a rare disease it is the common of the sarcoma sub-types. The average age of

patients diagnosed is 50-70 years old, however it is known to occur in young adults when it usually manifests as wild-type GIST. 60% of GIST tumours occur in the stomach, but they can occur anywhere along the GI tract and occasionally outside of it.

Patients often present with anaemia having had some kind of bleed and it can take time for the diagnosis to be made. They may have had symptoms of nausea, indigestion, pain, black stools, difficulty swallowing, and fatigue. The symptoms can be non-specific and for some patients it can take years to be diagnosed.

GIST patients and their families who contact Sarcoma UK's Support Line tell us that there is very little knowledge about GIST amongst their GP, friends and family, and that this worries and unsettles them. They tell us that because of the rare nature of the disease they have to quickly become the expert, often educating nurses and doctors caring for them about the disease. They often ask why there is so little option for sarcoma patients, when commoner cancers have many effective lines of treatment, and why there are so few clinical trial options.

The discovery of KIT mutation and KIT expression in 1998 had a huge impact on how patients are both diagnosed and treated. In the late 1990's, patients with unresectable GIST faced no effective treatment and a difficult death in hospital often as a result of bowel obstruction. The introduction of tyrosine kinase inhibitors in 2000 changed this for many patients, allowing them to live well, return to work and be active members of their families and community. The first trial of a TKI (Imatinib) was ground breaking and the results so exciting that patients originally discharged for best supportive care were invited to return to participate in the trial.

As the clinical experience with the drug and learning of the disease has developed, we now know that GIST is a family of tumours, which is heterogeneous in nature. (Ricci 2016) This heterogeneity has allowed for further targets, and the greater understanding has shown that a significant

percentage of patients develop resistance to the drug with a median time of onset of 2 years.

We know a small sub group of patients with Exon 9 mutation in the kit gene benefit from a doubling of the dose of imatinib to 800mg, but this helps only 10% of the GIST community. A Phase 3 trial (Demetri et al 2006) showed the efficacy of using sunitinib for those GIST patients where imatinib had failed and this is now routine second line treatment.

To summarise, there are only 2 significant lines of therapy for patients with GIST; resistance is probable within two years of each drug; some patients will be intolerant of imatinib and or sunitinib; and some wild-type GISTs do not respond to imatinib. The life expectancy of these patients is less than a year, without the option of regorafenib.

3. Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

For patients with GIST who contact Sarcoma UK's Support Line, increased life expectancy remains the most important outcome of any treatment. The average age at diagnosis is between 50-70 which a small but significant number being children and young adults. This relatively young age for diagnosis means that a second important outcome of treatment is quality of life. Many patients are still active in their professional field and want to contribute economically and socially for as long as possible. Families may be dependent on the income of the GIST patient and any treatment that would enable patients to work as long as possible is very important. Patients tell us that they have more living to do; they want to see their children through school; or to live to see their first grandchild. Patients talk often of hope and how a drug such as regorafenib gives them more time for a new treatment to be found and even a cure.

Crucially, patients tell us they tolerate regorafenib (and is backed up by data from the GRID study) and the extra time it gives them is useful, productive and meaningful.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

Current standard treatment for GIST and recommendations

All clinically significant GIST patients should be discussed in a sarcoma MDT, with the input of GI MDT if surgery is required. (However, many GIST patients are only seen by a local GI surgeon and therefore may miss out on the recommended treatment options and testing that would be provided at a sarcoma specialist service.)
Biopsy with mutational analysis is crucial.

Localised Disease
Surgery is the first line of treatment for GIST that is localised and able to be removed without significant morbidity. Laparoscopic procedure is possible. If the surgery is technically difficult, imatinib will be offered in the neo-adjuvant setting, with patients staying on the drug for 6-12 months prior to surgery. Patients report that imatininb is well tolerated, with fatigue being the most common reported side effect.

If the disease is assessed as high risk, the NICE guidelines for sarcoma support 3 years of adjuvant imatinib.

Metastatic Disease
For locally advanced, inoperable and metastatic GIST, treatment options are:

- 1st Line - imatinib standard dose 400mg
- 2nd Line – sunitinib. Patients report that sunitinib is harder to tolerate with significant fatigue, hand foot syndrome and sore mouth impacting on their daily quality of life.

- Exon 9 mutation patients have a longer progression free survival with 800mg dose of imatinib, and this should be the standard of care for this specific subtype. (MetaGIST 2010)

- Regorafenib is used in the 3rd line setting presently via the Cancer Drug Fund, or for those who are in tolerant to imatinib or sunitinib. Patients tell us it is easier to tolerate than sunitinib.

- Patients with no detectable mutation in KIT or PDGFRA gene in their tumour – 'wild-type' disease - have limited options, as imatinib is largely ineffective. Both sunitinib and regorafenib have some activity in these patients.

- Clinical trials are rare despite the fact that many patients are keen and well enough to participate.

- Maintaining patients on a TKI even when progression is identified can slow down the progression and help maintain quality of life. Symptom flare when stopping a TKI is a real phenomenon that is also reported in renal cancer. There is evidence from Korea that whilst there is limited duration of objective benefits, quality of life is maintained in the short term and valued by the patients. (Kang 2013 and Yoo 2016) This is common practice in the clinical settings with patients placing a high value on the extension to the quality of their life, even if it does not extend the quantity.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:
• the course and/or outcome of the condition
• physical symptoms
• pain
• level of disability
• mental health
• quality of life (such as lifestyle and work)

- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

- A third line treatment option that is well tolerated.
- Improved progression free survival and improved symptom control.
- An outpatient oral drug that does not requires frequent visits to the hospital.
- The ability to remain actively engaged in work and family life and to continue to have a good quality and useful life.
- It offers hope for as long as possible, reduces anxiety and improves overall patient experience.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

There are very limited treatment options for metastatic GIST patients. The drugs that are currently used are useful for many patients but they do not provide a cure and are limited in their ability to control the disease long term. Whilst patients recognise that regorafenib is not a cure for their disease, it offers them an important third option that gives quality of life and time.

A further advantage of regorafenib is its activity against secondary mutations that confer resistance to sunitinib. This offers a vital second line treatment to patients who GIST does not respond to sunitinib.

There are also a group of patients who cannot tolerate sunitinib and without regorafenib they would only have access to one line of therapy.

For some wild-type GIST patients, regorafenib can be their first active drug, providing the only possibility at the present time for control of their disease and an improvement in their symptoms.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

None

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

.

- The main concern is that there is a treatment for GIST that they may not be able to access if needed.

- There are limited treatments options overall for GIST patients and any restriction of access to new treatments will significantly impact on treatment options available.

- Concern that new treatments on the scale of the TKI breakthrough will not happen in the future due to funding restrictions.

- That treatments for sarcoma are generally not emerging as fast as for other cancer groups.

- The lack of clinical trials in this area.

Please list any concerns patients or carers have about the treatment being appraised.

- We have heard from patients that they are very concerned that a vital treatment in an already limited pool of drugs may become unavailable.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

None

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Regorafenib should be available for all types of GIST patients including "wild-type" patients and those with a secondary mutation who did not respond to standard 1st or 2nd line treatment.

There is hope within the medical teams that circulating tumour DNA can be sequenced from GIST patients' blood to inform them of appropriate treatment. This could become routine within a few years with the implication that patients with certain acquired mutations that do not respond to sunitinib could be treated immediately with regorafenib, rather than having to demonstrate disease progression on sunitinib. Patients are very aware of this potential.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

No

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for

the treatment?

Yes

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Yes

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

Yes.

I am not aware of any limitation in how the treatment has been assessed.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Not that I am aware of.

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

Yes

If yes, please provide references to the relevant studies.

Poole CD, Connolly MP, Chang J, Currie CJ. Health utility of patients with advanced GIST after failure of imatinib and sunitinib : findings from GRID. Gastric Cancer. 2015;18(3);627-34

Yoo C, Ryu MH,Nam BH, Ryoo BY, Demetri GD, Kang YK. Impact of imatinib rechallenge on health related quality of life in patients with TKI refractory GIST (RIGHT) Eur J Cancer. 2016, 52, 201-8.

The National Sarcoma Survey 2015. Transforming Patient Experience. http://sarcoma.org.uk/sarcoma-uk-national-patient-survey-2015

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having 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 treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Regorafenib has been approved as a third line therapy for GIST patients in both Scotland and Wales; it is vital that there is equality across the United Kingdom for GIST patients to avoid a postcode lottery.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

9. Other issues

Do you consider the treatment to be innovative?

Yes

If yes, please explain what makes it significantly different from other treatments for the condition.

- It offers a third line therapy – there are no other options.
- It is a significant step forward with its ability to treat patients with acquired resistance to imatinib and sunitinib

- For some patients it offers a first treatment that provides some activity.

Are there any other issues that you would like the Appraisal Committee to consider?

No

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Regorafenib is a vital third line option for GIST patients.
- It is unique in its ability to treat patients with acquired resistance to imatinib and sunitinib. (Resistance to these two drugs is probable within 2 years.)
- For a small group of patients it may be the only active treatment option for their disease.
- The life expectancy of these patients is less than a year, without the option of regorafenib.
- It is a well-tolerated drug that provides both an extension of life as well as quality of life.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Regorafenib for treating advanced gastrointestinal stromal tumours [ID1056]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Charlotte Benson

Name of your organisation
GIST support UK

Are you (tick all that apply):

X a specialist in the treatment of people with the condition for which NICE is considering this technology?

X a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?

- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

None

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Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How the condition is currently treated in the NHS?
Patients with metastatic gastro intestinal stromal tumour (GIST) should be referred to tertiary Soft Tissue Sarcoma centres where there is expertise in managing this rare tumour type in a multi-disciplinary team setting.
Standard first line treatment of metastatic GIST is with the tyrosine kinase inhibitor (TKI) Imatinib, 400mg daily which is a well-tolerated treatment. Treatment should continue indefinitely and median progression free survival on this drug is in the order of 2-3 years; although there are many long term responders and some may have complete response to treatment. Increase understanding of the molecular biology of GIST, and in particular the significance of mutations in KIT and PDGFRA genes has allowed clinicians to assess the likely success of treatment. Patients are monitored 3 monthly with regular cross sectional imaging and blood tests and clinic reviews. They also have access to clinical nurse specialist support to help deal with common side effects and concerns.
In the situation of oligo- disease progression consideration may be made for localised ablative approaches such as radio frequency ablation or even surgery. On evidence of multifocal disease progression on Imatinib patients are then switched to second line therapy with Sunitinib. The average duration of benefit of Sunitinib is around 6-12 months although this can vary. This treatment has more side effects than Imatinib and requires careful monitoring, dose adjustments and management of toxicity as it arises.
On multifocal disease progression on Sunitinib patients who are of performance status 0-2 are considered for third line Regorafenib treatment via the Cancer Drug Fund (CDF) criteria. Again patients are monitored through clinic visits and with regular scans and blood tests. As with Sunitinib the dose may need to be adjusted according to patient tolerance.
In addition to the treatment paradigm above, all eligible patients with GIST should be considered for clinical trials at appropriate decision making time points.

Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be?
There are no geographical variations in practice that I am aware of. All professionals working at Sarcoma centres and treating patients with metastatic GIST are cognisant of the ESMO GIST and guidelines and offer Regorafenib in the third line to patients that meet the eligibility via the CDF criteria. The only other alternative in this treatment setting is a clinical trial- however availability of clinical trials is variable. For example there is only one UK clinical trial in this setting currently open, and this is at one London centre only.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?
There are no alternative active treatment options in the third line setting for metastatic GIST. Availability of clinical trials is limited as mentioned above. There is evidence that patients with GIST that are progressing should be maintained on TKI therapy for as long as possible as this may slow down the rate of disease

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Single Technology Appraisal (STA)

progression and allow good disease palliation. (ESMO GIST guidelines). In other countries consideration is made to reverting to Imatinib treatment however this is not an option due to NHS funding constraints (*Kang et al Lancet Oncol 2013; 14; 1175-1182.*)

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?
There is long term follow up data from the Phase II trial of Regorafenib to suggest that patients with certain GIST subtypes are likely to benefit more from this treatment. This includes those with an Exon 11 mutation in the KIT gene (which is the most prevalent mutation in patients with metastatic GIST) and also the rarer group of patients with 'wild –type' GIST and are SDH (succinate dehydrogenase) deficient. *(Ben-Ami et al .Annals of Oncology .2016 Sep; 27(9):1794-9.)*

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?
As outlined above the majority of patients with metastatic GIST have an Exon 11 mutation in the KIT gene and are more likely to benefit from Regorafenib than those that don't. There isn't a group that could easily be identified that could be put at risk from the technology. Hypertension is a known side effect of the drug and thus those patients with uncontrolled hypertension or severe cardiovascular disease might not be deemed suitable but this is a relatively unusual occurrence in my own clinical experience.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?
Patients with GIST are treated in tertiary referral centres /specialist sarcoma units as per NICE IOG Guidelines 2006 where there is existing knowledge of the disease, its treatment and also dedicated clinical nurse specialist support.

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?
No additional input required this is already in place to support patients with GIST

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?
Regorafenib is currently prescribed under its licensed indications i.e. in the third line setting for patients with metastatic GIST who had progressed or are intolerant to imatinib or sunitinib. This is in keeping with the CDF criteria.

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Clinical guidelines:

1.Regorafenib is recommended for patients with metastatic GIST after confirmed progression on Sunitinib in the ESMO/ European Sarcoma Network Working Group Clinical Practice Guidelines for GIST- *Annals of Oncology 25 (supplement3); 2014.* Based on the results of the GRID study (level of evidence IB)

2. Regorafenib is recommended for patients with metastatic GIST following progression on suntinib in the US NCCN GIST guidelines 2016. https://www.nccn.org/professionals/physician_gls/f_guidelines_nojava.asp

3. Regorafenib is recommended in the 3rd line metastatic setting in the soon to be published British Sarcoma Group GIST guidelines 2016 (personal communication Professor Ian Judson- likely publication date May 2017

The advantages and disadvantages of the technology:

Questions:
1.NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

2.If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

3.If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

4. What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Replies:
Regorafenib has been shown to be of significant clinical benefit for patients with advanced GIST after failure of imatinib and sunitinib. This has been demonstrated in a large randomised Phase III international multicentre study (GRID study). (*Demetri Lancet 2012*). There was statistically significant improvement of progression free survival compared with placebo (4.8 months versus 0.9 months p<0.0001)There was

no significant difference in overall survival however crossover to active drug was allowed in the trial and 85% of patients on placebo did cross over to Regorafenib, thus confounding any potential survival difference between the groups.
Since the publication of this trial patients have had access to Regorafenib first through a managed access programme and then via the Cancer Drugs Fund. This has increased our experience with this drug which is generally well tolerated and allows clinically meaningful benefit to patients with this rare disease type for which no other treatment options are available.

1. There are no obvious practical implications as GIST services are already up and running and the management of Regorefnib treatment would take place under existing services at specialist centres.

2. The indications for starting treatment are clear on confirmed clinical and disease progression or intolerance to treatment with Imatinib and Sunitinib.

3. The patients that took part in the GRID trial were of performance status 0-1. The real world population of the majority of patients with metastatic GIST are in the performance status 0-2 range. We reported the UK experience of the managed access program for Regorafenib for 'real world patients' which confirmed that treatment was well tolerated and side effects were manageable in the majority of patients PS 0-2. (*Kollar et l Clin Sarcoma Res 2014 Dec 4*)
Some patients do require a dose reduction from recommended dose of 160mg to 120mg or 80mg (55% in this case series).
The most important outcomes in this patient group are quality of life which incorporates disease stability and tolerability of treatment. Work has been done on health utility of patients with advanced GIST who took part in the GRID study. (Poole *et al Gastric Cancer 2015 Jul; 18(3):627-34.*) The authors demonstrated a significant and clinically meaningful difference in health state utility values between progression free state and progression

4. Side effects:
Regorafenib has well known side effects including hypertension, hand foot syndrome, diarrhoea, mucositis and fatigue. These side effects can be managed with adjunctive medicines and appropriate dose modifications and delays. (*Grothey et al Oncologist 2014 Jun; 19(6):669-80*) . There is considerable cross over with Sunitinib side effects and there is existing confidence and knowledge among the specialist teams that manage patients with GIST. No new side effects have come to light since publication of the GRID study.

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Single Technology Appraisal (STA)

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. 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

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

No concerns.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

No none.

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Single Technology Appraisal (STA)

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

No extra training or resources required- these are already in place.

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Single Technology Appraisal (STA)

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Single Technology Appraisal (STA)

Regorafenib for treating advanced gastrointestinal stromal tumours [ID1056]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Dr V Ramesh Bulusu

Name of your organisation
Cambridge University Hospitals Foundation Trust

Are you (tick all that apply):

- **a specialist in the treatment of people with the condition for which NICE is considering this technology?**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

NONE

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Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

Metastatic Gastrointestinal tumours: Systemic Treatment Landscape

Metastatic disease – systemic treatment

First line treatment

1. In GIST patients with inoperable and metastatic disease, imatinib is the standard first line treatment including patients who had previously received the drug as adjuvant therapy without relapse during this treatment. This also applies to metastatic patients whose disease has been completely removed surgically. Imatinib is continued until progression.

Second line treatment

2. The standard second-line treatment is the tyrosine kinase inhibitor (TKI) sunitinib. This drug was proven to be effective in terms of PFS using a regimen of 50 mg daily 4 weeks on / 2 weeks off. Data have been published showing that continuous treatment with a lower daily dose of 37.5 mg is also effective and well tolerated.

Third line treatment—Regorafenib-subject of present STA

3. The standard third line treatment for patients with metastatic gist whose tumours progressed on imatinib and sunitinib is regorafenib. GRID trial is a prospective placebo-controlled randomized trial which demonstrated that regorafenib, at a dose of 160 mg daily on a 3 weeks on / 1 week off schedule, significantly prolonged PFS in patients progressing after both imatinib and sunitinib. Regorafenib is regarded as standard therapy for the third-line treatment of patients progressing on or failing to respond to imatinib and sunitinib. The key distinction between sunitinib and regorafenib, is its ability to inhibit tumours with secondary mutations in the activation loop of KIT, especially in exon 17. These mutations are known to confer resistance both to imatinib and sunitinib, hence the value of regorafenib in this setting.

Regorafenib is active in all subtypes of metastatic GISTs including wild type GISTs which do not harbour any KIT or PDGFRA mutations. The exception to this is probably the subtype of GISTS which harbour PDGFRA D842V mutation which seems to be resistant to the presently used tyrosine kinase inhibitors. These PDGFRA D842V mutant GIST patients should ideally be included in clinical trials.

Regorafenib should be used by experts in treating GISTs in specialist GIST clinics. It should be used by general oncologists who do not have experience in treating GISTs or using tyrosine kinase inhibitors.

The presently existing multidisciplinary teams including oncologists, radiologists, specialist nurses, and surgeons would be able to manage these patients without the need for any additional training or resources.

Regorafenib will be used within its licensing indications in NHS. The clinical guidelines supporting the use of Regorafenib are:

1. UK National guidelines by Ian Judson, Ramesh Bulusu et al. Clinical Sarcoma Research 2017.
2. European Society of Medical Oncology (ESMO) Consensus guidelines Annals of Oncology 2014.

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Single Technology Appraisal (STA)

Regorafenib is the only 3rd line therapy available for patients with metastatic GIST whose tumours have progressed on imatinib and sunitinib. There are no other alternatives to Regorafenib at present.
Our clinical experience suggests that Regorafenib is well tolerated in 'real life' with acceptable toxicity profile and dose/schedule modifications help to minimise the side effects maintain the clinical benefit.

The randomised clinical trial (GRID trial) on which the license for Regorafenib was granted has patient population whose tumours have progressed on prior lines of therapy. This reflects the clinical conditions observed in clinical practice in UK. Progression free survival as the main endpoint in this trial is a meaningful endpoint in the 3rd line palliative setting for this group of patients.

Proactive side effects management is critical to the wellbeing of patients on tyrosine kinase inhibitors. This applies to regorafenib as well. Patient and carer education is vital and ongoing education and training of healthcare professionals is mandatory. We have learnt from the 2nd line sunitinib, how to manage the side effects, minimize significant toxicity and maintain the clinical benefit. Again, this applies to regorafenib as well. Patient, carer and healthcare professional educational tools are already in place.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Equality and Diversity

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Single Technology Appraisal (STA)

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

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- 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

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

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Patient/carer expert statement (STA)

Regorafenib for treating advanced gastrointestinal stromal tumours [ID1056]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: Vicky Rockingham
Name of your nominating organisation: GIST Support UK
Do you know if your nominating organisation has submitted a statement?

x Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

x Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

x Yes ☐ No

- a carer of a patient with the condition?

☐ Yes x No

- a patient organisation employee or volunteer?

☐ Yes x No

Do you have experience of the treatment being appraised?

x Yes ☐ No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: No links

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

I was diagnosed with Wild-type GIST in 2007 following an emergency operation. In November 2011, metastatic GISTs were found in my liver – my last MRI in November 2014 showed 14 tumours spread throughout the liver. I have been on Regorafenib since February 2015. I started on a full dose (180mg) but could not tolerate this dose due to severe muscle cramps down by back and thighs at night; I also suffered from severe nose bleeds. I went down to 120mg, but struggled with bowel cramps. I dropped to 80mg but my scan showed that the drug was ineffective. I then went back up to 120mg in October 2015, reviewed my diet, and I have managed on this dose ever since. I am on a 3 week on, 1 week off cycle. However, I often reduce my dose to 80mg for a couple of days in my third week to reduce side effects, such as bowel cramps and diarrhoea. I will also take a 2 week break a couple of times in the year to allow me to build my weight up. Currently, my liver functions normally and when I am taking my breaks from treatment, I experience no effects from the cancer. However, I am able to work full time and I exercise regularly; in May 2016, I completed the Leeds' Half Marathon (raising funds for Gist Support UK to fund research). Mentally, I quickly learnt to accept my diagnosis after it had returned to my liver. I am married with two young boys (aged 11 and 13) and I made it clear to my consultant that I wanted to be around to see them grow up. However, my diagnosis has had a significant impact on my family in different ways. My work (the Environment Agency) are extremely supportive, allowing me time-off for appointments and my sickness record is extremely low. I lead a cancer network at work which helps support staff affected my cancer (patients, carers and line managers).

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would

you like treatment to achieve?) Which of these are most important? If possible, please explain why.

My main priority is for a treatment that will at least keep my tumours stable whilst allowing me to lead a near normal life. I accept that any treatment will have side effects but if those side effects allow me to continue to function as a mother, allow me to at least work part-time and that the side effects can be managed, then I can live with them. Being able to take a regular break from treatment also helps. Any treatment that helps shrink the tumours is my second priority.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

I am a patient at the Christie and the care I have received there has been excellent. I was on Imatinib for 6 months. Although the side effects were minimal, the drug was ineffective. I then went onto Sunitinib for 3 years. I suffered from fatigue, low white blood cells, foot syndrome (sore peeling skin), bleeding teeth and gums, sores in my mouth and periods of diarrhoea. However, the drug was only minimally effective in terms of one scan would be stable, the next would show the tumours had grown slightly, with this cycle being repeated (I had 3 monthly CT scans). On Regorafenib, I suffer fatigue, diarrhoea and bowel issues (similar to Crohn's disease), weight loss, thinning hair, severe cramps (in my bowels, hands, shins and feet). However, my last scan showed that over the last two years my tumours have shrunk slightly. I am able to manage the side effects by changing my diet (following advice for those with Crohn's), regular exercise, using nutribullets to ensure I ingest vitamin rich food in an easily absorbable form, lowering my dose for a couple of days, taking a two week break twice a year. I prefer Regorafenib because the drug is effective and I am able to manage the side effects.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms

- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

Oral, ability to take at home, manageable side effects, ability to continue with a near normal life (including working full time and regularly exercising), effectiveness of the drug (the first drug to actually shrink my tumours), ability to self-regulate the dose (i.e. on my 3 week on, 1 week off cycle I will often drop from 120mg to 80 mg for a couple of days in the last week).

Please explain any advantages that you think this treatment has over other NHS treatments in England.

Regorafenib is the first drug that has shrunk my tumours so is far more effective than Sunitinib. In addition, I found the foot syndrome that I experienced on Sunitinib debilitating whereas I don't experience this condition as severely on Regorafenib.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

I do not know enough other patients to compare against. I would imagine that a positive attitude, regular exercise and willingness to adapt your diet will help patients manage and tolerate the drug more effectively.

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse

- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

The bowel problems I suffer (cramps and diarrhoea) and weight loss are difficult to deal with mentally. However, the benefits in terms of the drug's effectiveness in shrinking the tumours outweigh these side effects.

Please list any concerns you have about the treatment being appraised.

My only concern is not knowing how long the drug will be effective and how long it will be available to GIST patients.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

None known

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

No; there are so few drugs available for GIST, it should be available for all GIST patients where Imatinib and Sunitinib have become ineffective.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

No

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐ Yes ☒ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

N/A

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

N/A

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

N/A

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

N/A

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

None

9. Other issues

Do you consider the treatment to be innovative?

x Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

N/A

Is there anything else that you would like the Appraisal Committee to consider?

GIST is an extremely rare cancer. I was only able to access Regorafenib due to it being on the cancer drug fund (CDF), shortly before it was removed and replaced back on the CDF. This drug has been the most effective drug to date and has allowed me to continue a near normal life, working full time and regularly exercising. I am not on a full dose, yet the drug is effective, helping me to achieve my aim, to see my children grow up.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- The drug is effective for GIST
- Side effects can be managed leading to a near normal life
- For rare cancers, there are limited number of effective treatments available
- A full dose has not been required for the drug to be effective for me (so being less costly)
- I am able to work, pay my taxes, so helping to fund my own treatment

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Regorafenib for treating advanced gastrointestinal stromal tumours [ID1056]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: Emma Tennant
Name of your nominating organisation: GIST Support UK
Do you know if your nominating organisation has submitted a statement?

x Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

x Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

x Yes ☐ No

- a carer of a patient with the condition?

☐ Yes x No

- a patient organisation employee or volunteer?

☐ Yes x No

Do you have experience of the treatment being appraised?

☐ Yes x No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

I had a high risk small bowel GIST resected in January 2009. I was first diagnosed with metastatic peritoneal and liver GIST in March 2011 and was started on 400mg of imatinib. Following mutation analysis when it was discovered that I was Exon 9 I moved to 800mg daily from December 2011. I was able to continue to work full time with the main side effect being occasional nausea and fatigue. In June 2014 disease progression meant that I commenced Sunitinib at 37.5mg daily. Side effects of Sunitinib were harder to live with. Included sore hands and feet, loss of sense of taste, hair turned white and fatigue. Progressive disease on Sunitinib confirmed November 2014 and so commenced Regorafenib from 8th December 2014 at 160mg daily dose. Initially I found it hard to tolerate the full dose and so cut the dose down for a few months and then following some changes in my diet which helped me manage the side effects I went back up to the 160mg daily dose and stayed on Regorafenib until March 2017. The main side effects I experienced were sore feet (and hands), fatigue and fluctuation between periods of constipation and diarrhoea. Other side effects of Regorafenib were that it increased my blood pressure, resulting in me being prescribed 50mg of Losarten daily and also give me hypothyroidism, resulting in me being prescribed 100mg of Levothyroxine daily. However this was all manageable and Regorafenib has allowed me to continue with my life as a parent of 2 daughters and the main wage earner for the family working full time, commuting from Leicestershire to London (2 hours each way) 4 days a week and maintaining a senior management role in a stressful environment. I believe it has extended my life by at least 2 years.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would

you like treatment to achieve?) Which of these are most important? If possible, please explain why.

My main priority is to extend my life so that I can spend time with my daughters, who are 14 and 12 and see them grow up. The most desirable treatment outcome would be the successful shrinkage of the tumours. However any stabilisation of the disease is very important. Any slowing down of the disease progression gives me more time with my family and allowing me to live a full and active life.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

I have used both of the currently available NHS treatments of imatinib and Sunitinib. Imatinib particularly worked well for me for over 3 years and I found to be very tolerable in terms of side effects, with the main ones being nausea and fatigue. Sunitinib I found harder in terms of side effects – I experienced sore feet and hands, periods of constipation and diarrhoea, loss of taste - although I was still able to continue to work and lead a relatively active life. It was however not effective for me in terms of halting the disease progression and so I was then moved to Regorafenib through the Cancer Drug Fund. For me therefore Imatinib would be the prefereable treatment and I know it is the first line treatment for all GIST patients.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)

- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

Effect on the progression or outcome of the disease

Extending life

Quality of life – being able to remain active, continue working and generally contributing to society

Manageable side effects

Easy to take – tablets every day, no nausea and can be taken at home

Offers a lifeline to not only the patient but also family and friends

Please explain any advantages that you think this treatment has over other NHS treatments in England.

After Sunitinib there are no other NHS treatments for GIST. Without Regorafenib the patient is just left with little or no hope and the spectre of unchecked disease progression.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

All GIST patients I am aware of unanimously want access to Regorafenib should they need it as at this stage there will be no other options for them

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)

- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

The main disadvantage of the treatment is the potential side effects. These will vary by patient, for me high blood pressure, hyprthroidsm, fatigue and sore hands and feet were the main ones. However these were all manageable and I was certainly willing to accept them.

Please list any concerns you have about the treatment being appraised.

None

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

None

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

This would be the 3rd line of treatment and so would only be for those who have already had progression on Imatinib and Suntinib

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

No

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐ Yes x No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

None

9. Other issues

Do you consider the treatment to be innovative?

x Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

This treatment has been shown to be effective for patients when other treatments have stopped working. It is therefore not an alternative to any other treatment but a treatment where no other treatment option existed before.

Is there anything else that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Regorafenib offers life extending treatment where no other option is available
- Although there are side effects these are manageable and all GIST patients I know would be willing to accept these given the option of the drug
- Regorafenib has given me at least a further 2 years with my daughters – it is a lifeline not only for patients but for their families too
- Regorafenib has meant that I have been able to continue to work, playing an active and positive role in my company and continue to contribute to society
- GIST is a rare cancer with few treatment options available

Regorafenib for previously treated unresectable or metastatic gastrointestinal stromal tumours

A Single Technology Appraisal

Produced by	Peninsula Technology Assessment Group (PenTAG) University of Exeter Medical School South Cloisters St Luke's Campus Heavitree Road Exeter EX1 2LU
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Contributions of authors

Tracey Jones-Hughes	Led the critique of the company's decision problem and clinical effectiveness evidence. Wrote the Summary, Background, Decision problem, Clinical effectiveness and Overall conclusions. Compiled the report. Provided overall project management.
James Dunham	Contributed to the critique of the economic model and contributed to writing the Cost-effectiveness and End-of-life sections.
Sophie Robinson	Led the critique of the company's literature searching for this submission. Wrote the review of the literature searches for the report. Contributed to the writing and editing of the report.
Mark Napier	Provided clinical advice on soft tissue sarcoma and its management within the NHS. Reviewed and revised a draft version of the report.
Martin Hoyle	Contributed to writing the Cost-effectiveness and End-of-life sections. Contributed to the critique of the economic model and is the guarantor of the report.

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Abbreviations

AESI	Adverse Events of Special Interest
AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
BSA	Body Surface Area
BSC	Best Supportive Care
CDF	Cancer Drug Fund
CEA	Cost Effectiveness Analysis
CEAC	Cost Effectiveness Acceptability Curve
CRD	University of York Centre for Reviews and Dissemination
CI	Confidence Interval
CrI	Credible Interval
CRUK	Cancer Research UK
ECOG	Eastern Cooperative Oncology Group
EED	National Health Service Economic Evaluations Database
eMIT	Electronic Market Information Tool
EPAR	European Public Assessment Report
EQ5D	EuroQol-5 Dimensions
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
FDA	Federal Drug Administration
GIST	Gastrointestinal stromal tumour
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
ICC	Interstitial cells of Cajal
IPCW	Inverse Probability of Censoring Weights
IPE	Iterative Parameter Estimation
ITT	Intent-to-treat
KM	Kaplan Meier
LYG	Life-Years Gained
MedDRA	Medical Dictionary for Regulatory Activities
NICE DSU	National Institute for Health and Care Excellence Decision Support Unit
ORR	Objective Response Rate
OS	Overall Survival
OSA	One-way Sensitivity Analysis
PFS	Progression Free Survival
PPS	Post-Progression Survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-Adjusted Life Year

RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria in Solid Tumours
RPSFT	Rank Preserving Structural Failure Time method (RPSFT)
SAE	Serious Adverse Event
SPC	Summary of Product Characteristics
TEAE	Treatment-Emergent Adverse Event
TSD	Technical Support Document
WHO	World Health Organisation

1 Summary

1.1 Critique of the decision problem in the company submission

The company defined the population as patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) whose disease has progressed on, or who are intolerant to, previous treatment with imatinib and sunitinib. This definition agrees with the population described in the NICE scope.[1]

The intervention in the decision problem was regorafenib, and the comparator was best supportive care (BSC), as in the NICE Scope. The outcomes in the company submission also match those in the Scope.

Although the NICE scope did not consider any subgroups, preplanned investigations by the company include geographic region, prior line of treatment, age, sex, baseline BMI, duration of imatinib treatment, ECOG performance status, and mutational status

1.2 Summary of clinical effectiveness evidence submitted by the company

The primary focus of the company's submission was the GRID study, which was a phase 3 randomised controlled trial. The GRID study was double-blind and multi-centre (57 centres, 17 countries).

Patients were randomised to regorafenib + best supportive care (N=133) or to placebo + best supportive care (N=66). Baseline characteristics were reported as being balanced between arms, however, there was a slight imbalance where 67% of participants receiving regorafenib and 83% receiving placebo had >18 months of previous imatinib therapy.

At the June 2015 cut-off, fifty eight participants in the placebo arm (87.9%) had crossed over to the regorafenib arm.

Outcome results were as follows:

Progression-free survival

The regorafenib group was assessed via blinded review to be superior to the placebo group (147 days [4.8 months] vs 28 days [0.9 months]), with the risk of progression or death in the regorafenib arm lower than in the placebo arm (Hazard ratio [HR] 0.27, 95% CI 0.19-0.39; p<0.000001).

Secondary endpoints

The uncorrected median OS for the regorafenib and placebo arms was 17.4 months. Following adjustment for crossover, median OS was shown to be longer in the regorafenib

group (529 days) than in the placebo group (338 days [p = 0.00095] using the Iterative Parameter Estimation method; 361 days [p = 0.00286] using the Rank-Preserving Structural Failure Time method). The estimated corrected hazard ratio of regorafenib to placebo using the RPSFT and IPE correction methods were 0.616 (95% CI 0.435 - 0.871) and 0.586 (95% CI 0.417 - 0.824), respectively.

Other secondary outcomes were reported as follows (Source: Bayer submission, section 1.3, p20):

- Median time to progression (TTP) was significantly longer in the regorafenib arm than in the placebo arm (5.4 months [165 days] versus 0.9 months [28 days], HR 0.248, 95% CI 0.170–0.364; p<0.000001).
- Tumour Response Rate, showed no statistically significant difference between arms despite the higher trend in the regorafenib group (4.5%) compared to the placebo group (1.5%).
- Disease Control Rate (DCR) was significantly higher in the regorafenib group (52.6%) vs. the placebo group (9.1%) (one-sided p<0.000001)
- For HRQoL, there was no statistically significant difference between patients receiving regorafenib and patients receiving placebo.

As noted above, no statistically significant difference was evident between treatment groups for tumour response rate. However, the company highlight that within-tumour necrosis promotes disease stabilisation without reduction in size, which is an observed effect of kinase inhibitors in TKI-resistant disease.

Subgroups

Bayer found regorafenib to be effective across all subgroups for progression-free survival except for the small subset of patients (n=22) with duration of imatinib treatment of less than 6 months.

Overall survival for subgroups was presented as uncorrected for crossover and corrected via RPSFT and IPE. The results were similar for the main OS results, however, confidence intervals were wide and indicating heterogeneity and a lack of statistical significance. Bayer do point out that the low number of events within subgroups will contribute to this.

Adverse events

During the double-blind study phase of the GRID study, drug-related adverse events were reported in 132 (100%) patients in the regorafenib group and 61 (92%) patients in the placebo group. Treatment discontinuations due to regorafenib-related events were reported

for 16.8% of patients and distributed across all system organ classes. Five deaths were reported as related to regorafenib treatment by investigators (cardiac arrest, acute hepatic failure, acute kidney injury, colonic perforation, and thromboembolic event).

The most serious adverse drug reactions in patients receiving regorafenib were haemorrhage, severe liver injury, and gastrointestinal perforation and the most common adverse events included hand-foot skin reaction (HFSR), hypertension, diarrhoea, mucositis and fatigue

1.3 Summary of the ERG's critique of the clinical effectiveness evidence submitted

The methods for the searches and systematic review were adequate and well described, therefore, the ERG concluded that the company did not miss any evidence.

The primary focus of the company's submission was the GRID study. This was an appropriately-designed double-blinded, multi-centre RCT. The treatment arms were balanced and patients were representative of the UK population.

The crossover of 87.9% of placebo-treated patients to open-label regorafenib following disease progression may cause the OS to be overestimated, assuming regorafenib provides a clinical benefit for this outcome. Therefore Bayer applied two correction methods, which have been assessed as appropriate by the ERG resulting in a statistically significant difference for OS in favour of regorafenib.

1.4 Summary of cost-effectiveness evidence submitted by the company

So far, we have received a total of three versions of Bayer's economic model and cost-effectiveness results.

We received Bayer's economic model and full report on 21st March 2017.

On 25th April 2017, after an earlier request for clarification from us, we received a second version of Bayer's economic model and cost-effectiveness results. This included some updated OS data, as discussed in Section 5.3.6, p74.

On 16th May 2017, in response to another request for clarification from us, we received a third version of Bayer's economic model and cost-effectiveness results. In addition to the updated OS data, this also included some updated data on treatment duration of regorafenib as discussed in Section 5.3.8.1, p102.

1.4.1 Company's systematic review of economic evaluations

Bayer conducted a systematic literature review of economic and cost-effectiveness studies. They considered only one study to be relevant, an analysis for the relevant patient population in England. The base case ICER for regorafenib vs placebo was £34,420 - £40,188 per QALY according to the method of adjustment for treatment switching.

1.4.2 Company's submitted economic evaluation

1.4.2.1 Methods

The company presented a model-based economic evaluation to address the decision problem.

Bayer submitted a partitioned survival model with three independent health states; progression-free survival (PFS), post-progression survival (PPS), and Death. Patients enter the model upon treatment commencing for either regorafenib or the comparator, best supportive care (BSC). The model uses a 28-day cycle length and a time horizon of 40 years. A half-cycle correction is applied. Outputs of the model (costs, life years and quality-adjusted life years [QALYs]) were discounted at 3.5% per annum.

Health state utility values in the base case were estimated using EQ-5D measurements from patients in the GRID trial. Paired samples and repeated measures methods were used to estimate the values, with paired comparisons preferred by Bayer. Bayer's base case HSUVs are independent of treatment group. Bayer extensively examine the effect of different HSUV estimates in their scenario analyses. The impact of adverse events on health-related quality of life was also directly modelled for the treatment groups.

Costs were modelled from the NHS and Personal Social Services perspective. Bayer's base case includes options for costing the drug at list price, as well as offering a confidential patient access scheme (PAS) applied to the cost of regorafenib.

Bayer's method of modelling the treatment duration of regorafenib changed substantially from the time of their original report submission to the time of our report submission. Regorafenib treatment in the regorafenib arm of GRID was continued after disease progression. However, instead, Bayer modelled regorafenib treatment only up to progression, as they claimed this would be as in clinical practice in England & Wales, citing surveys of physicians. In response to our question for clarification, they completely changed their method of modelling treatment duration. In particular, they now model treatment with regorafenib for the entire duration as experienced in GRID RCT. We agree with this approach.

Other resource costs for regorafenib and placebo patients were identified through using clinician surveys conducted by Bayer. This included one-off costs, such as end-of-life costs, as well as health state costs, which consisted of outpatient monitoring visits, regular tests and medication for pain management. A variety of sources were used to estimate unit costs, including: Published studies, PSSRU Unit 2015, NHS reference costs 2015/16, 2016/17 National Tariff, and the Drug tariff 01/2017. The costs of adverse events were also modelled, although they were negligible. Univariate and probabilistic sensitivity analyses were conducted to explore uncertainty in the incremental cost-effectiveness ratio (ICER) and to identify parameters to which the model was sensitive. Scenario analyses to examine the model's sensitivity to structural assumptions were also conducted.

1.4.2.2 Clinical outcomes in model

Treatment effectiveness was estimated using the GRID trial. The economic model considered progression-free survival and overall survival. In their base case, Bayer assume the lognormal distribution for PFS, which we consider reasonable.

87.9% of patients in the placebo arm crossed over to the regorafenib arm after disease progression. This introduces the possibility of overestimating OS in the placebo arm and hence confounding the cost-effectiveness estimates. Bayer considered three crossover correction methods; Iterative Parameter Estimation (IPE), Rank Preserving Structural Failure Time method (RPSFT), and Inverse Probability of Censoring Weights (IPCW). The IPCW method was rejected due to the high proportion of placebo patients crossing over, and we consider this reasonable. In their base case, Bayer assume the IPE method and we also consider this reasonable. The cost-effectiveness of regorafenib is extremely sensitive to the adjustment for treatment switching, specifically, Bayer's base case ICER of £38,000 per QALY assuming the PAS increases to over £100,000 per QALY based on the unadjusted ITT OS data.

In their original report, Bayer presented OS data with a cut-off date of June 2015. In our clarification letter, we ask Bayer whether they could provide us with more mature data, given that the existing data is now about two years out of date, and that a reasonable amount of extrapolation is required. In response, on 25th April 2017, we received OS data from Bayer with cut-off of 2017. Bayer also included an updated version of their economic results.

Despite the fact that the Kaplan-Meier graph for the placebo arm changed only very slightly from the 2015 to the 2017 data cut-off, Bayer estimate a shorter OS for placebo after correction for cross-over using the 2017 data, compared to the 2015 data. Specifically and importantly, the estimated mean OS in the placebo arm decreases by 24%. Bayer justify this as follows: "*This is a result of the greater follow-up time allowing for a longer potential*

censoring date within the crossover adjustment calculation" (Bayer response to clarification, p11). This reduction in mean OS substantially improves the cost-effectiveness of regorafenib. For example, assuming the PAS, the ICER for regorafenib vs. BSC decreases from £49,000 to £38,000 per QALY.

However, we have several important concerns with the switching adjustment applied to the 2017 data. Given these concerns, we use the 2015 data-cut for OS in our base case.

We turn now to the extrapolation of OS. Two consultant oncologists, who specialised in the disease area, validated the fittings of various parametric models, on behalf of Bayer. They argued that the loglogistic, Weibull and Gompertz models all looked clinically plausible. However, in their base case, Bayer chose the log-logistic distribution for OS based on the accuracy of the fit the data from GRID.

We surveyed the literature for studies that could help to inform the extrapolation of OS. We found just one relevant study, which suggested, if anything, a reasonably long tail for OS. However, we caution not to rely solely on this study to inform extrapolation, due to limitations in comparability with the GRID study. On balance, in our base case, we model OS as the average of the shorter-tailed Weibull and longer-tailed log-logistic distributions.

Bayer do not explicitly model background general population mortality. In our base case, we include this additional mortality.

1.4.2.3 End of Life criteria

We agree with Bayer that regorafenib meets the End of Life criteria.

1.4.3 Results

In Bayer's base case analysis (without/with PAS), treatment with regorafenib resulted in 1.7333 QALYs at a cost of [redacted]/£47,249, while treatment with the placebo resulted in 0.761 QALYs at a cost of £10,395. The QALY differential was 0.971 and the cost differential was £[redacted]/£36,854. The corresponding ICERs per QALY were £[redacted]/£37,941.

Regorafenib was predicted to result in QALY gains in both PFS and OS, with the benefits roughly similar in both health states. The overall QALY gain depends heavily on the treatment switching adjustments.

Drug acquisition costs were by far the largest cost in the regorafenib arm at £[redacted]/£[redacted] which was also the incremental cost as the placebo arm had zero drug costs. Other cost differentials were much smaller; the next largest incremental cost was +£[redacted] for monitoring costs in the regorafenib arm. Remaining costs were very similar between the two treatment arms.

In the probabilistic sensitivity analysis, the ICERs per QALY were similar to the deterministic case at £[redacted]/£38,494 without and with the PAS. Both costs and QALYs were very similar to the base case. At a willingness to pay threshold of £50,000 per QALY, regorafenib had a [redacted]/82% chance of being cost-effective.

Univariate sensitivity analyses were also carried out, indicating that results were sensitive to a number of parameters. Regorafenib drug costs and utility discount rates were the most impactful parameters, with HSUVs and cost discount rates also being significant.

Bayer also carried scenario analyses looking at assumptions for: OS extrapolation, treatment switching, resource use, and utility elicitation method. The most impactful of these were the choice of OS extrapolation, and the method of treatment switching adjustment.

1.5 Summary of the ERG's critique of the cost-effectiveness evidence submitted

The derivation of the PenTAG base case is shown in Table 1 below.

Total uncertainty in the cost-effectiveness of regorafenib versus BSC is high due to:

- Substantial uncertainty in the adjustment for widespread treatment switching on diseases progression, from BSC to regorafenib.
- Important uncertainty in the extrapolation of OS.

In key plausible scenario analyses, we suggest alternative plausible methods of extrapolating OS, and of modelling costs and QALYs only whilst patients are in PFS.

Table 1. Derivation of PenTAG base case ICERs Regorafenib vs. BSC (£ per QALY)

				Regorafenib price	
				PAS	List
	Bayer base case			**£38,000**	[redacted]
	PenTAG assumption	**Bayer assumption**			
1	OS from 2015 data-cut	OS from 2017 data-cut	(Section 5.3.6.2, p79)	£49,000	[redacted]
2	Include general mortality from UK population	Do not including general mortality from UK population	(Section 5.3.6.3, p87)	£41,000	[redacted]

3	OS average of Log-logistic / Weibull	OS average Log-logistic	(Section 5.3.6.3, p87)	£41,000	[redacted]
4	Utilities decrease with age	Utilities independent of age	(Section 5.3.7, p95)	£39,000	[redacted]
1 + 2				£52,000	[redacted]
1 + 3				£52,000	[redacted]
2 + 3				£43,000	[redacted]
1 + 2 + 3				£55,000	[redacted]
		ICER		**£56,000**	[redacted]
1+2+3+4	**PenTAG base case**	**Uncertainty**		**High, mostly due to switching adjustment, but also extrapolation.**	

Key: ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; QALYs, quality-adjusted life year(s); Dark shading indicates ICER > £50,000 per QALY.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

- Double-blind multi-centre randomised trial.
- The population recruited to the GRID study was representative of the typical UK population.
- Bayer's analysis has been clearly described.
- There were no noteworthy wiring errors in the economic model.

1.6.2 Weaknesses and areas of uncertainty

- Whilst Bayer were responsive to our questions of clarification, they sent us a total of three version of their economic model.
- The substantial amount of treatment switching introduces a great deal of uncertainty in the estimated cost-effectiveness.
- We are not convinced that Bayer have correctly adjusted for treatment switching in the most recent, 2017, data cut.

- Extrapolation of OS also introduces appreciable uncertainty in the estimated cost-effectiveness.

2 Background

2.1 Critique of company's description of underlying health problem

Gastrointestinal stromal tumours (GIST) are a rare type of soft tissue sarcoma that develops in the connective tissues of the digestive system, commonly (~60%) in the wall of the stomach. However, they may originate elsewhere such as the small intestine (~30%) or oesophagus and, very rarely, outside the gastrointestinal tract.[2]

GIST are the most common mesenchymal neoplasms of the GI tract, but actually represent less than 1% of tumours in this region. [3]

For many people with GIST, the c-kit oncogene which is found in all cells in the body has undergone a mutation. This oncogene directs the cell to produce the KIT protein, subsequently causing the cell to replicate. Within the interstitial cells of Cajal (ICCs), the c-kit gene is inactive unless there is a need for more cells. However, in most GISTs, there may be an inherited mutation of the c-kit gene leading to a high cell division rate.

A less frequent mutation also exists, known as PDGFRA, which causes the cell to overproduce a different protein (also called PDGFRA), but which has the same effect as KIT.

The majority of GISTs will have one or other of the mutations, but not both. There is also a small population of patients who have neither of these changes.

Bayer describe GIST in more detail as follows (Source: Bayer submission, section 3, p38):

> *Gastro-intestinal stromal tumours (GISTs) are rare connective tissue tumours that show a differentiation profile similar to the interstitial cells of Cajal involved in the regulation of the digestive system.[…] Pathologically, most of GISTs are caused due to oncogenic mutations in either KIT or PDGFRA (23). The majority of the cases (75% to 80%) have KIT mutations that typically affect the juxtamembrane domain encoded by exon 11, while 5% to 8% GISTs have PDGFRA mutation and 12% to 15% have KIT and PDGFRA wild-type mutations (23).*

The ERG believes the description given by the company is appropriate.

2.1.1 Epidemiology

According to Amelio et al. 2014, UK estimates of GIST annual incidence range from 1.32–1.50 per 100,000 population, which is equivalent to approximately 800–900 new cases each year.[4] No UK prevalence has been reported, however, reports from western Sweden estimate prevalence at 12.9 per 100,000.[4]

As mentioned above, most GISTs are sporadic and occur because of a c-kit or PDGFRA oncogene mutation encouraging the GIST cells to grow and multiply. There are also a number of rarer types of GIST some of which may be due to an inherited gene mutation:[5]

- Wild-type GIST: A type of GIST that is not caused by a known cell mutation
- Paediatric GIST: A GIST affecting children and young adults. Paediatric GIST is very rare
- Syndromic GIST: A type of GIST linked to Carney's Triad Syndrome and Carney-Stratakis Syndrome and Neurofibromatosis.
- Familial GIST: A rare inherited form of GIST

Risk factors include age and sex, as GIST most often occurs in people older than 50 and is slightly more common in men than in women.[6]

2.1.2 Diagnosis

The symptoms of GIST can vary according to size and location of the tumour. Initial diagnosis, following clinical examination may be via a diagnostic scan and biopsy. [5]

With regard to metastatic GIST, Bayer list the typical symptoms below (Source: Bayer submission, section 3.2, p39):

> *Metastatic GIST is a terminal disease for which patients may experience general systemic symptoms such as fever, nausea, abdominal discomfort and weight loss as well as psychological distress and functional impairments (5)*

Other symptoms may include fatigue, blood in stools or vomit and anaemia.

2.1.3 Prognosis and burden of disease

The overall 5-year survival rate for people with GIST has been reported as 76%.[6] However, this was estimated from data collected between 2003 and 2009 from the American Cancer Society and both diagnosis and available treatments have improved since then. The estimate reduces to 74% if the cancer has spread locally, and falls to 48% for distant metastasise.[6] Whereas, if the cancer is contained within the original organ, the 5-year survival rate is improved at 91%.

The most reliable prognostic factors for GIST are considered to be:[7]

- The size of the primary tumour,
- The mitotic index i.e., the ratio between the number of cells in a population undergoing mitosis to the number of cells in a population not undergoing mitosis.

- The location of the primary lesion, with small bowel and rectal primary GIST less favourable than gastric GISTs.
- PDGFRA mutations which are most commonly associated with gastric primary lesions have a more favourable prognosis.
- Histologic type may also impact prognosis, with spindle cell displaying a higher five-year survival rate than epithelioid or mixed histology. However, in contrast, others report a prognostic influence of the degree of cellularity but not histologic subtype.

The company submission provides the following details on prognosis for people with GIST: (Source: Bayer submission, Section 3, p38)

> *For people with GIST, the prognosis depends mainly on whether the tumour is resectable. Size, location, and stage of tumour at initial diagnosis are also important factors for the prognosis of the tumour (26).*
>
> *Surgery represents the cornerstone treatment of localised GISTs (26). Complete removal of GIST is potentially curative, especially when it is small in size and the risk classification is low. However, the risk of relapse after surgery can be substantial, as defined by available risk classifications […]*

2.2 Critique of company's overview of current service provision

2.2.1 Current UK GIST treatment pathway

A summary of treatment options for GIST are as follows:[8]

- Localized, smaller (resectable) tumours - surgery is the main treatment and for tumours that are small and are not growing quickly, this is often the only treatment needed. Recurrence is more likely if the tumour is larger, did not start in the stomach, or if the cancer cells have a high mitotic rate. In this case, an adjuvant treatment with imatinib may be recommended for a minimum of a year post-surgery. For tumours that are highly likely to come back, many doctors now recommend giving patients at least 3 years of imatinib.
- Localized, larger (marginally resectable) tumours - may require more extensive surgery leading to further health problems later on. Therefore, once a biopsy confirms the tumour is a GIST, treatment with imatinib is usually commenced and continues at least until the tumour stops shrinking. At this point, surgery may be possible. If the tumour is still too large for surgery, imatinib may be continued, followed by sunitinib if the first-line treatment is no longer effective. If sunitinib is no longer working, the targeted drug regorafenib may help some patients.

- Unresectable tumours and metastases - imatinib is usually the preferred first treatment option. It is continued as long as the tumour has a stable response. If the tumour progresses, it may respond to increasing the dose of imatinib. If the tumour continues to grow or the side effects from imatinib are too severe, a switch to sunitinib may be helpful. If sunitinib is no longer working, regorafenib may help some patients as a third-line treatment. If the tumour shrinks enough with targeted therapy, surgery may then be an option for some patients. This might be followed by more targeted therapy if it is still effective. If the cancer has spread to only 1 or 2 sites in the abdomen (such as the liver), the surgeon may advise removing the main tumour and trying to remove these other tumours as well. Usually this should be considered only for tumours that are slow growing or those causing local complications such as uncontrollable bleeding. Other options to treat cancers that have spread to the liver include ablation and embolization. These treatments may include radiofrequency ablation (RFA; using electric currents to heat the tumour), or ethanol ablation (injecting concentrated alcohol into the tumour). Cancers that are no longer responding to the targeted drugs discussed above can be hard to treat. Some doctors may recommend trying other targeted drugs, such as sorafenib (Nexavar®), dasatinib (Sprycel®), or nilotinib (Tasigna®), although it's not yet clear how helpful these drugs are.
- Recurrent tumours - Treatment options for GISTs that recur after treatment depend on the location and extent of the recurrence. For most recurrences, treatment with imatinib is probably the best way to shrink any tumours, as long as it is still effective and the patient can tolerate taking it. If the starting dose of imatinib does not work, the dose can be increased. Another option is to try sunitinib or regorafenib. If the cancer comes back as a single, well defined tumour, removing or destroying the tumour may be an option. Doctors are still not certain if removing GISTs that come back after treatment helps people live longer. Some studies have found that it does, but other studies disagree.

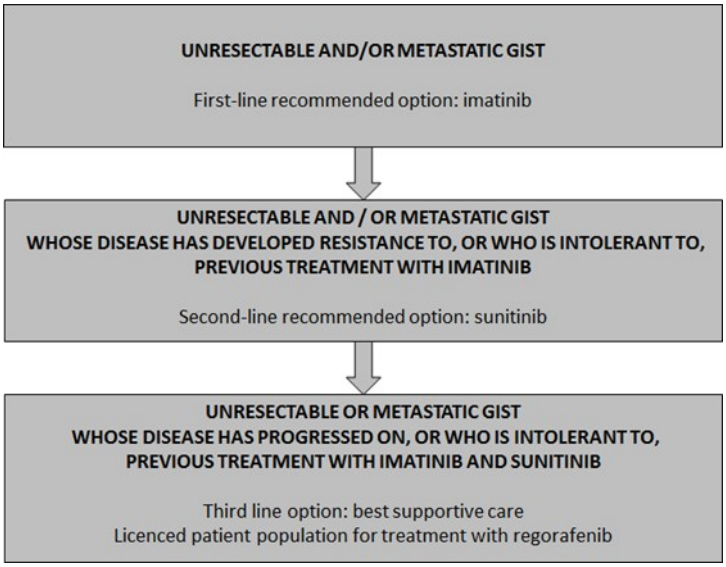
Best supportive care is provided to patients who fail to respond to imatinib and sunitinib. Although there is no strict definition, this generally involves care to prevent or treat the symptoms of GIST, side effects caused by treatment, and psychological, social, and spiritual problems related to a disease or its treatment. Radiation therapy is sometimes given as supportive care to relieve pain in patients with large tumours that have spread.[9]

Bayer report that pain management may be administered as follows: (Source: Bayer submission, Section 3, p39)

According to a survey conducted in 2013 and involving physicians from England and Wales, pain management treatments were confirmed to comprise co-codamol, tramadol, paracetamol, morphine sulphate and dexamethasone.

Within the UK, the clinical pathway falls under the NICE pathway for stomach cancer, as shown in Figure 1, which also includes the proposed position for regorafenib: (Source: Bayer Submission, Section 3, p40)

Figure 1. UK Clinical pathway for GIST



Source: Bayer submission, Section 3, p40, Figure 1

2.2.2 Anticipated place of regorafenib in clinical practice

In England, there are no other lines of therapy recommended by NICE for the treatment of patients with unresectable or metastatic GIST whose disease has progressed upon treatment with sunitinib. Therefore, Bayer anticipates that regorafenib will be an option for this population of approximately 60 new patients per year. The ERG considers this an appropriate figure, given approximately half of new cases of GIST are likely to be metastatic and/or unresectable on first presentation and will initially be treated with imatinib/sunitinib.[10]

3 Critique of company's definition of decision problem

The company presented their decision problem within the Executive Summary chapter, under the subheading 'statement of the decision problem' (Bayer submission, Section 1.1, p. 16). A summary table of the NICE Scope, the company's decision problem and the ERG's critique is presented below (Table 2).[1] Clearly, Bayer's definition of the decision problem is closely aligned with the NICE Scope.

Table 2. Summary table of decision problem critique

Decision problem	NICE Scope	Company's decision problem	ERG notes
Population	Patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) whose disease has progressed on, or who are intolerant to, previous treatment with imatinib and sunitinib.	As per Scope	No comments
Intervention	Regorafenib	As per Scope	No comments.
Comparator	Best supportive care (BSC)	As per Scope	No comments
Outcome	The outcome measures to be considered include: • Overall survival • Progression-free survival • Adverse events of treatment • Health-related quality of life	As per Scope	The company include additional secondary outcomes • time to progression, • tumour response • objective response rate • disease control rate • duration of response

Source: NICE Scope[1] and Bayer submission, Table 1, p. 16–17

3.1 Population

The defined population in the company's submission (patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) whose disease has progressed on, or who are intolerant to, previous treatment with imatinib and sunitinib), agrees with the population specified in the NICE Scope. Inclusion criteria also require an ECOG performance status of 0 or 1 which is standard for RCTs. [11]

3.2 Intervention

The company's decision problem specified the intervention as 'regorafenib', which matches the NICE Scope.[1]

Regorafenib is a multitargeted tyrosine kinase inhibitor with antiangiogenic activity. It has inhibitory action against several tyrosine kinases, including KIT, PDGFRA, bFGFR, VEGFR1-3, TIE2, RET, BRAF and BRAF V600E.[12]

Regorafenib (Stivarga®, Bayer) is approved for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumors (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib. The marketing authorisation is presented by the company as follows (Source: Bayer submission, Section 2.2, p29):

> *Initial marketing authorisation for regorafenib (Stivarga®) was received on June 27th, 2013 for the treatment of metastatic colorectal cancers who have been previously treated with, or are not considered candidates for, available therapies.*
>
> *On June 26th, 2014 the CHMP released its positive opinion on the extension of indication for regorafenib in the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib.*
>
> *Treatment with regorafenib (Stivarga®) for patients with unresectable or metastatic GIST whose disease has progressed on, or who are intolerant to, previous treatment with imatinib and sunitinib has been funded through the Cancer Drug Fund (CDF) since 2013.*

The recommended dose on the marketing authorisation is 160 mg once daily for three weeks followed by one week off therapy. The clinical evidence supplied by Bayer is in agreement with this.[11]

3.3 Comparators

The only comparator listed in the NICE scope and in the company submission is best supportive care (BSC).[1] Best supportive care is defined by the company as (Source: Bayer submission, Section 1, p13):

> *…any method to preserve the comfort and dignity of the patient, excluding disease-specific antineoplastic therapy, radiation therapy, or surgical intervention (8).*
>
> *[…]According to two surveys, conducted in 2013 and 2016 and involving physicians from England and Wales, pain management treatments were confirmed to comprise co-codamol, tramadol, paracetamol, morphine sulphate and dexamethasone.*

Similarly, the GRID study includes placebo+BSC (blind) for comparator, with BSC defined in study protocol as follows:[11]

> *any method to preserve the comfort and dignity of the patients, and excludes any disease-specific anti-neoplastic therapy such as any kinase inhibitor, chemotherapy, radiation therapy, or surgical intervention.*

Chemotherapy is also listed as an exclusion to BSC in the GRID study.

3.4 Outcomes

The outcomes in the company submission comply with the scope (Source: Bayer submission, Section 4.3, p68):

- Overall survival - Assessment of survival status was performed every 3 months.
- Progression-free survival (primary endpoint) - PFS was assessed by central radiology reviewers who were masked to assignment and data from patients. Two readers reviewed the images. Tumour assessments were made at baseline, then every 4 weeks for the first 3 months, every 6 weeks for the months 4 to 6, and every 8 weeks thereafter until the end of study drug administration.
- Adverse events of treatment - Investigators rated severity of adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) [NCI CTCAE V4.0].
- Health-related quality of life - Health-related quality of life questionnaires (EORTC QLQ-C30 and EuroQoL EQ-5D) were routinely completed by patients.

Other outcomes included in the study protocol include;

- time to progression,

- tumour response
- objective response rate
- disease control rate
- duration of response

4 Clinical effectiveness

4.1 Critique of the methods of review(s)

4.1.1 Searches

Bayer presented a literature search protocol to support its review of clinical effectiveness. This protocol included systematic searches of key biomedical databases using a literature search strategy, searching of conference websites and a search of clinical trials.gov. The literature search was last updated in December 2016.

The bibliographic database searching used a search strategy that took the following form:

1. (controlled index terms for gastrointestinal tumous and various sub-types of gastrointestinal tumour including gastrointestinal stromal tumour) OR
2. (free-text terms for gastrointestinal tumour and various related terms) AND
3. (controlled index terms for regorafenib or drug therapy or palliative therapy) OR
4. (free-text terms for regorafenib or drug therapy or palliative therapy) AND
5. (a range of search terms for study design (RCTs, clinical trials, controlled studies, comparative studies and prospective studies) NOT
6. (a range of search terms to exclude case studies, conference abstracts and letters) AND
7. (limited to 2000 onwards and humans).

The search strategy was applied in the following bibliographic databases: Medline-in-Process (PubMed), Medline and Embase (Elsevier at Embase.com) and The Cochrane Library.

The following conference websites were searched: American Society of Clinical Oncology (ASCO) in 2016 (month not stated) and European Society for Medical Oncology (ESMO) in 2016 (month not stated). Finally, clinicaltrials.gov was searched for relevant, unpublished studies (no date for this search is stated).

The literature searching for clinical effectiveness studies is reasonably well conducted and reported. However there are a few concerns.

- We do not have access to Embase.com so are unable to test the searches but the value of searching Medline and Embase simultaneously with one strategy is debatable since these databases use different indexing terms (Emtree for Embase and MeSH for Medline).

- The filter used to limit to RCTs is not the Cochrane search filter or any other validated filter that we recognize. It is unclear why a validated search filter was not used to limit to RCTs.
- Systematic reviews and meta-analyses were not searched for.
- The search for the intervention could have included further terms such as Stivarga and BAY 73-4506.
- The report describes 'hand-searching' clinicaltrials.gov, it is unclear what this entails and no further information is given.

There is insufficient information about the screening methods used for the review. Bayer have provided further details about their methods for screening in clarification but it is still not clear whether full text studies were double screened.

4.1.1.1 Quality of Life

Bayer presented a literature search protocol to support its review of health-related quality-of-life studies. This protocol included systematic searches of key biomedical databases using a literature search strategy and searching of conference websites. The literature search was last updated in December 2016.

The bibliographic database searching used a search strategy that took the following form:

1. (controlled index terms for gastrointestinal tumour and various sub-types of gastrointestinal tumour including gastrointestinal stromal tumour) OR
2. (free-text terms for gastrointestinal tumour and various related terms) AND
3. (a range of search terms for health utilities and quality of life) NOT
4. (a range of search terms to exclude conference abstracts) AND
5. (limited to 2000 onwards, English language and humans).

The search strategy was applied in the following bibliographic databases: Medline-in-Process (PubMed), Medline and Embase (Elsevier at Embase.com), EconLIT and NHS EED (The Cochrane Library).

The following conference websites were searched: American Society of Clinical Oncology (ASCO) in 2016 (month not stated), European Society for Medical Oncology (ESMO) in 2016 (month not stated), International Society for Pharmacoeconomics and Outcomes Research in 2016 (month not stated) and International Society for Quality of Life Research (ISOQoL) (month not stated).

The literature searching for health-related quality-of-life studies is reasonably well conducted and reported. However there are a few concerns.

- We do not have access to Embase.com so are unable to test the searches but the value of searching Medline and Embase simultaneously with one strategy is debatable since these databases use different indexing terms (Emtree for Embase and MeSH for Medline).
- It is not clear why NHS EED was included in the update search in December 2016 when this database has not been updated since April 2015.

There is insufficient information about the screening methods used for the review Bayer have provided further details about their methods for screening in clarification but it is still not clear whether full text studies were double screened.

4.1.1.2 Adverse events

Bayer did not undertake separate literature searches to identify studies reporting adverse events.

4.1.2 Inclusion criteria

Bayer's inclusion criteria in the search strategy are given below (Table 3) with an additional column added to the right of the table, taken from the Scope for reference and comparison. Comments about the differences in inclusion criteria are outlined below the table.[1]

Table 3. Scope of the literature review: PICOS criteria for study inclusion

Criteria	From Bayer Definition	From Scope
Population	Adult patients with metastatic, advanced, or unresectable GIST. Including 3rd line or later patients.	People with unresectable or metastatic gastrointestinal stromal tumours whose disease has progressed on, or who are intolerant to, previous treatment with imatinib and sunitinib
Interventions/ comparators	Regorafenib studies vs. placebo or BSC	Best supportive care
Outcomes	Efficacy outomes e.g. progression-free survival (PFS), overall survival (OS), Time to progression (TTP), disease control rate (DCR), response rate (ORR), duration of response (DOR). Safety outcomes e.g. adverse events Health-related Quality of life (HRQoL)	The outcome measures to be considered include: • Overall survival • Progression-free survival • Adverse effects of treatment • Health-related quality of life
Study Design	Randomised control trials (of any blinding status); non-randomised,	

Criteria	From Bayer Definition	From Scope
	controlled studies; uncontrolled single-arm trials; Cohort studies	

Key: GIST, gastrointestinal stromal tumour; BSC, best supportive care; PFS, progression-free survival; OS, overall survival; TTP, time to progression; DCR, disease control rate; ORR, overall response rate; DOR, duration of response; HRQoL, health-related quality of life.
Source: Bayer submission, Table 8, pp. 50–51 and NICE Scope[1]

4.1.2.1 Population

The population defined by Bayer differs slightly to the scope in that 3rd line or later patients are specified, whereas the population in the scope are intolerant to previous treatment with imatinib and sunitinib.[1] However, since 3rd line patients are likely to have received imatinib and sunitinib, the ERG believes the populations are essentially the same.

4.1.2.2 Interventions/comparators

The NICE Scope lists only best supportive care, whereas Bayer specify placebo or best supportive care. The use of a placebo would be necessary in blinded trials and is, therefore, appropriate.

4.1.2.3 Outcomes

The outcomes listed by Bayer include all those specified in the NICE Scope.

4.1.2.4 Study design

Bayer include several types of study design, including RCTs. Although the NICE Scope did not restrict study design, the NICE reference case guide to the methods of technology appraisal 2013 (Chapter 5.2.3)[13] recommends studies should be restricted to RCTs and when they are not available, non RCTs.

4.1.2.5 Study selection

The process for study selection as described by Bayer is standard for systematic reviews.

From 3,764 unique citations identified, 3173 were excluded and 591 were taken to full-text screening.

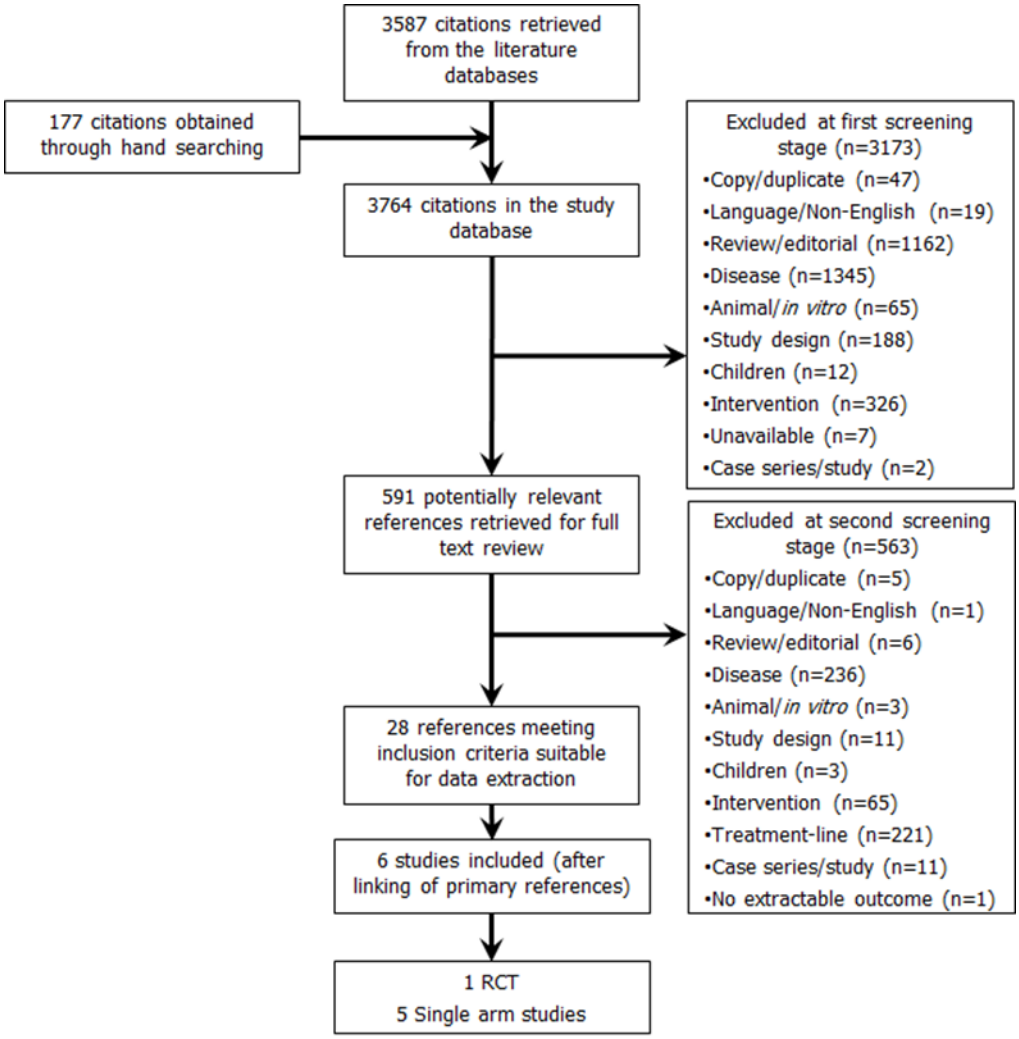
A further, 563 studies were excluded leaving the following (Source: Bayer submission, Section 4.1, p52):

Of relevance to the decision problem in this submission, 28 publications concerned the use of regorafenib. These publications related to 6 studies: one randomised controlled trial (RCT), and 5 single-arm studies. The single-arm studies included limited information and

patient numbers. This section further focuses on the identified RCT, the optimum design for assessing the benefits of treatments in oncology.

The PRISMA diagram reported in Bayer's submission is copied below (Figure 2).

Figure 2. PRISMA study flow diagram



Source: Bayer submission, Section 4.1, p52.

4.1.3 Critique of data extraction

The data extraction process is briefly explained for the one included study.[11] It is unclear if this was performed or checked independently by two researchers.

4.1.4 Quality assessment

Details of the company's critical appraisal of the GRID study,[11] alongside our critique, can be seen in Table 4.

Table 4. Critical appraisal of GRID study

Critical appraisal criterion	Bayer's Assessment	ERG Comment
Was randomisation carried out appropriately?	Yes Randomisation was performed via an interactive voice response system (IVRS). Investigators received the randomisation number for each participant through the IVRS and study drug supply was also managed via IVRS. Computer-generated randomisation lists were prepared by Bayer (pre-allocated block design, block size 12). Randomisation was stratified by treatment line (3rd vs. 4th line therapy or beyond) and geographical region (Asia vs. rest of the world).(Source: Bayer submission, Section 3, p58)	Block randomization with stratification is an appropriate method to ensure populations for the two treatments are approximately equal in size and balanced.
Was the concealment of treatment allocation adequate?	Yes Investigators received the randomisation number for each participant through the IVRS and study drug supply was also managed via IVRS. Regorafenib and placebo were identical in appearance.	The ERG agree that the method of allocation concealment is adequate.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes Demographics and baseline disease characteristics were comparable between the regorafenib and the placebo groups	The groups are generally balanced. However, the placebo group had a slightly larger population receiving >18 months of imatinib therapy (regorafnib 67% vs. placebo 83%).
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes Investigators received the randomisation number for each participant through the IVRS and study drug supply was also managed via IVRS. All patients, investigators, and the study sponsor were masked to treatment assignment through the use of the unique drug pack numbers preprinted onto each bottle, which was assigned to the patient by the IVRS. Regorafenib and placebo were identical in appearance in order to preserve blinding. Assessment of the primary endpoint (PFS) was carried out by central radiology reviewers who were masked to assignment and data from patients.	The ERG agree that the methods of blinding are adequate.
Were there any	No	The treatment duration was longer in the regorafenib arm, hence, the higher

Critical appraisal criterion	Bayer's Assessment	ERG Comment
unexpected imbalances in drop-outs between groups?	A higher number of patients withdrew from double-blind treatment in the regorafenib arm of the study (38%) than in patients receiving placebo (11%). This was mainly due radiological progression.	number of withdrawals due to radiological progression.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No Results of all pre-specified outcomes are reported in full.	The outcome measures listed in the protocol for the trial correspond with the outcome measures 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?	Yes/Yes/Yes The primary analysis was performed in the ITT population using radiological assessments taken during the double-blind phase of the study only. This was appropriate. Missing or unevaluable tumour assessments were not used in the calculation of derived efficacy variables unless a new lesion occurred, or the lesions that were evaluated already showed progressive disease (PD). No imputation was performed for missing lesion assessment and tumour response. For example, if a patient missed a scan visit and PD was documented at the next available scan visit, the actual visit date of the first documented PD was used. If a date was incomplete, such as only the year and month were available, day 15 of the month was used for the calculation.	Yes, we agree the main analysis adopts 'intention to treat' principles. The methods for dealing with missing data in this population appear to be standard.

Key: IVRS, interactive voice response system; IWRS, interactive web response system;
Source: Bayer submission, Appendix 3, p 36, Table 14

4.1.5 Evidence synthesis

From the searches, only one RCT was identified. Therefore synthesis of the evidence was not required.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Methods

The single RCT (study name GRID; main publication by Demetri et al. 2013) identified was presented in detail within the submission.[11] No additional relevant studies were identified by the ERG.

4.2.1.1 Study objective

The objectives are reported in the company submission as follows (Source: Bayer submission, Section 4.3, p51):

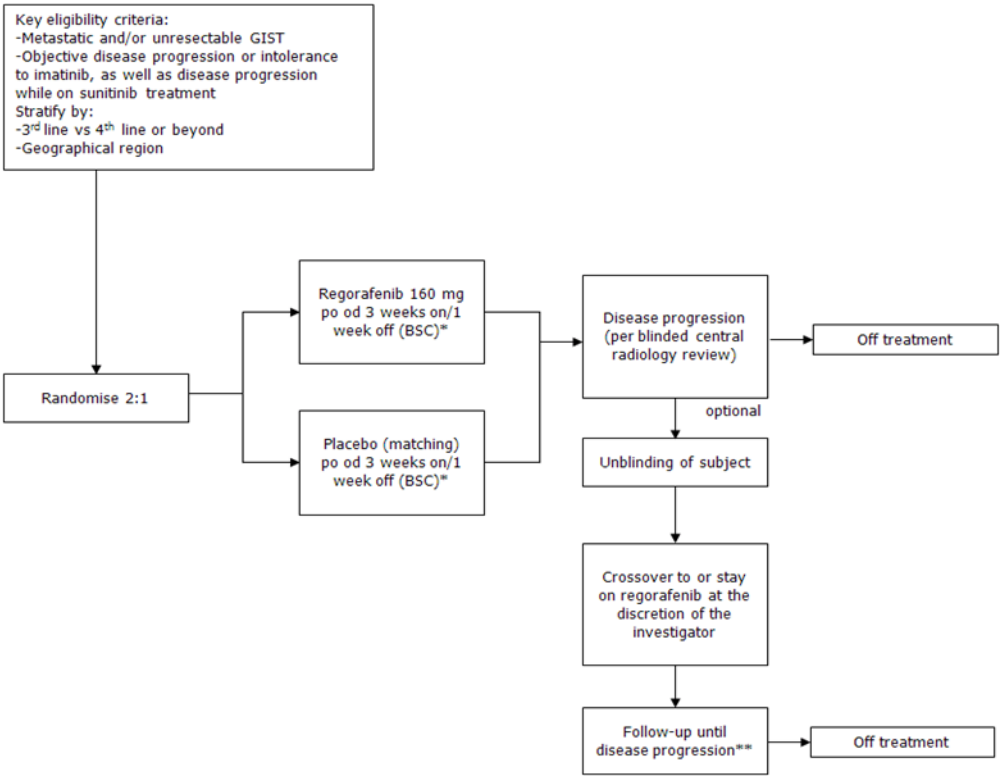
> *The primary objective of the GRID study was to compare regorafenib and placebo treatment in terms of progression-free survival (PFS) in patients with metastatic and/or unresectable GIST who have progressed after therapy with at least imatinib and sunitinib.*
>
> *Secondary objectives included evaluation of overall survival (OS), time to progression (TTP), disease control rate (DCR), tumour response rate (RR), duration of response (DOR), and safety of regorafenib. Health-related quality of life, pharmacokinetics, secondary PFS during open label treatment, and biomarker analysis were exploratory objectives within the study.*

The objectives correspond to the outcome measures detailed in the NICE Scope.[1]

4.2.1.2 Study design and treatment

The GRID study was a multicentre (57 centres; 17 countries), randomised, blinded, phase 3 trial investigating the efficacy of regorafenib for patients with GIST who have previously been treated with imatinib and sunitinib.[11] The overall trial design is displayed in Figure 3.

Figure 3. GRID trial design



Key: BSC, Best Supportive Care; GIST, Gastrointestinal Stromal Tumour; po, per os
Notes: ** Patients could continue treatment with regorafenib even after 1st progression (for regorafenib patients) or 2nd progression (for cross over patients)
Source: Bayer submission, Section 4.3, p58

As shown in Figure 3, participants receive either regorafenib or placebo once daily for the first 3 weeks of each 4-week cycle. Regorafenib was administered as 4 x 40 mg tablets, with a matching placebo for the control arm and both were stored in identical containers. Patients continued to receive treatment until disease progression, clinical progression, toxicity or consent withdrawal.

The intervention and control arms also included BSC, which is defined by the company as follows (Source: Bayer submission, Section 4.3, p 61):

> *BSC was defined as any method to preserve the comfort and dignity of the patient, and included any concomitant medications or treatments: antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy necessary to provide BSC, except other investigational anti-tumour agents or anti-neoplastic chemo/hormonal/immune/radio-therapy.*

Concomitant medication was permitted at the discretion of the principal investigator and in accordance with the protocol.

A pre-specified schedule was followed with regard to dose modification for unacceptable toxic effects, hand-foot skin reaction and hypertension. A maximum of two dose-reductions due to toxicity were permitted (from 160 mg to 120 mg to 80 mg) (Table 5). A subsequent dose re-escalation was allowed, subject to resolution of toxicities (Table 6).

Table 5. Regorafenib dose levels

Dose level	Dose	Form
Dose level 0 (standard dose)	160mg po od	4 tablets of regorafenib, 40mg/tablet, or 4 matching placebo tablet
Dose level -1	120mg po od	3 tablets of regorafenib, 40mg/tablet, or 3 matching placebo tablet
Dose level -2	80mg po od	2 tablets of regorafenib, 40mg/tablet, or 2 matching placebo tablet

Source: Bayer submission, Section 4.3, p62

Table 6. Dose modification for toxicities related to study drug (except hand-foot skin reaction and hypertension)[a]

NCI-CTCAE v4.0	Dose Interruption	Dose Modification	Dose for Subsequent Cycles
Grade 0-2	Treat on time	No change	No change
Grade 3[b]	Delay until < grade 2[b]	Reduce 1 dose level	If toxicity remains <grade 2, dose re-escalation can be considered at the discretion of the treating investigator. If dose is re-escalated and toxicity (≥ grade 3) recurs, institute permanent dose reduction
Grade 4	Delay until < grade 2[b]	Reduce by 1 dose level. Permanent discontinuation can be considered at treating investigator's discretion.	

Notes: a, excludes alopecia, non-refractory nausea/vomiting, non-refractory hypersensitivity and asymptomatic laboratory abnormalities; b, If no recovery after a 4-week delay, treatment will be permanently discontinued

Source: Bayer submission, Section 4.3, p62

With regard to hand-foot skin reaction, dose modification was adjusted according to skin toxicity grade with supportive measures. According to the level of toxicity or the number of occurrences, treatment may be discontinued or re-escalated.

[redacted]

Randomisation

Randomisation and allocation was performed with stratification by treatment line (3rd vs. 4th line therapy or beyond) and geographical region (Asia vs. rest of the world) as follows: (Source: Bayer submission, Section 4.3, p58):

> *Randomisation was performed via an interactive voice response system (IVRS). Investigators received the randomisation number for each participant through the IVRS and study drug supply was also managed via IVRS. Computer-generated randomisation lists were prepared by Bayer (pre-allocated block design, block size 12).*

With regard to stratification, overstratification can lead to loss of information, but unstratified analyses are not appropriate when there is heterogeneity between strata. Given the variables used for stratification are considered prognostic indicators, this suggests that the stratified analyses are appropriate

Study duration

Patients continued masked study treatment until disease progression, unacceptable toxicity or withdrawal of patient from the study.

Participants receiving placebo were given the option to cross-over to regorafenib if they experienced disease progression. For participants on regorafenib, open-label regorafenib was offered upon progression, if this was considered clinically beneficial.

Blinding

Treatment allocation was masked for patients, investigators and the study sponsor. This was achieved with the appearance of regorafenib and placebo being identical and unique pack numbers pre-printed onto bottles. Central radiology reviewers were blinded for PFS assessment.

Inclusion/exclusion

Table 7 gives a summary of the inclusion/exclusion criteria for the GRID trial. Those listed are in keeping with the NICE Scope.[1, 11]

Table 7. Eligibility criteria

Key inclusion criteria	Key exclusion criteria
• At least 18 years of age • Histologically confirmed metastatic and/or unresectable GIST in people who have experienced disease progression or intolerance to imatinib, as well as disease progression while on sunitinib. • At least one measurable lesion with CT or MRI (according to RECIST, version 1.1). A lesion in a previously irradiated area was eligible as long as there was objective evidence of progression of the lesion prior to study enrolment. • An ECOG PS score of 0-1 at study entry • Adequate haematological, hepatic, cardiac, and renal function. • Resolution of all toxic effects of previous therapy to grade 1 or lower (excluding alopecia, anaemia, and hypothyroidism).	• Prior treatment with regorafenib, or any VEGFR inhibitor except sunitinib. • Use of any approved tyrosine kinase inhibitors or investigational agents within 1 week or a minimum 5 half-lives of the agent, whichever is shorter, prior to receiving study drug. • Previous or concurrent cancer that is distinct in primary site or histology from GIST within 5 years prior to randomisation EXCEPT for curatively treated cervical cancer in situ, non-melanoma skin cancer, and superficial bladder tumours • Congestive heart failure ≥ New York Heart Association (NYHA) class 2. • Unstable angina, new-onset angina, myocardial infarction less than 6 months before start of study drug. • Cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted). • Uncontrolled hypertension • Pheochromocytoma. • Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischaemic attacks), deep vein thrombosis, or pulmonary embolism within the 6 months before start of study drug. • Ongoing infection > grade 2 National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. • Symptomatic metastatic brain or meningeal tumours unless the patient is > 6 months from definitive therapy, has a negative imaging study within 4 weeks of study entry, and is clinically stable with respect to the tumour at the time of study entry.

Key: ECOG PS, Eastern Cooperative Oncology Group performance status; RECIST, Response Evaluation Criteria in Solid Tumors
Source: Bayer submission, Section 4.3, p59

Location

The multi-centre GRID study was conducted in 57 sites across 17 countries including Asia, China, Japan, Singapore, South Korea, Austria, Belgium, Canada, Netherlands, Poland,

Spain, United Kingdom, United States Finland, France, Germany, Israel and Italy. The proportion of patients based in Europe was 58%.

Study endpoint

The study endpoints and definitions are presented in Table 8

Table 8. Study endpoints

End point	Timing of assessment	Definition
	Primary end point	
Progression free survival (PFS)	At baseline, then every 4 weeks for the first 3 months, every 6 weeks for the months 4 to 6, and every 8 weeks thereafter until the end of study drug administration.	The date of randomisation to the date of first observed radiological progression according to blinded central radiology review, or death due to any cause, if death occurred before progression. The actual date of radiological assessment was used as the date of progression. Patients without tumour progression or death at the time of analysis were censored at their last date of radiological tumour assessment.
	Secondary end points	
Overall survival (OS)	Every 3 months	The date of randomisation until the date of death due to any cause. If a patient was alive at the date of database cut-off, they were censored at this point. All patients were followed for survival until death was documented, except for those who specifically withdrew consent to follow-up.
Time to progression (TTP)	As for PFS	The date of randomisation until the date of radiological progression. Patients without tumour progression at the time of analysis were censored at their last date of radiological tumour assessment. The date of progression was the date of first observation of progression.
Tumour response rate (ORR)	As for PFS	The proportion of patients with the best overall tumour response of partial response (PR) or complete response (CR) according to RECIST version 1.1 criteria that is achieved during treatment or within 30 days after termination of study medication.
Disease control rate (DCR)	As for PFS	The rate of complete response or partial response plus stable disease lasting for at least 12 weeks.

End point	Timing of assessment	Definition
Duration of response (DOR)	As for PFS	The number of days from the date of first documented objective response of PR or CR, whichever is noted earlier, to first disease progression or death before progression. Patients without progression or death before progression at the time of analysis were censored at the date of their last tumour assessment.
Safety	Days 1 and 15 of each treatment cycle for the first six cycles. Cardiac function was assessed at screening, day 1 of the first two treatment cycles (and subsequent cycles at the discretion of the investigator), and at treatment end.	Investigators rated severity of adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) [NCI CTCAE V4.0].
Exploratory endpoints		
Health-related quality of life (HRQoL)	At baseline (Day 1 of Cycle 1), on day 1 of cycles 2-4, and day 1 of every other cycle thereafter and within 14 days at the end of treatment.	Health-related quality of life questionnaires (EORTC QLQ-C30 and EuroQoL EQ-5D) were routinely completed by patients.
Pharmacokinetics	Day 15 of cycles 1 and 2	Only performed in patients from selected sites.
Biomarker evaluation	At screening, on day 1 and day 15 of cycle 1, day 15 of subsequent cycles, and at the end of treatment)	Including tumour genotype for mutational status of target oncogene.
Secondary PFS during open label treatment	Only investigator assessments were made during the open-label period.	The time from first progression until second progression or death, whatever came first, during or after open-label treatment with regorafenib per investigator assessment

Key: CR, Complete response; ORR, objective response rate; OS, overall survival; PFS, progression free survival; PR, partial response
Source: Bayer submission, Section 4.3, Table 15, pp 68-70.

Tumour response was based on Response Evaluation Criteria In Solid Tumours (RECIST) (v1.1), with the following modifications: *no lymph nodes and no bone lesions were chosen as target lesions, and PET scan was not considered acceptable for radiological evaluation*. (Source: Bayer submission, Section 4.3, p66)

Furthermore, progression was defined as a growing new tumour nodule within a pre-existing tumour mass expanding on at least two sequential images or must be at least 2 cm in size and a new active lesion.

In order to minimise bias, PFS was assessed by blinded central radiology reviewers. Each image was reviewed by two readers, with adjudication by another radiology reviewer with discordant results.

These endpoints agree with the publication [11] and the protocol for the trial. The ERG considers them appropriate for a study investigating GIST.

4.2.1.3 Statistical analysis

The company state that their primary hypothesis is as follows (Source: Bayer submission, Section 4.4.3, p76):

> *The null hypothesis that both treatment arms have the same PFS distribution was tested against the alternative hypothesis that the distribution of PFS times in the regorafenib arm is different from the control arm according to the Lehmann alternative.*

This statement is in keeping with the study objective of the trial.

4.2.1.3.1 Analysis population

The different populations reported within Bayer's submission for their analyses, along with their definitions are presented in Table 9.

Table 9. Analysis population

Analysis Population	Definition
Intent-to-treat population (ITT)	The full study data set from the GRID study containing data on randomised patients (n= 133 for regorafenib; n=66 for placebo). The ITT population was used for the analysis of the primary efficacy analysis. Subjects in the ITT population were analysed as randomised.
HRQoL evaluable population	Full analysis set patients with evaluable patient reported outcome assessments at baseline and at least one post-baseline assessment. EORTC QLQ-C30 global health status was completed by 183 (92%) patients at baseline, 167 (84%) patients at cycle 2, and 126 (63%) patients at cycle 3.
Safety analysis set	All randomised patients who received at least one dose of study medication (n=132 for regorafenib; n=66 for placebo)[a]
Patient Reported Outcome analysis set (PROAS)	All full analysis set patients with evaluable PRO assessments at baseline and at least one post-baseline assessment (n=123 for regorafenib; n= 62 for placebo).

Notes: a, One patient in the regorafenib group was not treated with study drug
Source: Bayer submission, Table 17, p75

The ITT and safety populations are defined appropriately.

4.2.1.3.2 Determination of sample size

Bayer report that sample size was based on assuming a 100% improvement in PFS for regorafenib, with 199 patients randomised (2:1 regorafenib to placebo), a one-sided alpha of

0.01 and a power of 0.94. It should be noted that the one-tailed test provides more power to detect an effect. However, this test is appropriate since regorafenib is unlikely to be less effective than placebo

As such, the number of events required for final analysis were 144 events, which corresponds to 81 events within the regorafenib group of 133 patients (61%) and 63 events in the placebo group of 66 patients (95%).

Bayer also include the following assumptions of (i) exponential distribution of the PFS event times, (ii) median time of PFS in the control group of [redacted] and [redacted] drop-out rate of patients evaluable for PFS. (Source Bayer submission, Section 4.4, p77)

Missing data

The methods used for handling missing data were as follows: (Source: Bayer submission, Section 4.4, pp 77-78)

> *Missing or not evaluable tumour assessments […] were not used in the calculation of derived efficacy variables unless a new lesion occurred, or the lesions that were evaluated already showed progressive disease (PD). No imputation was performed for missing lesion assessment and tumour response. For example, if a patient missed a scan visit and PD was documented at the next available scan visit, the actual visit date of the first documented PD was used.[…]*

The ERG considers this approach acceptable

4.2.1.3.3 Primary, secondary and tertiary outcomes

Primary outcome – progression-free survival

A stratified log rank test (by prior therapies and geographical region) with a one-sided alpha of 0.01 was used to compare PFS of regorafebin vs. placebo.

Median times to PFS were estimated using the Kaplan-Meier method. Hazard ratios (HR) and 95% confidence intervals (CI) were derived from a Cox proportional hazard model.

Preplanned subgroups for PFS were: (Bayer submission, Section 4.4, p81)

- Line of treaments: 3rd line, 4th line and beyond
- Geographical region,
- Age: <65 years, ≥65 years
- Sex,
- ECOG performance status 0, 1

- Baseline body mass index (BMI) (kgm^{-2}):<25, 25≤BMI<30, 30≤BMI
- Duration of imatinib treatment (months): <6, ≥6<18, ≥18
- Mutational status: initial KIT Exon 11 mutation, initial KIT Exon 9 mutation

Sensitivity analysis included the number of PFS events originally planned in the protocol (no. of events=122), unstratified PFS analyses and PFS analysis according to the assessment of local investigators.

Secondary PFS, assessed during open label treatment, was considered a tertiary outcome.

Secondary outcomes – overall survival

The methods used for TTP and OS analysis were as for PFS. The Cochran-Mantel-Haenszel test was employed for ORR and DCR, whereas DOR received a descriptive analysis. The methods used for adjusting for crossover from placebo to open-label regorafenib are described below: (Source: Bayer submission, Section 4.4, p80)

> *A pre-planned interim analysis of overall survival was done at the time of the final PFS analysis… An updated analysis of OS, was performed as of the cut-off date of 08 June 2015, when approximately 160 deaths had occurred. For the updated analysis of OS, a secondary analysis was performed which applies the Rank Preserving Structural Failure Time (RPSFT) method and the Iterative Parameter Estimate (IPE) method to correct for the effect of cross-over of patients from the placebo treatment to regorafenib treatment on the OS endpoint.*

These methods of adjustment are discussed in more detail in Section 5.3.6.2, p79. However, in our opinion, both the IPE and RPSFT are reasonable candidate adjustment methods.

Tertiary outcomes

Data on HRQoL were obtained via the EORTC QLQ-C30 and EuroQol EQ 5D assessment tools and analysed as described by Bayer: (Source: Bayer submission, Section 4.4, p80)

> *…using an analysis of covariance (ANCOVA) model, comparing the time-adjusted AUCs between the two treatment groups with covariates for baseline HRQoL score and stratification factors. Least-squares mean estimates, standard errors, and 95% confidence intervals (CI) were estimated for each treatment group and for the treatment group difference.*

Exploration of covariates was performed using linear mixed effects models and sensitivity analysis assessed via various imputation methods for missing data.

Descriptive analysis was performed on safety parameters and exploratory endpoints.

Subgroup analysis for OS was as for PFS, with the exception of mutational status. This analysis was also adjusted for crossover using the RPSFT and IPE method (see 5.3.6.2, p79).

Overall, the ERG agrees the statistical analysis were appropriate.

4.2.2 Results

4.2.2.1 Population distribution

Of 199 people recruited, 133 were randomised to receive regorafenib+BSC and 66 to placebo+BSC.

The number of participants evaluable for each of the different populations (ITT, safety and patient reported outcomes), are presented in Table 10.

Table 10. Population distribution for analysis

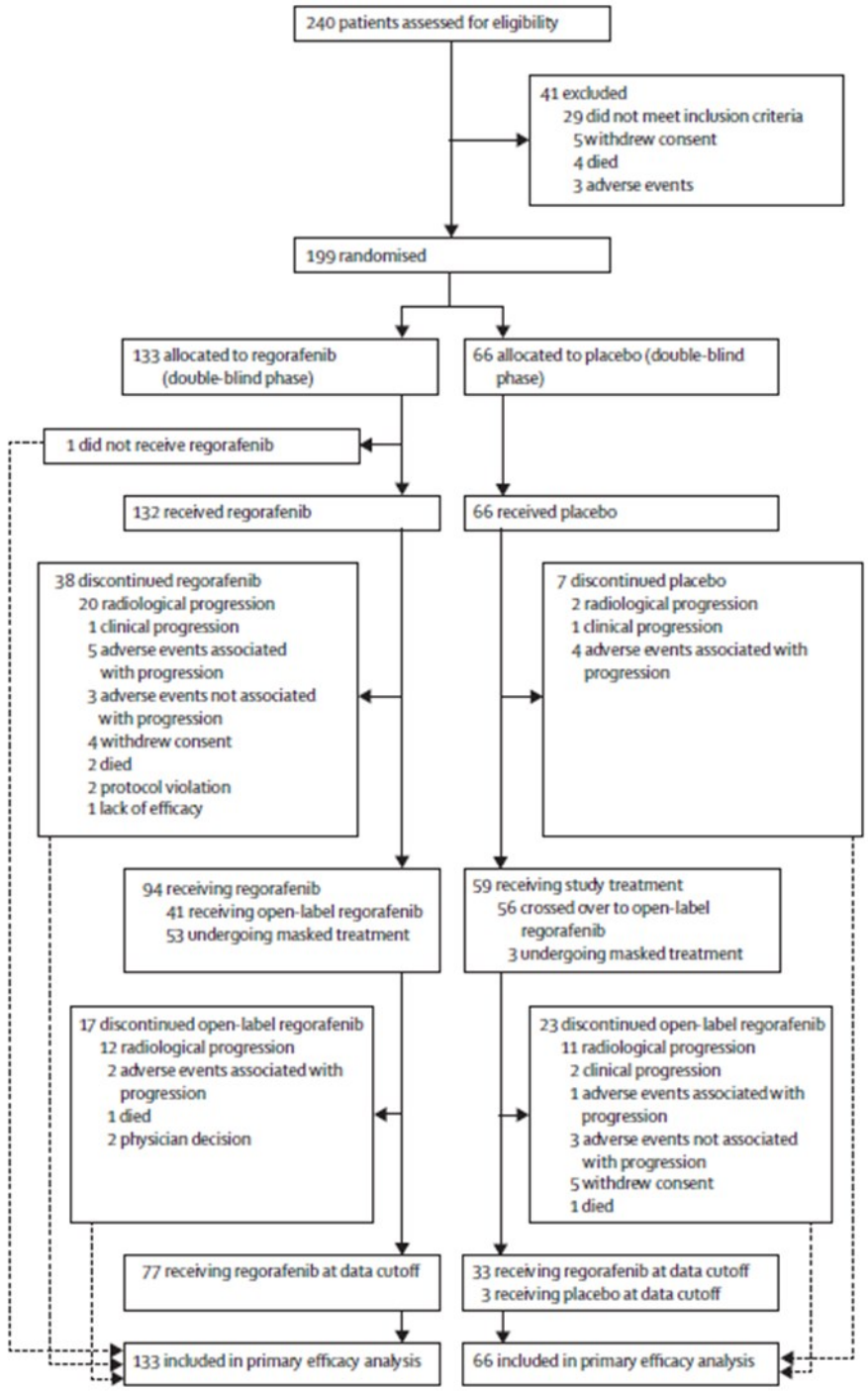
Analysis population	Regorafenib+BSC (n=133)	Placebo+BSC (n=66)
ITT	133 (100%)	66 (100%)
Safety[a]	132 (99.2%)	66 (100%)
Patient Reported Outcomes	123 (92.5%)	62 (93.9%)

Key: ITT, intent-to-treat
Notes: a, One patient in the regorafenib group was not treated with study drug
Source: Bayer submission, Section 4.4, p. 75

4.2.2.2 Participant flow

The participant flow is displayed in Figure 4.

Figure 4. CONSORT diagram for GRID study



Source: Bayer submission, section 4.5, Figure 4, p83

Participants assigned to the regorafenib arm were offered open label regorafenib on progression, if considered appropriate (n=41). For participants receiving placebo, 56 crossed over to regorafenib on experiencing disease progression (follow-up every 6 weeks).

[redacted]

[redacted]The most common reason for termination of study treatment was radiologically confirmed disease progression.

However, the overall treatment duration for the double-blind period for those on regorafenib was a median of 22.9 weeks and a mean of 20.2 weeks. For placebo, the median was only 7.0 weeks and mean 9.1 weeks, hence the difference in patient withdrawal between arms.

4.2.2.3 Baseline characteristics and demographics

Baseline characteristics of the ITT population are summarised in Table 57 (Appendix 1). The demographic characteristics are generally well balanced between those randomised to the regorafenib and placebo groups.

The median age was 60 (range 51-67) and 61 (range 48-66) for regorafenib and placebo, respectively. The proportion of men to women in both groups was 64%:36%.

There was a slight imbalance where 67% of participants receiving regorafinib and 83% receiving placebo had >18 months of previous imatinib therapy.

4.2.2.4 Clinical effectiveness results

The results in the company submission are as of 26 Jan 2012, however, OS was analysed as of 8 June 2015, when approximately 160 deaths had occurred. Following a request to the company, we received updated analyses for OS in 2017, however, at the time no CSR was available to confirm results.

4.2.2.4.1 Primary efficacy analysis – progression-free survival

Progression-free survival is presented in Table 11 and Figure 5 for blinded review:

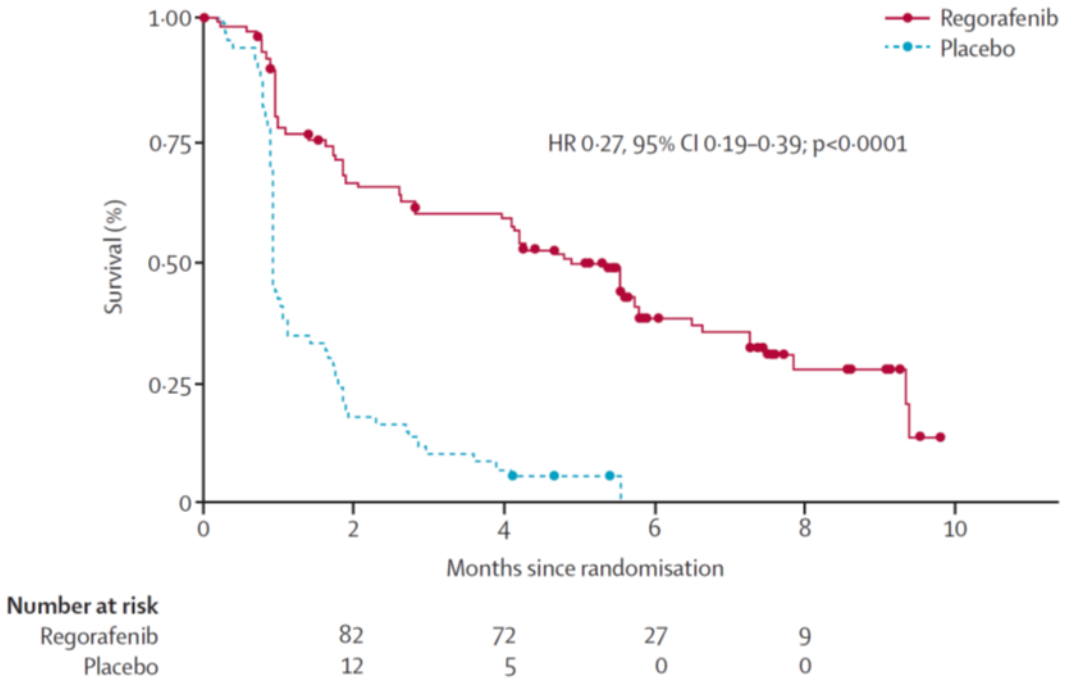
Table 11. Summary of progression-free survival analysis for ITT population

	Regorafenib+BSC (n=133)	Placebo+BSC (n=66)
Blinded review, median PFS, months (IQR)	4.8 (1.4-9.2)	0.9 (0.9-1.8)
Investigator assessment, median PFS, months (IQR)	7.4 (2.7-not calculable)	1.7 (0.9-2.7)
Median PFS, months (IQR		
Blinded review, hazard ratio (95% CI; p value)	0.27 (0.19-0.39; p<0.000001)	
Investigator assessment, hazard ratio (95% CI; p value)	0.22 (0.14-0.35; p<0.0001)	
3 month PFS rate, % (95% CI)	60 (51-68)	11 (3-18)

6 month PFS rate, % (95% CI)	38 (29-48)	0 (0-0)
After 144 events, as specified in the protocol, n (%)	81 (60.9)	63 (95.5)

Source: Bayer submission, Section 4.7, p90

Figure 5. KM estimates of the PFS rate (144 events) during the GRID trial, (central assessment, ITT)



Source: Bayer submission, Section 4.7, p95

The study met the protocol-defined primary endpoint of a one-sided alpha of 0.01. Overall, the results indicate a median PFS for blinded review which is higher in the regorafenib arm than placebo (4.8 months [95% CI: 1.4, 9.2] versus 0.9 months [95% CI: 0.9, 1.8], respectively; HR = 0.27; p <0.000001).

The company state that the sensitivity analyses also showed a statistically significant difference and were consistent with the primary analyses. As with the blinded independent review, the investigator's assessment produced a statistically significant result for PFS in favour of regorafenib. However, the ERG have been unable to locate and verify these results.

4.2.2.4.2 Secondary efficacy analysis

Overall survival

Analysis for OS is displayed in Table 12 and Figure 6 which is unadjusted for crossover (database cut-off 08 June 2015).

Table 12. Summary of overall survival analysis with stratification for ITT population unadjusted for crossover

	Regorafenib+BSC (n=133)	Placebo+BSC (n=66)	Regorafenib+BSC (n=133)	Placebo+BSC (n=66)
	2015 cut-off		2017 cut-off	
Median OS, months	17.4	17.4		
Blinded assessment hazard ratio (95% CI)	0.909 (0.653-1.265)		[redacted]	
Investigator assessment, hazard ratio (95% CI; p value)	0.22 (0.14-0.35; p<0.0001)			
No. events at data cut off 08 June 2015, n (%)	109 (82.0)	53 (80.3)		

Source: Bayer submission, Section 4.7, p91

Figure 6. KM estimates of OS during the GRID trial, (central assessment, ITT; data cut-off June 2015)

[redacted]

Source: Bayer submission, Section 4.7, p96

For the unadjusted analysis, regorafenib shows no benefit for overall survival. However, this includes 56 participants from the placebo arm, who following progression, were allowed to cross over to open-label regorafenib. Therefore, adjustments were performed by the company as shown in Table 13 and Figure 7 to Figure 9. Table 13 and Figure 9 also contain data for the 2017 cut-off.

Table 13. Summary of overall survival analyses with corrected cross-over analyses with stratification

	Data cut-off 2012		Data cut-off 2015		Data cut-off 2017	
	Regorafenib (n=133)	**Placebo (n=66)**	**Regorafenib (n=133)**	**Placebo (n=66)**	**Regorafenib (n=133)**	**Placebo (n=66)**
Median OS, months	NA	NA	17.4	11.9[a], 11.1[b]		
Blinded assessment hazard ratio corrected RPSFT (95% CI)[a]	0.537 (0.286-1.007) p-value 0.024725		0.616 (0.435-0.871; p-value 0.002862)		[redacted] p-value 0.000011[e]	
Blinded assessment hazard ratio corrected IPE (95% CI)[b]	0.565 (0.302-1.055) p-value 0.034931		0.586 (0.417-0.824) p-value 0.000949		[redacted] p-value 0.0000022)[e]	
Number of patients with event, n (%)	29 (21.8%)	17 (25.8%)	[redacted]	[redacted]		
Number of patients censored, n (%)	104 (78.2%)	49 (74.2%)	[redacted]	[redacted]		

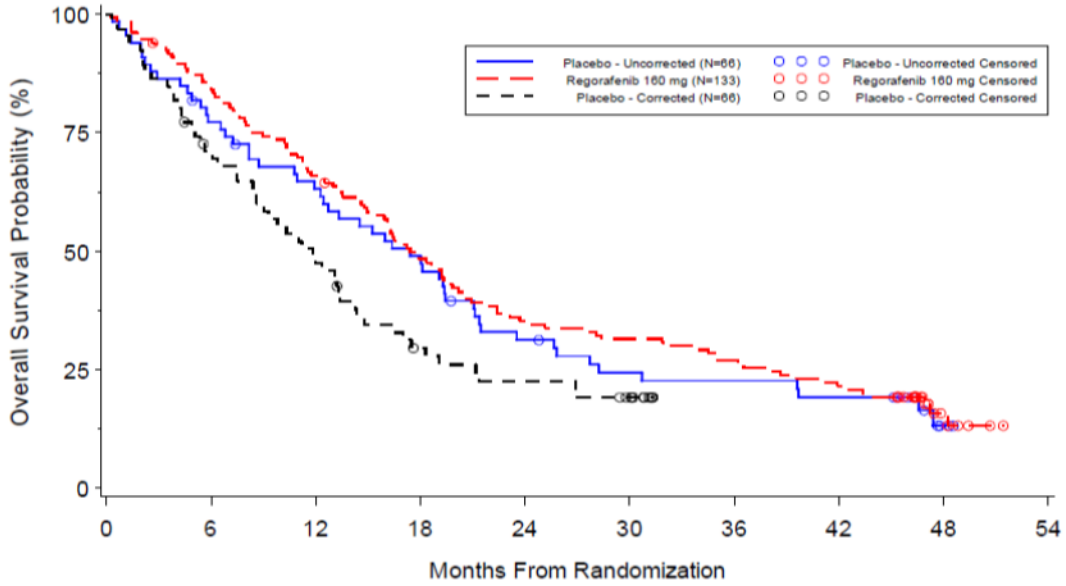
Key: BSC, best supportive care; CI, confidence interval; IPE, iterative parameter estimation; ITT, intention-to-treat; NA, Value cannot be estimated due to censored data; RPSFT, rank preserving structural failure time.

Notes: a, Corrected for the effect of cross-over from the placebo to the regorafenib arm on the OS endpoint by RPSFT method; b, Corrected for the effect of cross-over from the placebo to the regorafenib arm on the OS endpoint by IPE method; c, Using the RPSFT cross-over correction method, the number (%) of patients with an event in the placebo group is 51 (77.3%); d, Using the RPSFT cross-over correction method, the number (%) of patients censored in the placebo group is 15 (22.7%); e,

taken from additional data for stratified analysis supplied by Bayer in response to clarification questions

Source: Bayer submission, section 4.7, p92.

Figure 7. Overall Survival, cross-over correction by RPSFT method (ITT; data cut-off 08 June 2015)

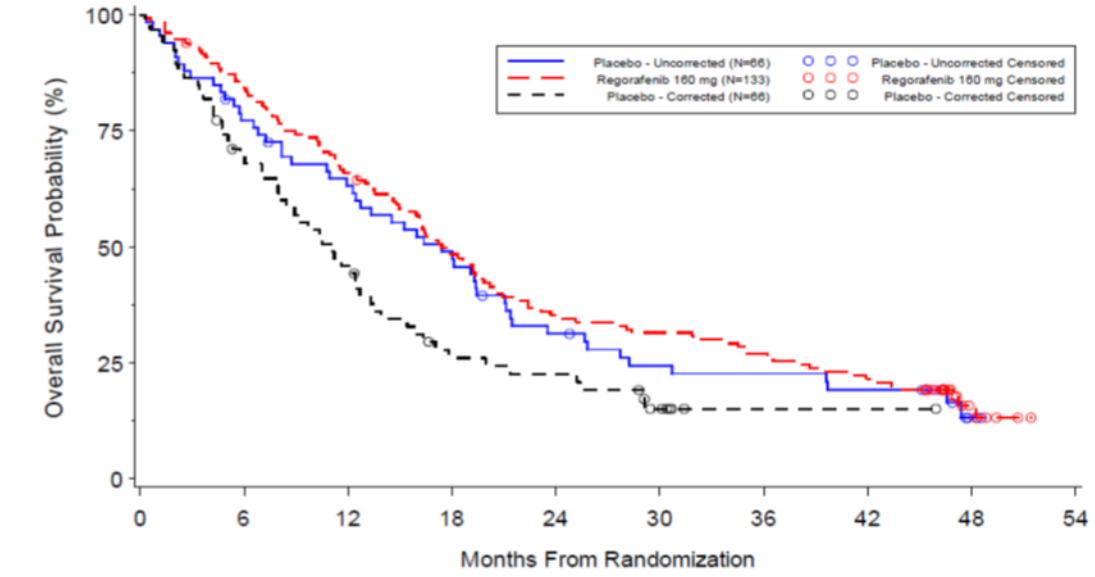


Patients at Risk

Placebo – Uncorrected	50	40	31	19	14	13	11	2
Regorafenib 160 mg	111	87	63	46	41	35	28	6
Placebo – Corrected	45	31	17	13	9	0	0	0

Source: Bayer submission, Section 4.7, p96

Figure 8. Overall Survival, cross-over correction by IPE method (ITT; data cut-off 08 June 2015)



Patients at Risk

Placebo – Uncorrected	50	40	31	19	14	13	11	2
Regorafenib 160 mg	111	87	63	46	41	35	28	6
Placebo – Corrected	44	29	15	13	6	1	1	0

Source: Bayer submission, Section 4.7, p97

Figure 9. Overall Survival, cross-over correction by IPE method (ITT; comparison of 2015 and 2017 data)

Source: Bayer submission, response to clarification

Following adjustment for crossover, both the 2015 and 2017 data, indicate a statistically significant difference in overall survival favouring regorafenib (median OS 17.4 months) over placebo (median OS 11.9 months using RPSFT method or 11.1 months using IPE method).

Time to progression

For the cut-off date of 26th January 2012, 57.1% of participants in the regorafenib group experienced disease progression and 93.9% in the placebo group. Median TTP was reported as 165 days in the regorafenib group and 28 days in the placebo group (HR 0.248, [95% CI: 0.170-0.364, p<0.000001]). Therefore, there is a statistically significant difference between arms, in favour of regorafenib for TTP.

Objective Response Rate, Disease Control Rate and Duration of Response

For ORR, although numerically in favour of regorafenib, there was no statistically significant difference between the two arms: 4.5% with regorafenib (PR n = 6/133) vs. 1.5% with placebo (PR n = 1/66) and there were no cases reported of complete response [redacted]

The disease control rate (DCR) reflects the percentage of patients with metastatic cancer who have achieved complete response, partial response and stable disease, as opposed to ORR which only includes CR or PR. Stable disease was reported by the company to be 71.4% (95/133 patients) in the regorafenib arm as compared to 33.3% (22/66 patients) in the placebo arm. Therefore, DCR for the regorafenib group was 52.6% (n=70/133) compared with 9.1% (n=6/66) in the placebo group (95% CI: –54.72, –32.49; p<0.0001). Bayer suggest this outcome indicates the clinically meaningful tumour control of regorafenib as a third-line treatment in patients with advanced GIST.

With regard to median duration of response, only one patient in the placebo group reported PR, which was 30 days, whereas the median duration of response for patients receiving regorafenib was 99 days.

Maximum percent reduction in the size of target lesions

[redacted]

4.2.2.4.3 Exploratory endpoints

Secondary PFS (SPFS)

Bayer investigated secondary PFS for participants who crossed over from placebo to regorafenib (n=56; 151 days) and for participants who continued on open label regorafenib,

following progression during the masked period (n=41; 137 days) (Figure 10). Therefore, the company suggest that regorafenib may delay subsequent progression.

Figure 10. KM curves of PFS during treatment with regorafenib by double blind and open label treatment groups

Source: Bayer submission, Section 4.7, p98

Patient reported outcomes

Analysis of HRQoL via the EORTC QLQ-C30 and the EQ5D revealed no statistically significant difference between regorafenib and placebo. Mean changes from baseline were not clinically meaningful (defined as ≤10 points), except for the role function subscale in the regorafenib group.

Mean changes in scores from baseline for EQ-5D index reflected a deterioration in health status for both groups. However, the results for the EQ-VAS appear more variable, with a change from baseline indicating a general reduction in health status for the regorafenib group, but an improvement for the placebo group. However, the company report that analysis of time-adjusted AUC for the EQ-5D index and VAS showed that regorafenib treatment maintained patients' health-related quality of life.

No statistically significant difference in HRQoL was noted in regorafenib-treated patients with dose reduction vs. no dose modification.

Mutational analyses

Mutation data were available for 48% of patients in the GRID study (53% KIT Exon 11; 16% KIT Exon 9; 8% no KIT and no PDGFR mutation).

The company report that both exon 9 mutant and exon 11 mutant subgroups have improved PFS on regorafenib compared to placebo, although this appears to be comparable to the results for the ITT population overall (Table 11):

- KIT Exon 11 (HR of 0.21; 95% CI: 0.10, 0.46)
- KIT Exon 9 (HR of 0.24; 95% CI: 0.07, 0.88)

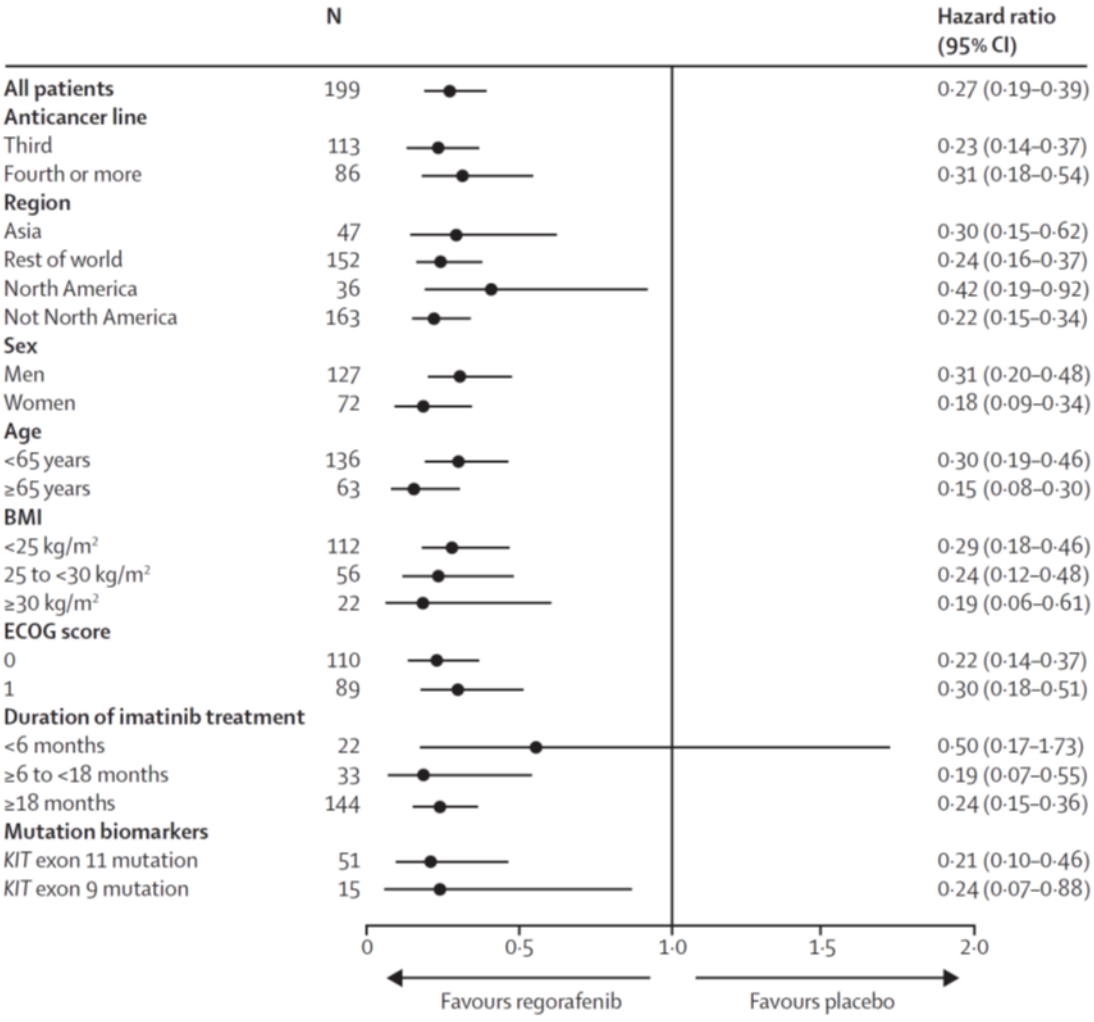
The benefit for other mutations is not reported.

4.2.2.4.4 Subgroup analysis

Progression-free survival

Pre-planned subgroup analysis was performed for PFS as displayed in Figure 11.

Figure 11. Progression-free survival by subgroup



Key: BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group
Source: Bayer submission, Section 4.8, p103

The majority of subgroups in Figure 11 show a statistically significant benefit in PFS for regorafenib. There is little heterogeneity, with similar HRs and generally narrow confidence intervals. The group where this is not the case is for the population who received imatinib for less than 6 months. Bayer suggest this is due to the small sample size of 22.

At the request of some health authorities, Bayer also report:

- there was no correlation between hypertension and length PFS,
- low patient numbers meant conclusions could be drawn on mitotic index and PFS,.
- median PFS times in patients in the regorafenib group who had dose modifications were similar to those in the overall primary analysis .

Overall survival

The subgroup analysis for OS was performed uncorrected and corrected for the effect of crossover using the RPSFT model and the IPE method.

The uncorrected analysis in Figure 12 includes 58 (87.9%) of patients in the placebo + BSC group crossed over to regorafenib treatment. The HRs for most subgroups are close to one, with broad intervals, indicating no statistically significant difference in OS between the two arms. However, as noted by the company, these results should be interpreted with caution due to the low number of events in some subgroups.

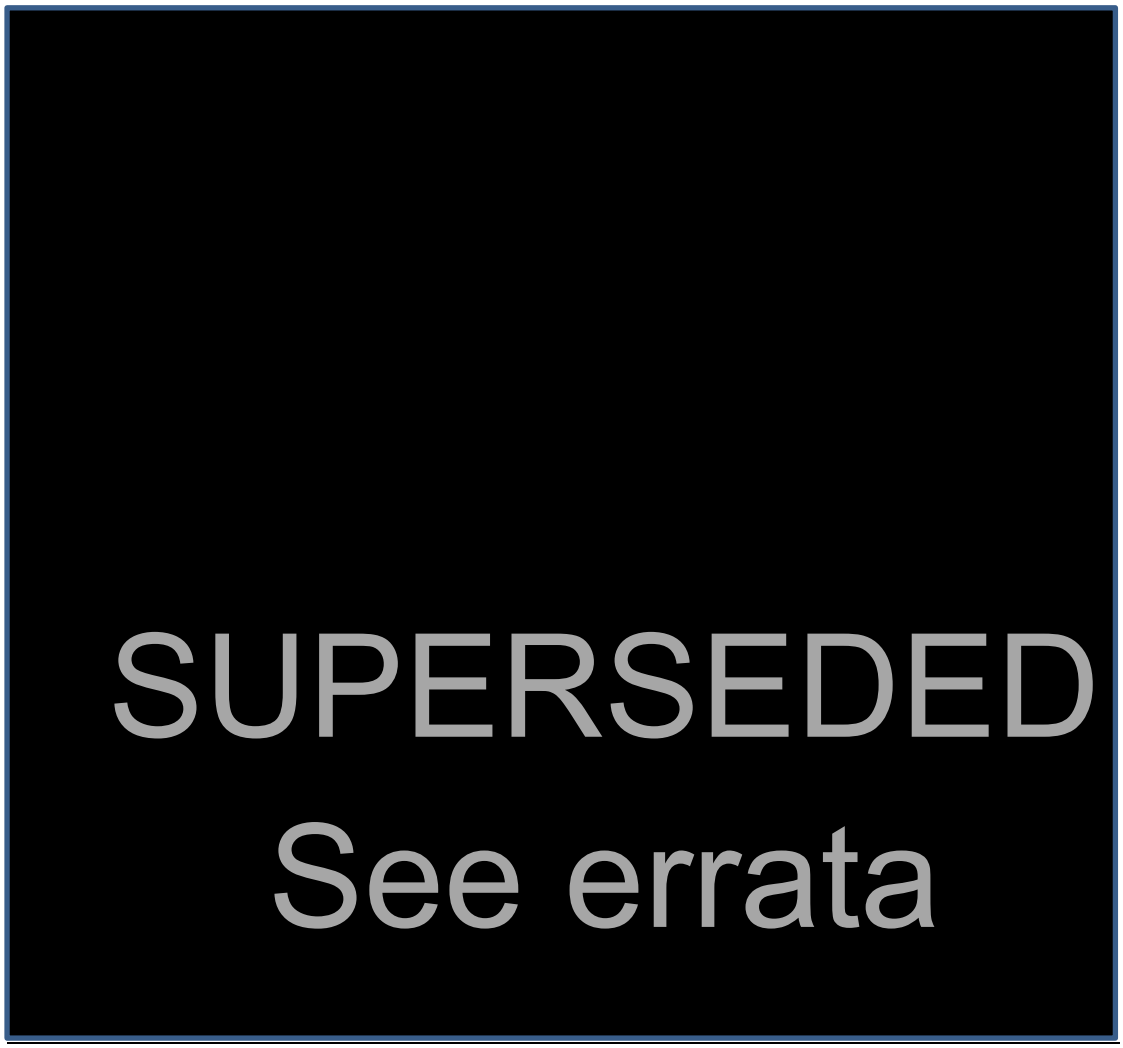
Figure 12. OS with regorafenib by double blind and open label treatment groups

Source: Bayer submission, Section 4.8, p106

Figure 13. Overall survival by subgroup, RPSFT correction (data cut-off 08 June 2015)

Source: Bayer submission, Section 4.8, p107

Figure 14. Overall survival by subgroup, IPE correction (data cut-off 08 June 2015)



Source: Bayer submission, Section 4.8, p108

4.2.2.4.5 Adverse events

The GRID study included 198 participants in the safety population, which included 162 in the regorafenib arm and 66 participants in the placebo arm who received at least one dose of regorafenib. The analysis included treatment-emergent adverse events (TEAEs) occurring up to the primary efficacy analysis cut-off date of 26th January 2012.

Secondary analyses included patients who crossed over to regorafenib from placebo (n=132+58) and a subgroup of patients who received regorafenib for over 1 year (n=75).

A summary for all grade adverse events (AEs) is presented in Table 14 which reports the incidences of AEs for > 10 % of people in any treatment arm. The main groups are included, with further detail on individual conditions provided in Appendix 2.

Table 14. Summary of all grade adverse events

	Double-blind treatment (data cut-off 26 January 2012)		Data cut-off 08 June 2015	
	Regorafenib + BSC	Placebo + BSC	Regorafenib-treated at any time during study	Subgroup treated with regorafenib for >1 year
	N=132 n (%)	N=66 n (%)	N=190 n (%)	N=75 n (%)
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Blood and Lymphatics				
Cardiac				
Ear and Labyrinth				
Endocrine				
Gastrointestinal				
General and Administrative Site Conditions				
Hepatobiliary disorders				
Infection and Infestations				
Injury, poisoning and procedural complications				
Investigations				
Metabolism and Nutrition				
Musculoskeletal and Connective Tissue				
Nervous System				
Psychiatric disorders				
Insomnia				
Renal and urinary				
Reproductive system and breast disorders				
Respiratory, Thoracic and Mediastinal				
Skin and subcutaneous tissue				
Vascular				

Key: BSC; Best supportive care; TEAE; Treatment-emergent adverse event; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0; A patient may have experienced more than one TEAE.

Source: Bayer submission, Section 4.12, p122

In the double-blind study phase, drug-related adverse events were reported by Bayer to be 130 (98%) patients in the regorafenib group and 45 (68%) patients in the placebo group. The most common drug-related AEs were PPES (HFSR), hypertension, fatigue, diarrhoea, and oral mucositis.

Adverse Events of Special Interest

Bayer comment that the toxicity profile of regorafenib is typical for molecule of its type and that as such, events including hypertension, skin (hand-foot syndrome, rash) and gastrointestinal toxicities (diarrhoea, mucositis) are not unexpected. Table 15 displays specific adverse events of interest with regard to regorafenib treatment.

Table 15. Adverse events of special interest during the GRID trial

	Double-blind treatment (data cut-off 26 January 2012)		Data cut-off 08 June 2015	
	Regorafenib + BSC	Placebo + BSC	Regorafenib-treated at any time during study	Subgroup treated with regorafenib for >1 year
	N=132 n (%)	N=66 n (%)	N=190 n (%)	N=75 n (%)
Cardiac	[redacted]	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders			[redacted]	[redacted]
Alanine aminotransferase increased (ALT)			[redacted]	[redacted]
Aspartate aminotransferase increased (AST)			[redacted]	[redacted]
Blood bilirubin increased			[redacted]	[redacted]
Proteinuria			[redacted]	[redacted]
Palmar-Plantar Erythrodysaesthesia Syndrome	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Bleeding events			[redacted]	

Source: Bayer submission, Section 4.12, p123

Clearly, the most common adverse event was [redacted]

Serious adverse events

During the double-blind phase, 38 (29%) serious adverse events were reported in the regorafenib group and 14 (21%) in the placebo group. The company report the most common SAEs to be [redacted]

Laboratory parameters

The majority of laboratory abnormalities were grade 1–2, the most common being anaemia for regorafenib-treated patients (144 [77.0%] patients, hyperglycaemia (93.0%), AST increased (67.6%), hypertriglyceridaemia (63.3%), hypoalbuminaemia (62.0%), hypophosphatemia (61.2%), alkaline phosphatase increased (57.4%), and ALT increased (48.9%).

Adverse events leading to withdrawal

Bayer report the following withdrawals due to adverse events during the double-blind phase of the study: (Source, Bayer submission, Section 4.12, p126):

9 patients discontinued due to an AE in the regorafenib-treated group (6.1%) versus 5 patients in the placebo group (7.6%).
[redacted]

Deaths

Bayer report 5 deaths considered to be due to regorafenib (cardiac arrest, acute hepatic failure, acute kidney injury, colonic perforation, and thromboembolic event). Of the patients treated with regorafenib,
[redacted]

Long term safety

With regard to long term safety, Bayer report that: (Source: Bayer submission, section 4.12, p126)

The safety profile of patients on long-term regorafenib treatment (> 1 year; n=75) was comparable with the safety profile of the overall patient population...
[redacted]
….
[redacted]
For hypothyroidism, the decreasing but not completely absent event rates over time emphasise the label-defined regular monitoring recommendation of thyroid function during regorafenib treatment.

Of note, long-term responders showed around a [redacted] *incidence rate in drug-related grade 3 events as compared to the overall patient population, mainly due to respective increases in grade 3 PPES (HFSR) and hypertension rates. …Treatment discontinuation rates due to regorafenib-related events were comparable between long-term responders and overall patient population* [redacted]

4.2.3 Interpretation

Key efficacy findings from the RCT reported in the submission were as follows:

Progression free survival

Median PFS was more favourable for the regorafenib group than in the placebo group (4.8 months vs. 0.9 months; [HR] 0.27, 95% CI 0.19–0.39; p<0.0001).

The treatment effect of regorafenib was generally consistent across pre-specified subgroups. The company also report the effect is maintained following sensitivity analyses for PFS, however, the ERG have been unable to locate these results.

[redacted]

Overall survival

Prior to adjustment for crossover, median OS time was 529 days (17.4 months) in both treatment groups (HR = 0.909).

Following correction, median OS time was longer in the regorafenib group (529 days or 17.4 months) than in the placebo group (338 days or 11.1 months IPE [p = 0.00095]; 361 days or 11.9 months RPSFT [p = 0.00286]). The estimated corrected hazard ratio of regorafenib to placebo using the RPSFT and IPE correction methods were 0.616 and 0.586, respectively.

Secondary endpoints

Median time to progression (TTP) was significantly longer in the regorafenib arm than in the placebo arm (5.4 months [165 days] versus 0.9 months [28 days], HR 0.248, 95% CI 0.170–0.364; p<0.000001).

Although there was a numerical difference in overall response rate, this was not statistically significant (4.5% vs. 1.5% for the regorafenib and pllacebo group, respectively)

The disease control rate (DCR), which also includes stable disease, was significantly higher in the regorafenib group (52.6%) vs. the placebo group (9.1%) (one-sided p<0.000001).

Adverse events

Common adverse events included hand-foot skin reaction (HFSR), hypertension, diarrhoea, mucositis and fatigue. The most serious adverse drug reactions in patients receiving regorafenib were haemorrhage, severe liver injury, and gastrointestinal perforation. However, in general, treatment with regorafenib was not associated with a substantial reduction in patient reported quality of life compared to placebo

[redacted]

4.2.3.1 Strengths and limitations

Strengths

- Large, prospective, randomised, double-blind, placebo-controlled, multicentre trial.

- A majority of the recruited population were representative of the typical UK patient population
- Subgroup and sensitivity analyses indicate robust results

Limitations

- No ‘active’ comparator due to the lack of approved treatment options available to patients with metastatic or unresectable GIST after they have progressed on imatinib and sunitinib.
- Confounding by crossover of 58 (87.9%) patients from the placebo group to regorafenib treatment upon disease progression.Therefore, two correction methods were used.

5 Cost-effectiveness

5.1 History of Bayer's economic evaluation

So far, we have received a total of three versions of Bayer's economic model and cost-effectiveness results.

We received Bayer's economic model and full report on 21st March 2017.

On 25th April 2017, after an earlier request for clarification from us, we received a second version of Bayer's economic model and cost-effectiveness results. This included some updated OS data, as discussed in Section 5.3.6, p74.

On 16th May 2017, in response to another request for clarification from us, we received a third version of Bayer's economic model and cost-effectiveness results. In addition to the updated OS data, this also included some updated data on treatment duration of regorafenib as discussed in Section 5.3.8.1, p102.

5.2 ERG comment on company's review of cost-effectiveness evidence

5.2.1 Searches

The company conducted a systematic literature review (SLR) of economic and cost-effectiveness studies. The company conducted one primary search in a range of databases indexing published research for cost-effectiveness analyses for treating adults with unresectable and/or metastatic GIST, who have failed to respond to both sunitinib and imatininb. The initial search was from database inception to 21 December 2011, and was then updated 3 times: 21 December 2011 – July 2013, 21 July 2013 – 06 May 2016, and 06 – May to 19 December 2016.

The following electronic databases were searched: MEDLINE, MEDLINE (R) In-Process, EMBASE, EconLIT, and NHS EED. In addition, 3 major conferences were searched for relevant research: American Society of Clinical Oncology, European Society for Medical Oncology, and the International Society for Pharmacoeconomics and Outcomes Research.

5.2.2 Inclusion/exclusion criteria

The company developed a set of inclusion and exclusion criteria which were applied to the search results. The titles and abstracts were independently reviewed by two people and any disparity in decisions whether to include/exclude were reviewed by a third party. The inclusion/exclusion criteria presented by the company are shown below in Table 16.

Table 16. Inclusion/exclusion criteria for review of cost-effectiveness evidence

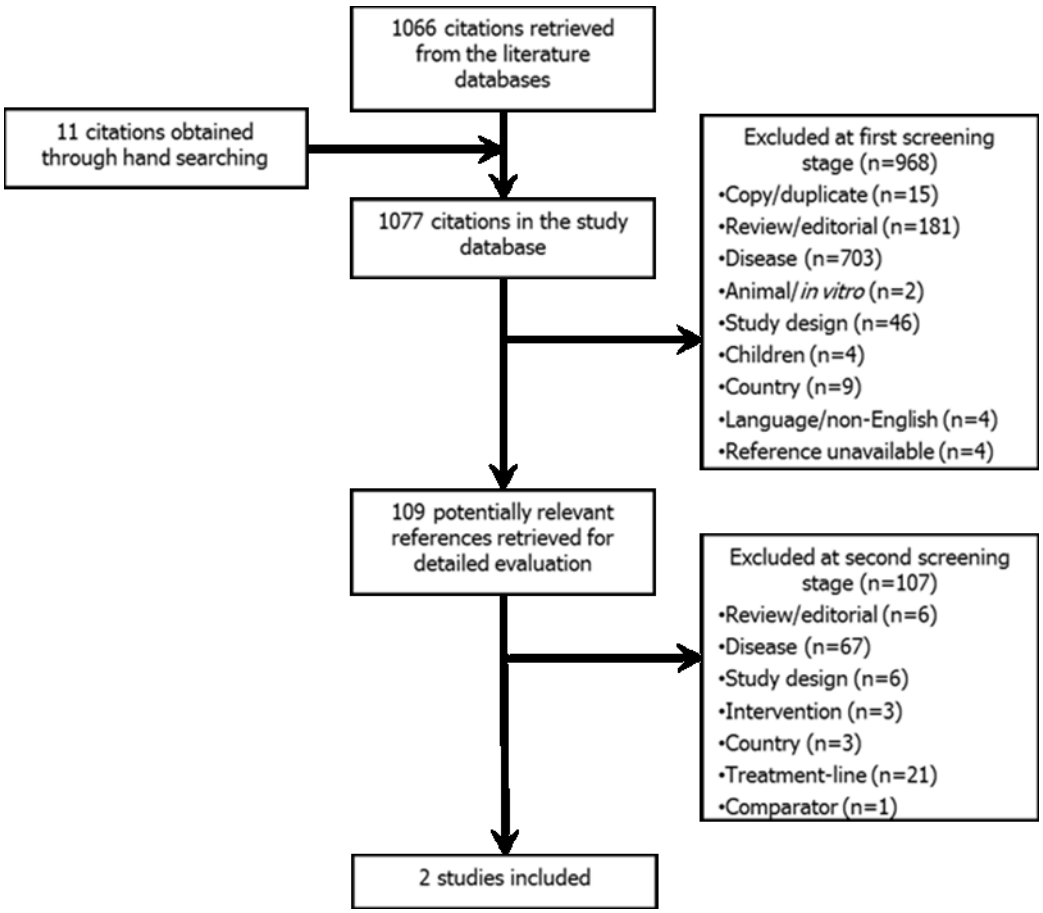
	Inclusion criteria	Exclusion criteria
Study design	Study design appropriate to report the cost of illness and/or resource use for GIST (cost studies analyses, database studies collecting cost or resource use data [including claims databases and hospital records], cross-sectional studies [including surveys] containing cost data, cohort studies containing cost data, longitudinal studies containing cost data, RCT containing piggy-back economic evaluation, cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses, cost-minimisation analyses, budget impact models, cost consequence studies)	Literature and systematic reviews Database studies or epidemiology studies, not collecting cost data RCTs (with no piggy-back economic evaluations) Studies published in non-English language (with/without English abstracts)
Patient population	Studies including adult patients (aged ≥18 years) Studies reporting data in countries of interest (US, Canada, Australia, France, Germany, Italy, Spain, UK, Brazil, Mexico, Japan, China, Korea)	Studies in children or adolescents Studies conducted in animals or in vitro
Disease/ therapy	Studies including patients with metastatic, advanced, and/or unresectable GIST, defined as such using the study author's definition Studies of third-line patients (who have failed two pharmacological therapies). However, as it is was anticipated that studies focused on third-line patients were rare, studies in first- and second-line patients were only excluded at the final stage of the second pass (at the first pass stage there was no exclusion based on therapy line)	Studies that did not include patients with a specific GIST diagnosis (including gastrointestinal leiomyosarcoma that appeared to behave as GIST, soft-tissue sarcoma that appeared to behave as GIST, oesophageal leiomyosarcoma, gastric leiomyoma, gastric leiomyoblastoma, small intestinal leiomyoma and leiomyosarcoma, colonic and rectal leiomyoma and eiomyosarcoma, gastrointestinal autonomic nerve tumour, eiomyoma and leiomyosarcoma of omentum and mesentery, retroperitoneal leiomyosarcoma)
Intervention	Regorafenib	Any other intervention
Comparator	Placebo/BSC	Any other comparator

Key: BSC, best supportive care

5.2.3 Results

Figure 15 shows the PRISMA flow diagram of the included economic studies.

Figure 15. PRISMA flow diagram of economic studies



Two studies were included. Sanz-Granda et al. (2015) is a study which is based in a Spanish healthcare setting, and the company deemed it to not be relevant for England and Wales.[14] Pitcher et al. (2016) is a UK based cost-utility analysis for the relevant patient population in

England.[15] This study utilised a partitioned survival model with 3 states; PFS, PPS, and death. A summary of the included studies is shown in Table 17 .

Table 17. Included studies in cost-effectiveness review

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Pitcher, 2016 (UK)[a]	2016	A partitioned survival model was used to model three health states: progression -free, progressed, and dead, over a lifetime horizon.	NA	QALYs using IPE crossover adjustment method: Regorafenib: 1.717 Placebo: 0.969 QALYs using RPSFT crossover adjustment method: Regorafenib: 1.717 Placebo: 1.080	Costs Using IPE crossover adjustment method Regorafenib: £36,258 Placebo: £10,513 Costs using RPSFT crossover adjustment method Regorafenib: £36,258 Placebo: £10,659	**ICERs per QALY gained: For IPE: £34,420 For RPSFT, £40,188**

Key: QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio
Notes: a, Results presented at ISPOR 19th Annual European Congress

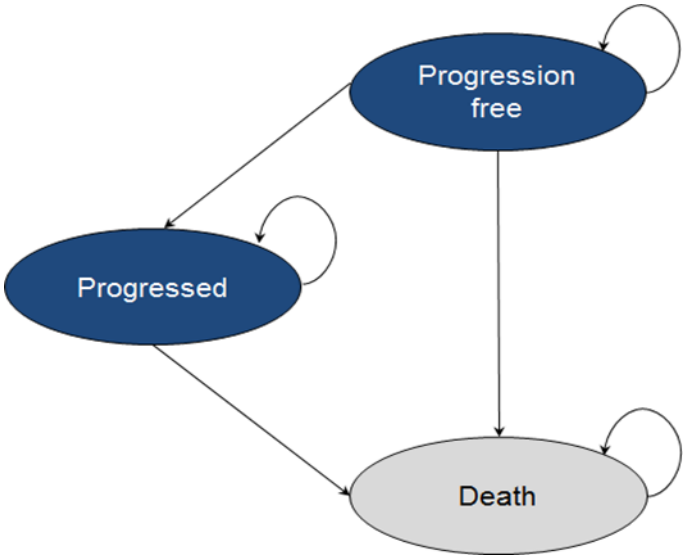
5.3 Summary and critique of company's submitted economic evaluation by the ERG

5.3.1 NICE reference case checklist

5.3.2 Model structure

Bayer submitted a partitioned survival model with three independent health states; PFS, PPS and death (Figure 16). Bayer argues that this structure is commonly used and best reflects the GRID trial as Kaplan-Meier curves for the health states can be used directly.

Figure 16. Bayer's partitioned survival model



Source: Bayer submission, Figure 15, p.147

- Patients start in the PFS state and can remain there, their disease can progress or they can die.
- Patients in the PPS health state can remain there or die.
- Death is the absorbing state.

Patients enter the model upon treatment commencing for either regorafenib or the comparator, BSC. The proportions of patients in each state are calculated as a function of time using parametric extrapolations due to the GRID trial exhibiting significant censoring for both PFS (due to patients dropping out of follow-up) and PPS. The parametric models were fitted to the Kaplan-Meier (K-M) curves from the trial to help inform extrapolation choice. The model uses a 28-day cycle length, corresponding to the proposed regorafenib treatment cycle of 3 weeks on daily treatment followed by 1 week off treatment. A half-cycle correction is applied.

Table 18 (reproduced from Bayer's report) gives a summary of some of Bayer's key modelling assumptions.

Table 18. Model assumptions

Assumption	Reason	Section
Health state assumptions		
Initially all patients begin in the progression free on treatment health state and are assigned progression free disease utility and costs of treatment while on therapy.	This is in line with trial	5.2.2
Patients discontinuing treatment prior to progression are not assigned a cost of active treatment and are assigned progression free utility and other routine costs. Patients can move to the death state based on the OS curve. As there are no cost or outcome implications, the placebo arm does not track patients between on treatment and off treatment states.	This is in line with trial	5.2.2
While in the progressed state, patients are assigned progression state disease utility and costs of disease management. In the progressed state, patients are not assigned costs of regorafenib treatment. Patients can only move from the progressed state to the death state.	Treatment with regorafenib should continue as long as benefit is observed or until unacceptable toxicity occurs	5.2.2
Other assumptions		
Time horizon of 40 years	This should be sufficiently long to capture all the lifetime benefits.	5.2.2
BSC as the only comparator	There are no approved treatments for patients in the given indication for regorafenib.	5.2.4
IPE crossover adjustment	Crossover causes significant bias in the effectiveness estimate if uncorrected. The IPE method provided the least bias for crossover adjustment.	

Log-logistic function used for long term extrapolation of OS	This provided the best statistical fit according to the AIC.	5.3.2
Same utilities used for each treatment arm	No statistically significant treatment effect was found between treatment arms in the utility analyses, therefore the same utilities were applied in both arms.	5.4.1
Resource use based on 2013 physician survey	Physicians were oncologists that had practiced in the area of GIST. The resource use assumptions were then re-evaluated by clinical experts in 2016, and changes to resource use assumptions were explored in scenario analyses.	5.4.1

Source: Bayer submission, Table 61, p.195

5.3.3 Population

The target population is comprised of adults with metastatic and/or unresectable GIST who were previously treated with at least imatinib and sunitinib. Patients enter the model at age 60, the median age from patients in the GRID trial (mean: 58.2 years).

Bayer did not identify any subgroups that would have clinically or economically relevant differences in benefit for regorafenib. We consider this appropriate.

5.3.4 Interventions and comparators

The intervention being investigated is once daily regorafenib at a recommended dosage of 160mg a day in addition to best supportive care (BSC) compared to BSC alone, the "placebo" (Source: Bayer submission, p. 149). Over a 4 week cycle, regorafenib is administered daily for the first 3 weeks, followed by a 1 week break. In the GRID trial, regorafenib could be continued by patients experiencing disease progression based on investigator opinion, and patients on the placebo could also cross over to regorafenib. Despite this, Bayer argue that in accordance with standard practice in England and Wales, regorafenib would only be given to patients whose disease had not progressed in actual practice (Source: Bayer submission, p. 150).

Bayer justify the comparator being solely BSC by referring to physician surveys in 2013 and 2016 in which they found no standard, approved or recommended treatment for patients who had already failed on imatinib and sunitinib. Our clinical expert confirmed that BSC is the sole relevant comparator

5.3.5 Perspective, time horizon and discounting

In the model, the perspective on costs was related to the NHS and Personal Social Services, and direct health effects on patients were considered, in accordance with the NICE reference case.

The time horizon used is 40 years, which Bayer argue is long enough to capture all expected lifetime benefits. In accordance with NICE reference case, benefits and costs are discounted at the standard 3.5 per cent rate. Health effects are measured in quality-adjusted life years (QALYs).

5.3.6 Treatment effectiveness and extrapolation

Treatment effectiveness was estimated using the GRID trial and post-hoc analyses on the data collected.

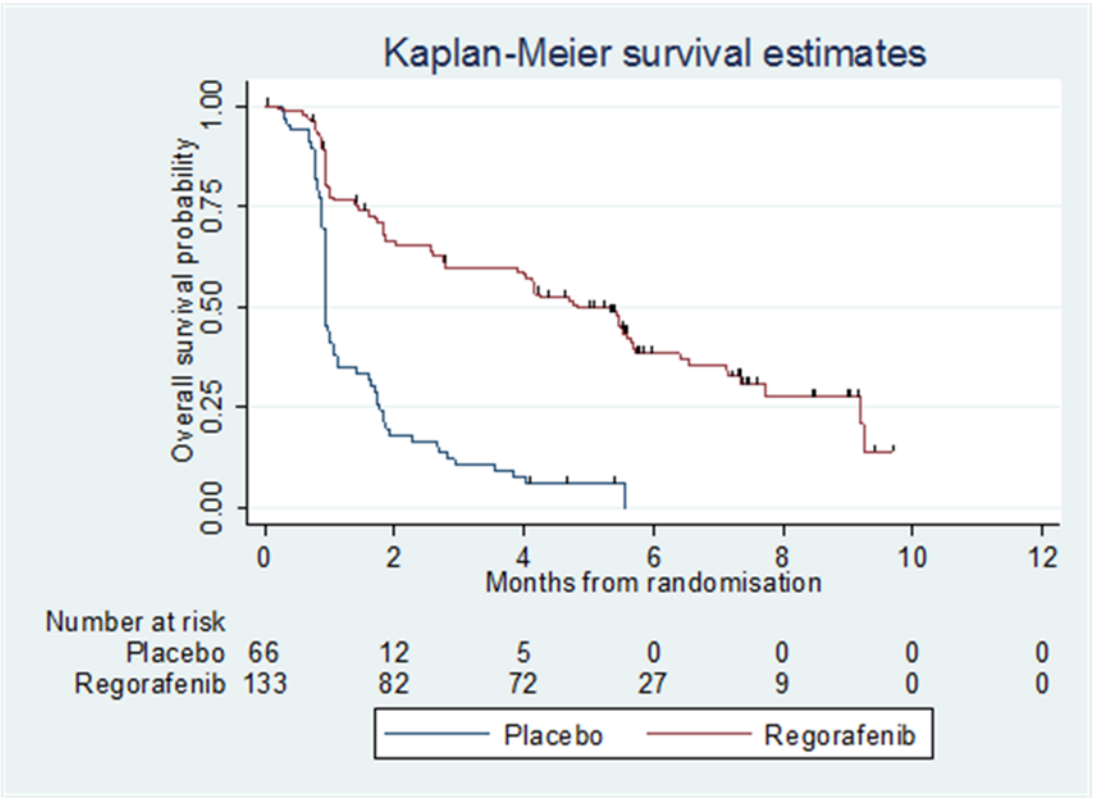
The economic model used the following clinical endpoints:

- Overall survival (OS), the time from entering the model to death from any cause;
- Progression free survival (PFS), the time from entering the model until disease progression (or directly dying);
- Post progression survival, the time from disease progression until death.

In their original report, Bayer presented OS data with a cut-off date of June 2015. In our clarification letter, we ask Bayer whether they could provide us with more mature data, given that the existing data is now about two years out of date, and that a reasonable amount of extrapolation is required. In response, on 25th April 2017, we received OS data from Bayer with cut-off in 2017. Bayer also included an updated version of their economic results.

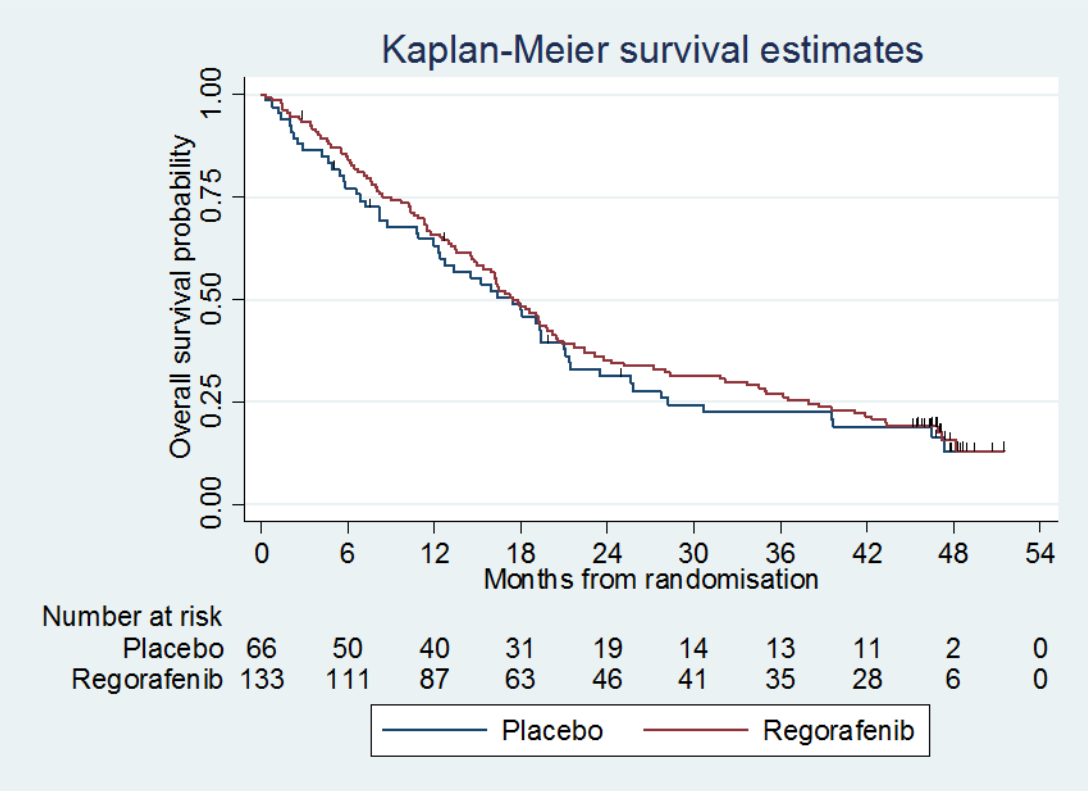
Extrapolation in the model is entirely parametric, as both OS and PFS data from the GRID trial exhibited significant censoring. Figure 17 and Figure 18 below show Kaplan-Meier data for PFS and OS respectively. Bayer have not updated their PFS Kaplan-Meier data, they still use the PFS cut off from back in 26th Jan 2012. This seems curious, because the PFS data is not fully run off. However, given that cost-effectiveness is far less sensitive to PFS than to OS or treatment duration, we pursue this matter no further.

Figure 17. K-M data for PFS in GRID*



Source: Bayer submission, Figure 16, p. 153
*Bayer's Y-axis should read "Progression-free survival".

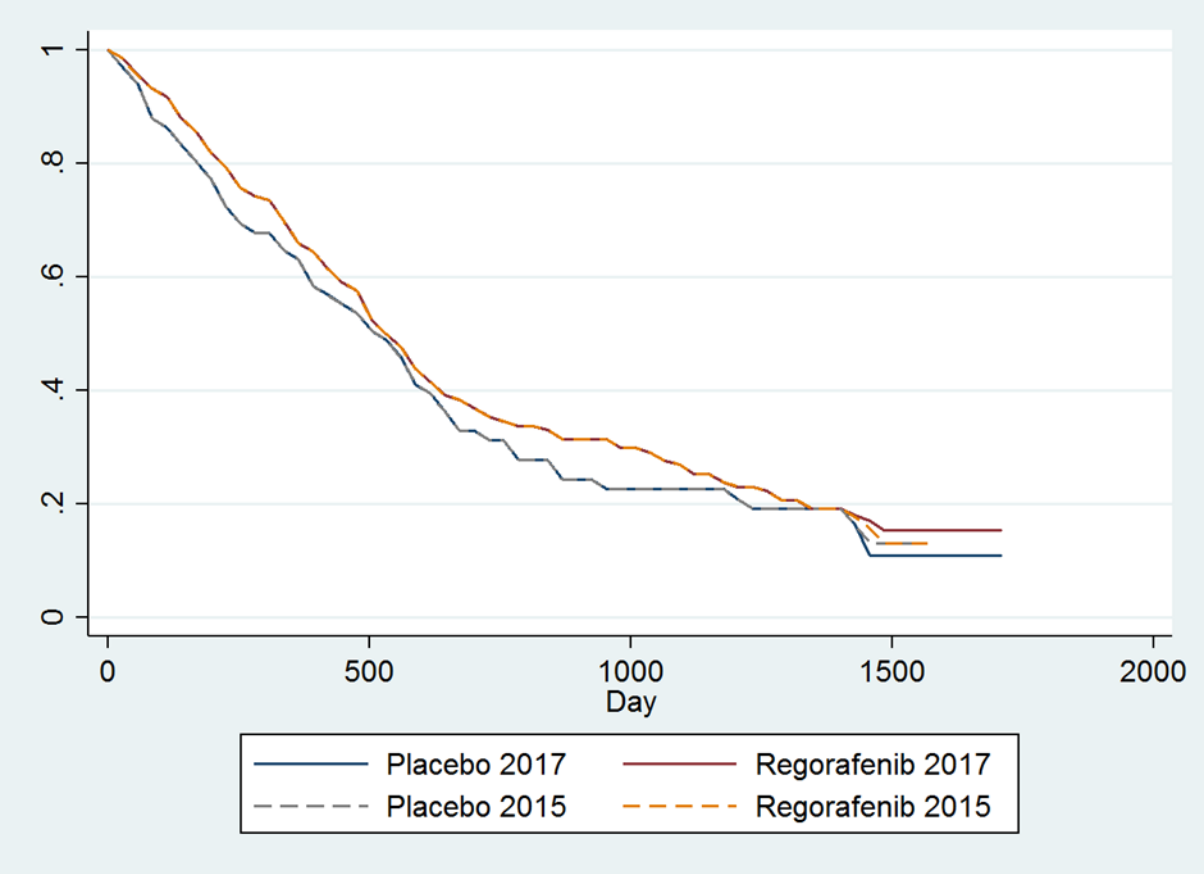
Figure 18. K-M data for OS in GRID (not adjusted for treatment switching)



Source: Bayer submission, Figure 17, p.154

Figure 19 demonstrates that the OS Kaplan Meier curve for the regorafenib arm changes only very slightly using the 2017 data, compared to the 2015 data. The OS is slightly more mature. Similar comments apply to the BSC arm.

Figure 19. Comparison of K-M OS curves not adjusted for treatment switching (2015 vs. 2017 data cut-off)



5.3.6.1 PFS extrapolation

To extrapolate PFS and OS, several parametric models were fitted to the existing GRID trial data:

- Exponential;
- Loglogistic;
- Weibull;
- Lognormal;
- Gompertz.

The parametric models were then assessed for quality of fit to the K-M data visually. Citing the uncertainty of this visual inspection, Bayer also statistically investigated the fits using the Akaike and Bayesian Information Criteria (AIC and BIC). These methods help determine the relative fit of the models by assessing the explanatory power of the model and penalising the number of parameters (to prevent over-fitting), with a lower AIC/BIC value being better. Table 19. AICs and BICs for PFS extrapolation below shows Bayer's AIC and BIC values for

the placebo and intervention for the PFS parametric models, the numbers in bold showing the lowest combined AICs/BICs.

The reason that the AICs/BICs are summed for the two treatments arms is that different parametric models have shapes, which Bayer argue should be avoided (Source: Bayer submission, p.157). Summing the AICs/BICs then gives a single "best" choice for both arms. Bayer therefore chose the lognormal model in the base case and the fit is shown in Figure 20.

We find that the cost-effectiveness of regorafenib is rather insensitive to the choice of distribution function. For example, assuming the shorter-tailed Weibull, Bayer's base ICER assuming the PAS increases only slightly, from £37,900 to £38,800 per QALY.

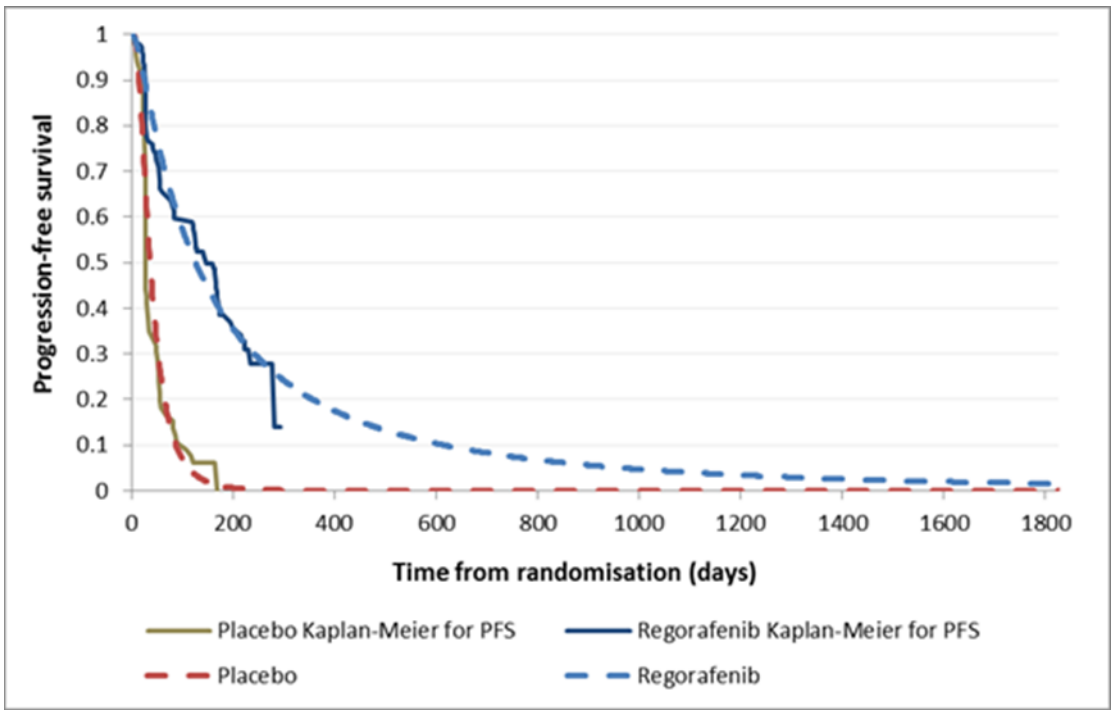
Given this, we accept Bayer's choice of base case, and consider this matter no further.

Table 19. AICs and BICs for PFS extrapolation

Parametric Model	AIC			BIC		
	Placebo	Regorafenib	SUM AIC	Placebo	Regorafenib	SUM BIC
Exponential	170.886	349.477	520.363	173.078	352.368	525.446
Loglogistic	139.045	348.561	487.605	143.424	354.341	497.765
Weibull	162.487	350.95	513.437	162.487	356.731	519.218
Lognormal	142.055	343.396	**485.45**	146.434	349.177	**495.611**
Gompertz	172.009	351.475	523.484	176.388	357.255	533.643

Source: Bayer submission, Figure 31, p. 157

Figure 20. Lognormal model (base case) for PFS compared to GRID PFS K-M data



Source: Bayer submission, Figure 20, p. 158

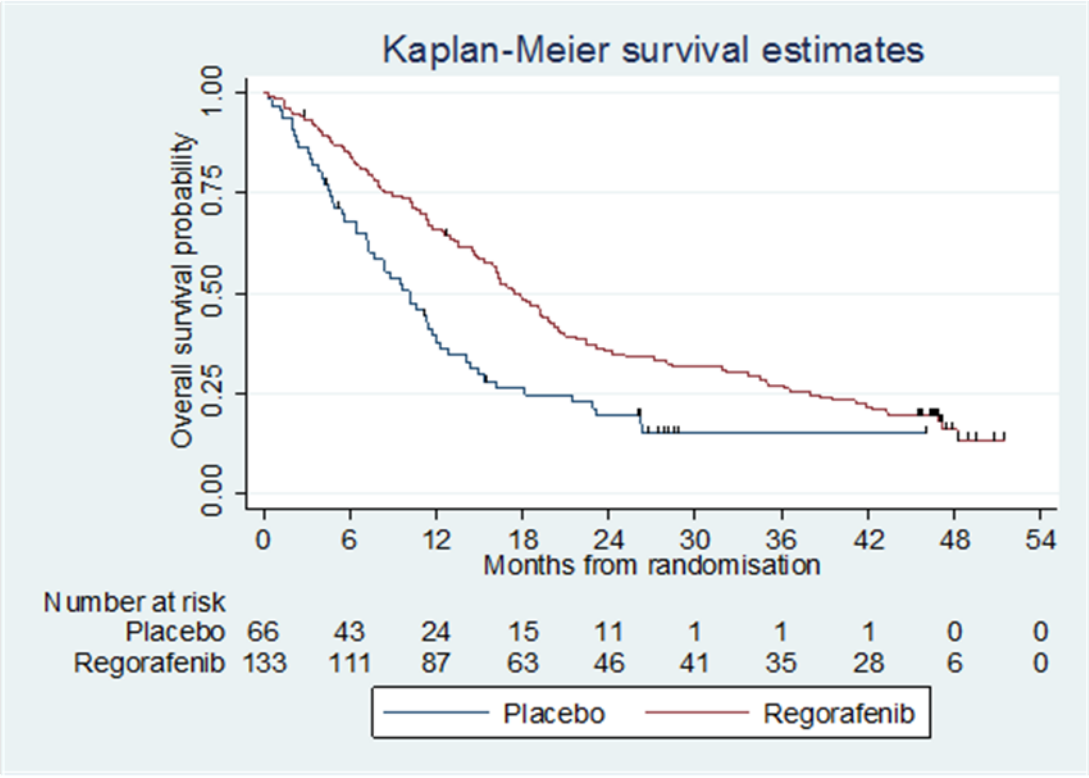
5.3.6.2 OS and crossover adjustments

Due to the crossover design of the GRID trial, estimating OS is more complex than PFS. Cross-over was only permitted after disease progression for the placebo arm, so no adjustment was required for PFS. However, 87.9% (n=58/66) of patients in the placebo arm crossed to the regorafenib arm after disease progression. This introduces the possibility of overestimating OS in the placebo arm if regorafenib gave them benefits in the PPS state and hence confounding the cost-effectiveness estimates.

Three crossover correction methods were considered; Iterative Parameter Estimation (IPE), Rank Preserving Structural Failure Time method (RPSFT), and Inverse Probability of Censoring Weights (IPCW). The aim of these methods is to reconstruct the OS patient level data in the placebo arm as if there had been no crossover in order to get an unbiased estimate of OS in the BSC arm. The IPCW method was discarded due to the high proportion of placebo patients crossing over, which Bayer argue is likely to result in high amounts of bias in treatment effect estimates (Source: Bayer submission, p.152). We agree that the IPCW method can be unreliable if the proportion of patients that switch is high. However, we understand that the method is considered unreliable only if the weights that are applied to the survival data corresponding to the patients that do not switch at very high. Nonetheless, we accept Bayer's justification in rejecting the IPCW method.

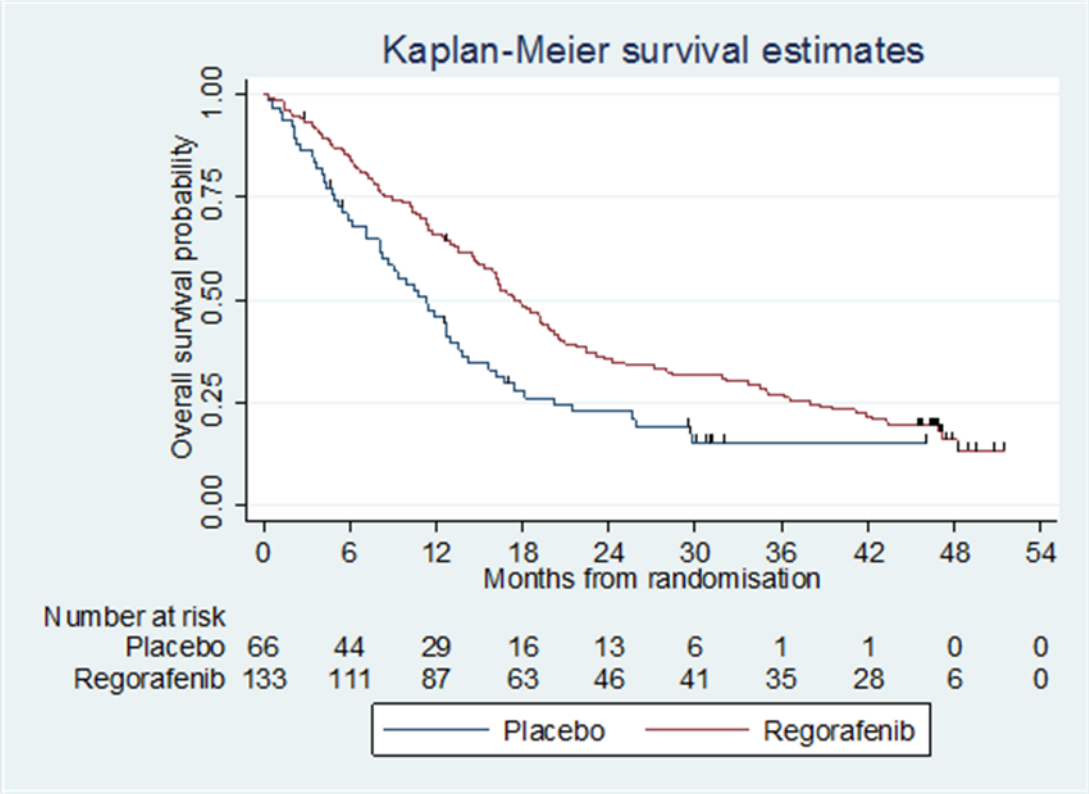
IPE-adjusted and RPSFT-adjusted K-M data for OS are shown in Figure 21 and Figure 22, respectively for both the 2015 data cut-off. Notice that after correction for cross-over, Bayer predict a clear OS benefit of regorafenib versus placebo. Compare this to the unadjusted OS data, in which OS for Regorafenib and placebo were very similar (Figure 19). This alerts us to the fact that the cost-effectiveness of regorafenib is very sensitive to the adjustment for treatment switching. Indeed, without adjusting for treatment switching, allowing for the PAS, Bayer estimate that their base case ICER increases massively, from £38,000 to £149,000 per QALY (Bayer model "Executive Summary" tab, Crossover adjustment method set to "Unadjusted"). We caution that we are not convinced of the accuracy of this figure for two reasons. First, the estimated mean OS for regorafenib changes when we set the adjustment method to "Unadjusted" and second because under the "Unadjusted" method, Bayer's model allows for no cost of regorafenib post-progression in the placebo, whereas we believe it should. However, we can say that the cost-effectiveness of regorafenib is very sensitive to the adjustment for treatment switching.

Figure 21. IPE crossover-adjusted Kaplan-Meier OS data (2015 data cut-off)



Source: Bayer submission, Figure 18, p.155

Figure 22. RPSFT crossover-adjusted Kaplan-Meier OS data (2015 data cut-off)



Source: Bayer submission, Figure 19, p.156

Despite the fact that the Kaplan-Meier graph for the placebo arm changed only slightly from the 2015 to the 2017 data cut-off, Bayer estimate a shorter OS for placebo after correction for cross-over using the 2017 data, compared to the 2015 data (Figure 23). Specifically and importantly, the estimated mean OS in the placebo arm decreases from 1.64 to 1.25 years, a reduction of 24%. Bayer justify this as follows: "*This is a result of the greater follow-up time allowing for a longer potential censoring date within the crossover adjustment calculation*" (Bayer response to clarification, p11). This reduction in mean OS substantially improves the cost-effectiveness of regorafenib. For example, assuming the PAS, the ICER for regorafenib vs. BSC decreases from £49,000 to £38,000 per QALY.

Given the importance of recensoring, we now give a brief explanation of this process. Recensoring involves data being recensored at an earlier time-point to avoid informative censoring and is therefore associated with a loss of longer-term survival information. Some observed events will become censored if the recensoring time is shorter than the counterfactual event time. The time-point at which recensoring occurs is related to the magnitude of the estimated treatment effect; the larger the treatment effect the earlier the recensoring time-point.[16]. Recensoring may lead to biased estimates of the "average" treatment effect in circumstances where proportional treatment effect assumptions do not hold, because longer term data on the effect of treatment may be lost.[16] We understand

that, whilst the NICE TSD recommends recensoring, whether to perform recensoring remains a subject of academic debate. Hence it is probably best to perform the adjustment both with and without recensoring. We further understand that the estimated treatment effect is generally greater when recensoring is performed compared to the analysis without recensoring. **The PenTAG base case employs a similar recensoring approach to Bayer, via the IPE method for treatment switching.**

Figure 23. OS Kaplan-Meier (2015 and 2017 data cut-off comparison)

Source: Bayer response to clarification, Figure 1, p.9

We have several important concerns with the 2017 OS data:

- Only the 2015 data cut appears in Bayer's Clinical Study Report. The 2017 data does not appear in this document. We imagine that the switching adjusted OS data from the 2015 data cut is more likely to be correct, given that it appears in the Clinical Study Report. We have no other means of judging the accuracy of the adjustment for the 2017 data other than Bayer's Addendum.
- Next, we assumed that the maximum follow-up time shown in the Kaplan-Meier graphs for the switching-adjusted placebo OS data would be greater for the 2017 data-cut compared to the 2015 cut, given that the 2017 data is more mature. However, as can be seen in Figure 23, the maximum follow up times are equal, specifically at 1,397 days.

- Next, we remain to be convinced that that a relatively small increase in the maturity of the survival data can results in such a substantial reduction in estimated mean OS for the placebo, of 24%.
- We do not have access to the underlying individual patient data, to enable us to check the switching adjustment.
- Finally, under the RPSFT and IPE methods, by definition, the p-values for the OS HR hazard ratios for the unadjusted (ITT) and switching adjusted data should be identical. However, Bayer quote very different values:
    - 2015 data cut: ITT p value = 0.285777, IPE-adjusted p value = 0.000949, RPSFT-adjusted p value = 0.002862 (Bayer's original report Table 22, p92).
    - 2017 data cut: ITT p value = 0.2298251, IPE-adjusted p value = 0.0000021, RPSFT-adjusted p value = 0.0000071 (Section 4.2.2.4.2, Table 13, p52)

Given all these concerns, we use the 2015 data-cut for OS in our base case.

We understand that the RPSFT method is commonly used in NICE assessments, but the IPE method less so. The IPE method is an extension of the RPSFT method using parametric methods.[16] The same accelerated failure time model is used as for the RPSFT method, but a parametric failure time model is fitted to the original unadjusted ITT data to obtain an initial estimate of the treatment effect. The failure times of switching patients are then re-estimated using this, and this iterative procedure continues until the new estimate is very close to the previous estimate, at which point the process is said to have converged.[16].

The IPE procedure makes similar assumptions to the RPSFTM method – for example the "common treatment effect" assumption. An additional assumption is that survival times follow a parametric distribution, and thus it is important to identify suitable parametric models, which in itself can be problematic.[16] The IPE method is expected to perform similarly, provided a suitable parametric distribution can be identified. Indeed, the results using the IPE and RPSFT methods are similar in our case.

Bayer chose the IPE method for their base case cross-over adjustment method due to Morden et al's study demonstrating this method's efficacy specifically that it performed particularly well in terms of reducing bias in the estimates of the true treatment effect. In line with NICE Decision Support Unit guidance, recensoring was applied to both methods in order to avoid bias.

Hazard ratios for OS for unadjusted, IPE-adjusted, and RPSFT-adjusted models estimated using a Cox model are presented below in Table 20. Figure 24 gives a visual comparison of the 2017 and 2015 OS hazard ratios with the different adjustment methods. Bayer say that their methods allow for recensoring. They further add that the OS HRs corresponding to the 2015 data cut, and reported in the Clinical Study Report, of 0.586 and 0.616 for the IPE and RPSFT methods respectively, were estimated without recensoring.

In our opinion, both the IPE and RPSFT are reasonable candidate adjustment methods. We are not convinced by Bayer's rationale for choosing the IPE method as the base case. It is our understanding that both methods are reasonable candidates. However, Bayer do not say why the IPE is more relevant than the RPSFT method in the specific case of the GRID RCT. Fortunately, **the two methods give reasonably similar estimates of OS for placebo**. Specifically, using the RPSFT method, Bayer's base case ICER under the PAS of £38,000 increases only slightly, to £39,000 per QALY. Therefore, we do not dwell on this issue.

Table 20. OS hazard ratios in for 2015 and 2017 data cut-offs

Crossover Adjustment	2015 cut (no recensoring)	2015 cut (recensoring)	2017 cut (recensoring)
Unadjusted*	0.909	0.909	[redacted]
IPE	0.586	[redacted]	[redacted]
RPSFT	0.616	[redacted]	[redacted]

Figure 24. Visual comparison of OS HRs

At the NICE Decision Problem Meeting on 12th January 2017, we asked Bayer to send us all the data necessary to recreate their adjustment for treatment switching, e.g. the relevant individual patient data from GRID. They replied that they would be very unlikely to send this to us, because it would be against Bayer policy to release such data. Indeed, Bayer have not provided us with the data required for us to check their switching adjustment. Whilst we understand that there may be issues concerning data confidentiality, this does present us with the problem that we are unable to check that the methods have been implemented correctly.

In their original report, Bayer provided some information on the implementation of the IPE and RPSFT methods. They said the methods were implemented in STATA, and the IPE method was implemented using the Weibull parametric failure time model, as in the study by Morden et al [17] similarly, and the RPSFT method was implemented using the logrank test, also recommended by Morden et al[17]. Bayer stated that, in line with the methodological approach recommended by NICE Decision Support Unit[16], recensoring was applied in order to avoid bias for the IPE and RPSFT methods. They noted further that recensoring was not applied for the IPE and RPSFT crossover corrections presented in the GRID clinical study report.

At the clarification stage of this appraisal, given the importance of these methods, we asked Bayer to provide more details on how the implementation of the methods, for example whether the treatment effect of regorafenib was assumed to apply only while regorafenib was being taken, or for the whole period from the start of regorafenib treatment until death.

Bayer responded as follows:

The IPE and RPSFT methods were implemented using Stata 11 and the strbee program developed by White et al. 2002.[18] (http://ageconsearch.umn.edu/bitstream/115957/2/sjart_st0012.pdf), as described by Morden et al. 2011[17] (https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/1471-2288-11-4). The commands implemented for IPE and RPSFT were as follows (square brackets represent inputs from data):

IPE:

Strbee [treatment], test(weibull) xo0([time to crossover] [crossover flag]) endstudy([study follow-up duration]) ipe

RPSFT:

strbee [treatment], test(logrank) xo0([time to crossover] [crossover flag]) endstudy[study follow-up duration])

A logrank test is implemented for the RPSFT method in order to calculate the test statistic for independence between patients' counterfactual event time and the treatment arm to which they were assigned, as recommended by Morden et al. 2011. For the IPE method, where a likelihood-based analysis is undertaken a Weibull distribution is utilised, also consistent with Morden et al. 2011[17]

Recensoring was implemented directly within the strbee program, using a maximum potential censoring time equal to the duration of study follow up. Recensoring was applied in order to reduce bias from potentially informative censoring as a result of switching (switching itself may potentially be informative if it is related to prognosis). Recensoring is applied in a manner consistent with Morden et al. 2011[17], and discussed further in White et al. 2002 [18].

The entire data for overall survival was used for the crossover adjustment; the assumption is therefore that treatment effect of regorafenib is applied from initiation of treatment until death, regardless of discontinuation. The treatment effect of regorafenib is therefore likely reduced as it will be an average of patients on and off treatment. Only placebo patients who crossover to regorafenib have their survival times adjusted, non-crossers and those in the regorafenib arm are unchanged.

In general, we are satisfied with their response. We do however note the strong assumption in the last paragraph, regarding the assumed duration of the treatment effect of regorafenib.

Given this, we perform a scenario analysis in which we assume that regorafenib improves survival only whilst the patient is taking the drug. In this case, and making a further simplifying assumption that approximately similar proportions of patients are alive on progression in the treatment arms, then to a good degree of accuracy, we model the costs and QALYs only whilst patients are in PFS. We further assume a dose intensity of 87% during PFS, or a mean dose of 139.8mg (compared to the standard dose of 160mg). In this case, Bayer's base case ICERs of £38,000 and [redacted] per QALY increase substantially, to £52,000 and [redacted] per QALY.

5.3.6.3 OS extrapolation

All parametric models for IPE-adjusted placebo and regorafenib OS are shown below for both the 2017 cut-off (Figure 25 and Figure 26).

Figure 25. Parametric models for OS and GRID Kaplan-Meier data, 2017 cut-off (IPE-adjusted placebo)

Source: Bayer response to clarification, Figure 3, p.11

Figure 26. Parametric models for OS and GRID Kaplan-Meier data, 2017 cut-off (Regorafenib arm)

Source: Bayer response to clarification, figure 2, p. 11

As in the extrapolation for the PFS parametric model, Bayer selected the best fit by minimising the sum of the AIC/BIC. The full list of AIC/BICs are shown in the Appendices, for both the 2015 and 2017 cut-offs.

Bayer acknowledge that the lowest AIC/BIC values come from the loglogistic/exponential models. For the 2015 analysis, Bayer settles on the loglogistic model by arguing (Source: Bayer submission, p.160):

> *"…the difference between the BIC values for the exponential and loglogistic models results being smaller compared to the other parametric models. Hence, the loglogistic model was selected for use in the model base case."*

For the 2017 cut-off (base case), Bayer continues to use the log-logistic model for the base case by arguing (Source: Bayer addendum, p. 13):

> *"The loglogistic model gives the minimum AIC for regorafenib OS and for both the RPSFT and IPE methods used in the placebo arm…. Following visual inspection of the parametric functions applied to the Kaplan-Maier curves for the two study arms and analysis of the AIC and BIC, log-logistic was selected as best fitting model."*

Bayer also had the fittings of the 5 parametric models validated by 2 consultant oncologists who specialised in the disease area. They argue that, from a clinical perspective, the

loglogistic, Weibull and Gompertz models all looked clinically plausible (for the 2015 data cut-off). The base case log-logistic model used for the regorafenib arm and the IPE-adjusted placebo arm for OS is shown in Figure 27 (2017 data cut-off).

Bayer also explores using hazard ratios for the regorafenib arm to extrapolate the placebo arm as a sensitivity analysis (rather than extrapolating arms separately). Bayer are unable to reject the proportional hazards assumption, which validates this approach. Bayer settles on using parametric models fitted separately to individual PFS and OS curves for the base case.

Figure 27. Log-logistic models for OS (2017 data cut)

We agree with Bayer that it is good practice to use the same functional form (e.g. log-logistic) for both treatment arms, in accordance with guidance from the NICE Decision Support Unit.[16].

As stated above, Bayer claim that 2 consultant oncologists, who specialise in the disease area believe that, from a clinical perspective, the loglogistic, Weibull and Gompertz models all look clinically plausible for the 2015 data cut-off. Bayer's only justification for choosing the log-logistic for their base case is that it provides the best fit to the trial OS data as measured by AIC / BIC. Whilst we acknowledge that the fit to trial data is a consideration,

we understand that the clinical plausibility of the extrapolations to be critical. The cost-effectiveness of Regorafenib is sensitive to choice of statistical distribution. For example, using the Weibull, Bayer's ICER with the PAS increases from £38,000 to £45,000 per QALY. With the Gompertz, the ICER increases to £47,000 per QALY. Given this, it is worth considering carefully the choice of statistical function.

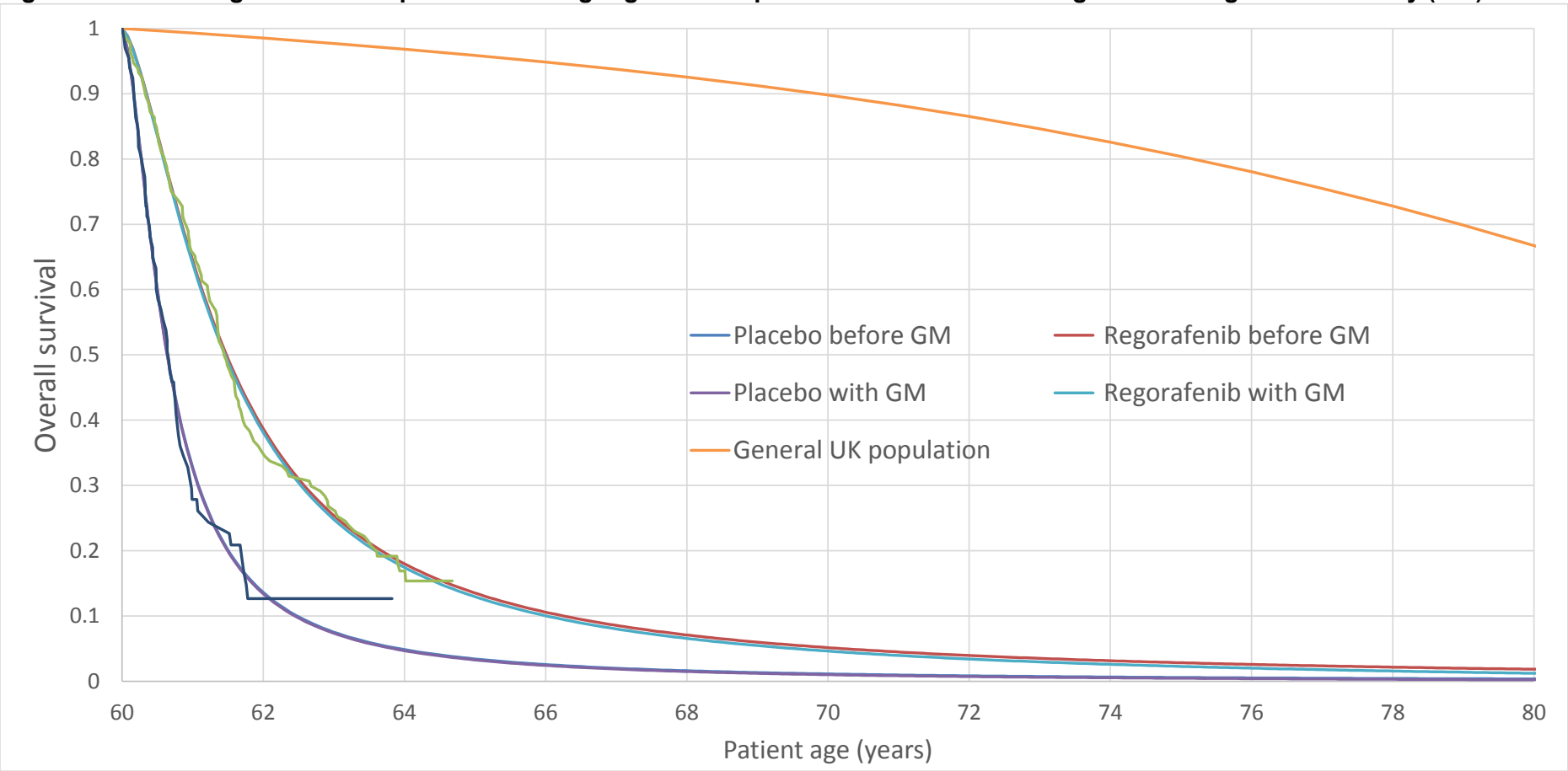
We believe essential to incorporate background mortality. This is because mortality in GRID will be due almost exclusively to causes related to GIST. However, many years later, a much larger proportion of deaths is likely to be due to causes unrelated to GIST, such as heart disease, or diabetes. Bayer's extrapolations make no allowance for this additional mortality.

We have adapted Bayer's model to allow for the extra cause mortality for the general population (Figure 28). Specifically, this change is implemented in worksheet "OS Parametric GRID". Then, the ICERs (£/QALY) increase for log-logistic and Weibull and Gompertz as follows for the example of the PAS:

- £38,000 to £41,000 log-logistic.
- £45,000 to £46,000 Weibull.
- £47,000 to £48,000 Gompertz

The ICERs increase markedly in the case of the log-logistic distribution because this is the longest-tailed distribution, and thus background mortality is more influential as the cohort ages.

Figure 28. OS for regorafenib and placebo with log-logistic extrapolations with and without general background mortality (GM)



Additional searches limited to the previous 10 years were carried out in Medline to identify studies with survival curves for GIST. This was not a systematic review, but we searched for

- Terms for gastrointestinal stromal tumour OR GIST AND
- Terms for survival curve OR Kaplan Meier

Fifty eight papers were identified with potentially relevant data. On screening for the correct population, our search yielded three relevant publications.

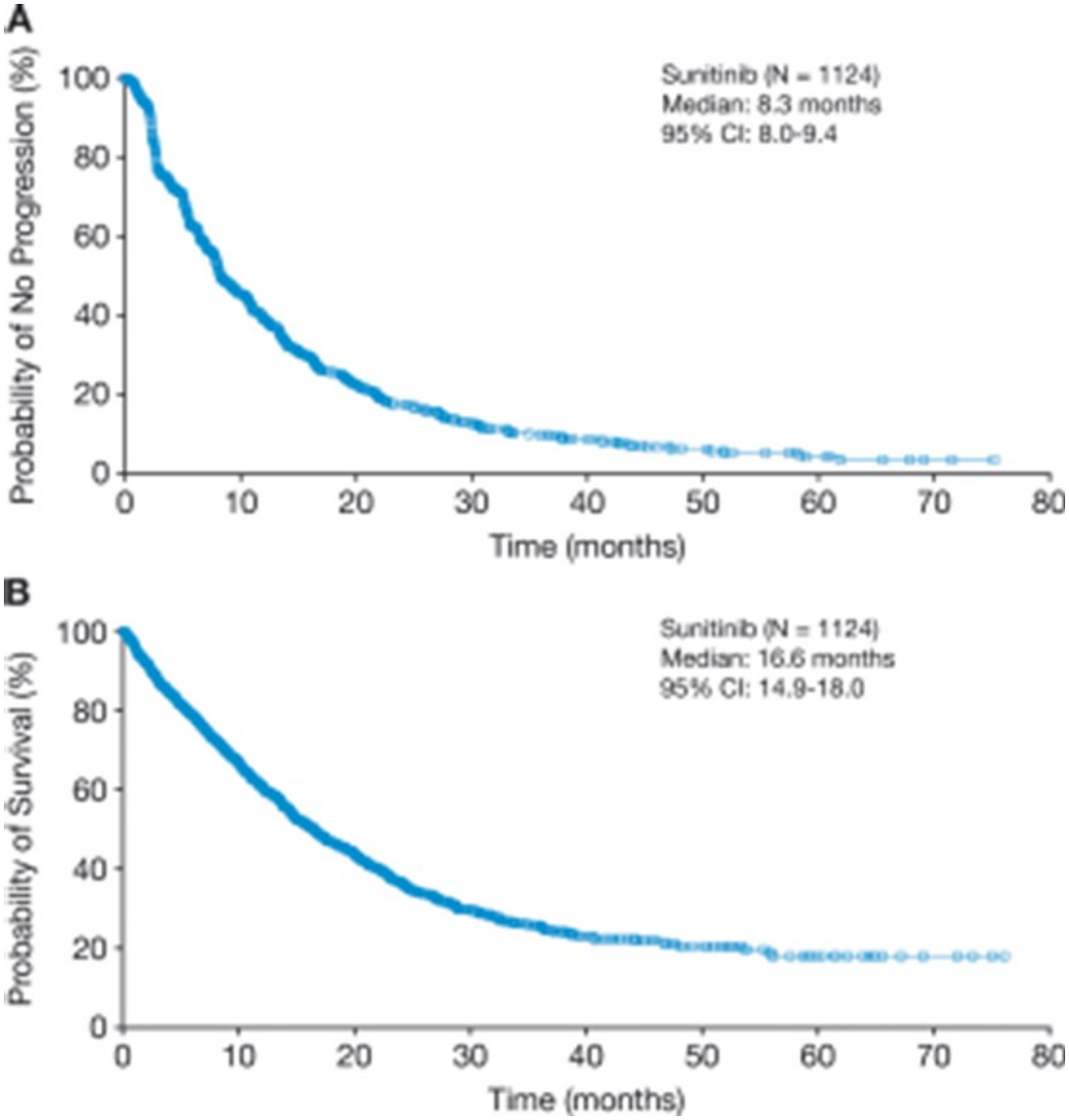
Kang et al (2013)[11] consider a patient population relevant to the current appraisal, namely patients with metastatic or unresectable GIST after failure of imatinib and sunitinib. However, we are unable to use data from this study to inform extrapolation OS in the current HTA because the data is insufficiently mature. Indeed, follow-up in this study was shorter than in GRID.

Yoon et al (2012)[19] consider a patient population less relevant. Whilst patient had failed imatinib, they had not necessary also failed sunitinib. Again, the data from this study is insufficiently mature to guide extrapolation in the current HTA.

The third study, Reichardt et al (2015)[20] is, however, useful because the OS data is slightly more mature than in GRID. Patients had advanced GIST and had previously failed imatinib, not but sunitinib. All 1,124 patients in this large international study took sunitinib. Median patients age was 59, virtually the same as in GRID, at 60 years. 60% of patients were male, again similar to the 64% in GRID. The ECOG distribution was similar compared with that in GRID, with patients typically with a slightly worse ECOG than in GRID.

Median time to progression was substantially longer, at 8.3 months than in the regorafenib arm of GRID (4.8 months). Median OS on sunitinib, at 16.6 months, was however very similar to that of the regorafenib arm of GRID, at 17.3 months (Figure 29).

Figure 29. A: PFS and B: OS from Reichardt et al. (2015) trial of sunitinib



Source: Figure is reproduction of Figure 1 in Reichardt et al. (2015)[20]

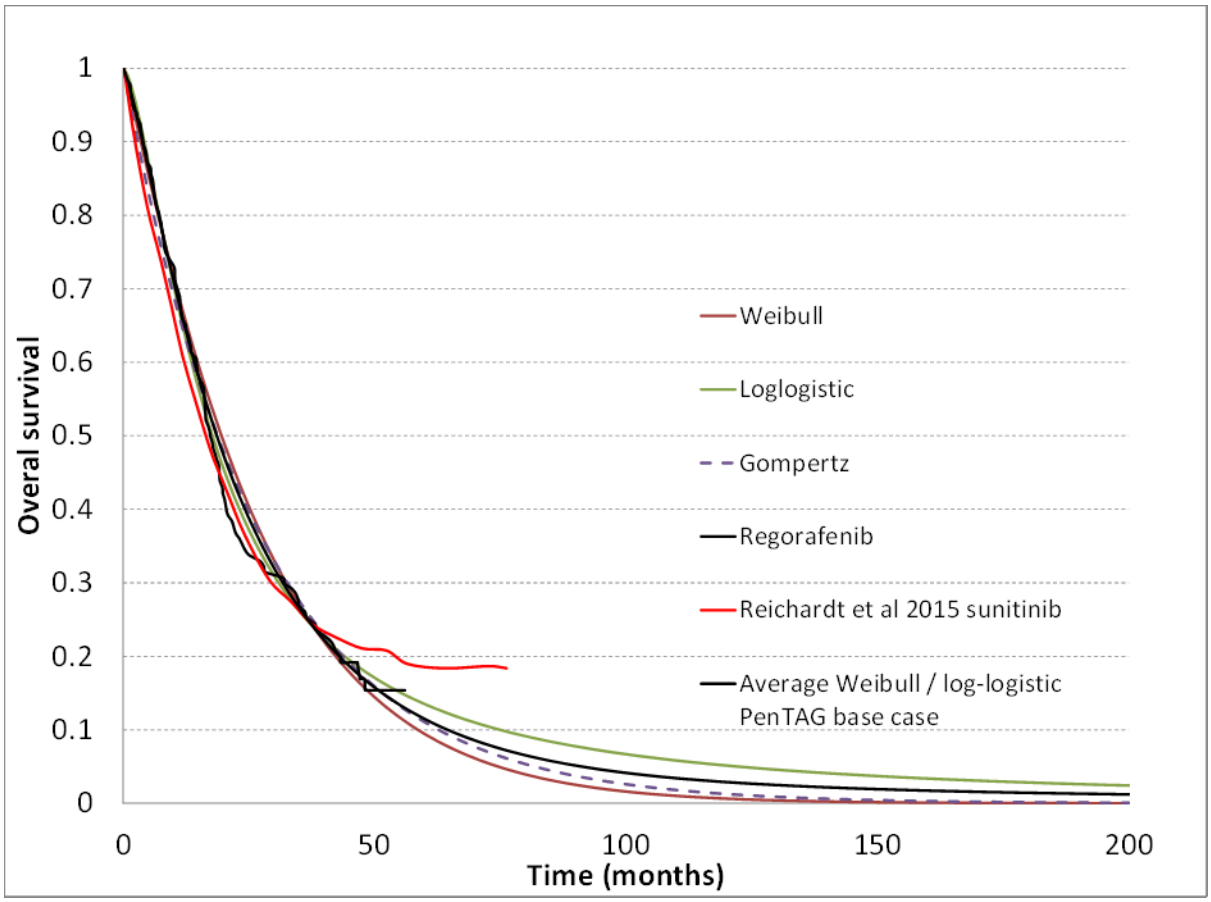
The OS for sunitinib in Reichardt et al. (2015) is slightly more mature than in the regorafenib arm of GRID. Observe also that OS is rather longer-tailed in Reichardt et al. (2015) than in the regorafenib arm of GRID (Figure 30). This might favour the choice of the log-logistic extrapolation over that of the Weibull or Gompertz. However, we caution against relying too much on the data from Reichardt et al. (2015), as:

(a) the uncertainty in the tail of OS in Reichardt et al. (2015) may be large, as the number of patients at risk in the tail might be low (but not reported),

(b) the patients in Reichardt et al. (2015) differed from those in GRID in that they had not previously been treated with suntinib, whereas all patients in GRID had,

(c) the patients in Reichardt et al. (2015) all took sunitinib, verus regorafenib in the regorafenib arm of GRID.

Figure 30. A: OS from Reichardt et al. (2015) trial of sunitinib and PenTAG base case



Source: Figure is reproduction in Reichardt et al. (2015)[20]
Notes: The lognormal fit is not displayed, as it is very similar to the log-logistic, which is shown. Similarly, the exponential fit is not displayed, as it is very similar to the Gompertz, which is shown.

In their base case, Bayer choose the log-logistic distribution to model OS in both treatment arms. As explained above, their two consultant oncologists believed that the log-logistic, Weibull and Gompertz models all look clinically plausible. Bayer's only justification for choosing the log-logistic for their base case is that it provides the best fit to the trial OS data as measured by AIC / BIC. Whilst we acknowledge that the fit to trial data is a consideration, we understand that the clinical plausibility of the extrapolations to be critical.

Having considered everything above, we believe that the evidence in favour of the longer-tailed and shorter-tailed distributions appears evenly balanced. **Therefore, in our base case, we model OS as the average of the Weibull and log-logistic distributions, adjusted for general background mortality (**Figure 30**).** Expressed formally, this is a

form of model averaging, with Bayesian prior weights of 50% applied to the shortest tailed Weibull and longer tailed log-logistic.

In this part of our case, Bayer's base case ICER under the PAS increases from £38,000 to £43,000 per QALY.

We also present Scenario analyses using just the Weibull adjusted for background mortality and Gompertz adjusted for background mortality.

5.3.7 Health related quality of life

Health effects were measured in quality adjusted life-years (QALYs) in accordance with the NICE reference case. Utility estimates were taken directly from the GRID trial using both the EQ-5D and the EORTC QLQ-C30 (Cancer Core Quality of Life Questionnaire) questionnaires, and both were used to estimate health state utility values (HSUVs).

5.3.7.1 EQ-5D

Data were taken from patients who had baseline EQ-5D assessments and at least one post-baseline assessment, and the Patient Reported Outcome Analysis Set (PROAS) was used. Paired-samples comparison and repeated measures analysis was then used to obtain HSUVs.

The paired-samples comparison based on t tests was used to assess intra-patient differences in the EQ-5D at baseline (day 1, cycle 1) and the first post-progression observation (which had to be after the patient knew they had progressed). A total of 77 paired samples were obtained (Table 21). An alternative comparison was also performed where the progression-free state was split into the regorafenib and placebo arms, and the first post-baseline measurement was used in lieu of the first baseline measurement in order to incorporate the treatment effect. Results are shown in Table 22.

Table 21. EQ-5D HSUVs from paired-samples

Health state	Mean utility	Observations, N	SD	SE
Progression-free	0.767	77	0.221	0.025
Progressed	0.647	77	0.343	0.039

Source: Bayer submission, Table 36, p.166

Table 22. EQ-5D HSUVs from paired-samples splitting by treatment in the progression-free state

Health state	Mean utility	Subjects	SD	SE
Progression Free - Placebo	0.583	12	0.341	0.098
Progression Free - Regorafenib	0.702	27	0.281	0.054
Progressed Disease	0.649	49	0.320	0.046

Source: Bayer submission, Table 37, p. 166

Bayer also estimates a linear mixed model with a first-order, autoregressive covariance structure (with subject identity modelled as a random effects) to estimate HSUVs, their repeated measures analysis. Results are shown below in Table 23. Bayer considers this a sensitivity analysis.

Table 23. EQ-5D HSUVs from repeated measures

Health state	Mean utility	SE	95% CI
Progression free	0.743	0.016	0.712, 0.775
Progressed	0.703	0.023	0.657, 0.748

Source: Bayer submission, Table 38, p.167

The repeated measures analysis was also repeated, splitting the progression-free state into the regorafenib and placebo arms (Table 24). This yields a slightly lower HSUV for regorafenib PFS compared to placebo.

Table 24. EQ-5D HSUV from repeated measures and splitting treatment during PFS

Health state	Mean utility	SE	95% CI
Progression Free - Regorafenib	0.741	0.018	0.706, 0.777
Progression Free - Placebo	0.750	0.027	0.698, 0.802
Progressed Disease	0.681	0.023	0.637, 0.725

Source: Bayer submission, Table 39, p. 167

The paired-samples without splitting by pre-progression treatment utility estimates (Table 21**) were used in the base case analysis.** Bayer justifies this by first arguing that the repeated measures analysis is likely to be biased because more measurements were taken for patients in the progression-free state. As utility generally declines over time with age and tumour burden, this could bias estimates. They also note that there were no clinically meaningful differences in EQ-5D between the two treatment arms.

Furthermore, due to the high level of cross-over, the repeated measures analysis would compare non-homogeneous progressed populations; utility observations would be taken for those people in the initial diagnosis of progressed disease and also those under active treatment with regorafenib.

Despite noting that utility often declines with age, Bayer argue that the utility estimates from the GRID trial are constant over time, citing Poole et al (2015)[21] as justification. Bayer do acknowledge that HRQL may decline in the progressed state towards the end of a patient's life, but note that this decrement would apply to both arms and hence no incremental effect would exist, making it reasonable to omit.

Age-related utility decrements were applied to the model for the PenTAG base case. It was assumed that Bayer's baseline utility values incorporated time-invariant characteristics (such as gender), hence the only adjustments needed to be made would be the decrements associated with aging. The values themselves are taken from the Health Survey for England (2012)[22], which give regression coefficients for age and age squared. Therefore, the formula for utility as function of time is:

$$u_{it} = \alpha_i + \beta_{1t}t + \beta_{2t}t^2$$

Where *i* refers to disease state and *t* is time (or age). Since patients enter the model at age 60, the base line utilities values are when *t* = 60. To extrapolate beyond this to *t* + *x*, the equation becomes:

$$u_{it} = \alpha_i + \beta_{1t}(t+x) + \beta_{2t}(t+x)^2 \mid_{t=60}$$

$$= [\alpha_i + \beta_{1t}60 + \beta_{2t}60^2] + \{\beta_{1t}x + 2\beta_{2t}60x + \beta_{2t}x^2\}$$

Where the bracketed term refers to the baseline utilities and term in the curly brackets refers to the added decrement (as β_{1t} and β_{2t} are negative). This has a modest effect on the ICER per QALY, increasing it by around £1,000.

5.3.7.2 EORTC mapping

As with the EQ-5D, paired-samples and repeated measures were used to generate alternative utility estimates. The EORTC QLQ-30 is a commonly used measure of quality of life for cancer patients. Answers were mapped to utilities using the method proposed by Rowen et al[23]. Their mapping algorithm was then applied to the GRID EORTC data to obtain utility estimates. There were 78 paired-samples observations, and the estimates of this method are shown in Table 25. In order to gain a greater number of data points, Bayer used a similar autoregressive covariance structure method as with the EQ-5D, with results shown

below in Table 26. Only patients with non-censored time to progression dates, a baseline assessment and at least one post-baseline assessment were included (n=133). Regardless of the EORTC utility derivation method, the NICE reference case states that EQ-5D results are preferred over other utility measures when they are available, and hence, in the base case, Bayer use the EQ-5D.

Table 25. EORTC mapped utilities from paired-samples

Health state	Mean utility	Observations, N	SD	SE
Progression-free	0.818	78	0.138	0.016
Progressed	0.751	78	0.158	0.018

Source: Bayer submission, Figure 40, p. 169

Table 26. EORTC mapped utilities from repeated measures analysis

Health state	Mean utility	Observations, N	SE	95% CI
Progression free	0.794	320	0.011	0.771, 0.816
Progressed	0.756	128	0.013	0.730, 0.783

Source: Bayer submission, Figure 41, p.169

5.3.7.3 Adverse events

Bayer note that the three most common AEs – hand foot skin reactions (HFSR), diarrhoea, and fatigue – are all easily manageable and their effects on health-related quality of life are negligible. However, they assume that the EQ-5D values obtained from repeated measures, where PFS was split into treatment arms, were inclusive of the treatment-associated adverse events. The results of this analysis are shown in Table 24 (section 5.3.7.1), with the regorafenib arm showing a slightly lower pre-progression utility than the placebo arm.

5.3.7.4 Health-related quality of life studies

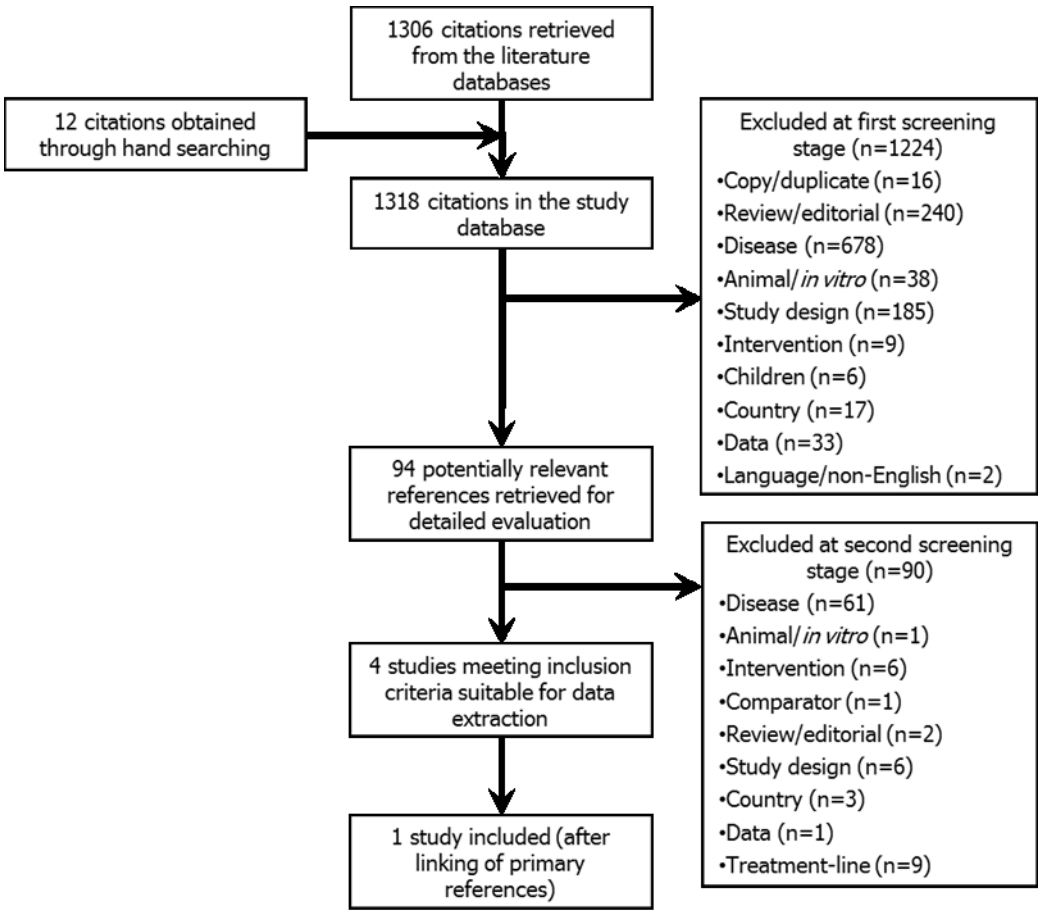
Bayer carried out a full systematic review of published literature to identify health-related QoL studies relevant to the decision problem. The objective was to identify research on utilities associated with GIST and/or studies investigating HRQoL outcomes. The following databases were searched (from inception to 19 December 2016): MEDLINE, MEDLINE (R) In-Process, EMBASE, EconLIT, and NHS EED. The database search was updated 3 times from December 2011 to December 2016. The following conferences were also searched: American Society of Clinical Oncology, European Society for Medical Oncology, International Society for Pharmacoeconomics and Outcomes Research, and the International Society for Quality of Life Research. The set of exclusion/inclusion criteria and the PRISMA flow diagram are shown below in Table 27 and Figure 31.

Table 27. Inclusion/exclusion criteria for cost-effectiveness publications

	Inclusion criteria	Exclusion criteria
Study design	• Study design appropriate to report the HRQoL/utility associated with GIST (patient preference studies, utility mapping studies, cohort studies / longitudinal studies (retrospective), cohort studies / longitudinal studies (prospective), case control studies, cross sectional studies, analysis of hospital records/databases, cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses)	• Literature and systematic reviews • Database studies or epidemiology studies, not collecting utility data • RCTs (with no piggy-back economic evaluations) • Studies published in non-English language (with/without English abstracts)
Patient population	• Studies including adult patients (aged ≥18 years) • Studies reporting data in countries of interest (US, Canada, Australia, France, Germany, Italy, Spain, UK, Brazil, Mexico, Japan, China, Korea)	• Studies in children or adolescents • Studies conducted in animals or *in vitro*
Disease/ therapy	• Studies including patients with metastatic, advanced, and/or unresectable GIST, defined as such using the study author's definition • Studies of third-line patients (who have failed two pharmacological therapies). However, as it is was anticipated that studies focused on third-line patients were rare, studies in first- and second-line patients were only excluded at the final stage of the second pass (at the first pass stage there was no exclusion based on therapy line)	• Studies that did not include patients with a specific GIST diagnosis (including gastrointestinal leiomyosarcoma that appeared to behave as GIST, soft-tissue sarcoma that appeared to behave as GIST, oesophageal leiomyosarcoma, gastric leiomyoma, gastric leiomyoblastoma, small intestinal leiomyoma and leiomyosarcoma, colonic and rectal leiomyoma and eiomyosarcoma, gastrointestinal autonomic nerve tumour, eiomyoma and leiomyosarcoma of omentum and mesentery, retroperitoneal leiomyosarcoma)
Intervention	• Regorafenib	• Any other intervention
Comparator	• Placebo/BSC	• Any other comparator

Source: Bayer submission, Table 42, p.172

Figure 31. PRISMA flow diagram for HRQoL studies



Source: Bayer submission, Figure 24, p.173

After a full text review, only one relevant study was found, the GRID study, shown in Table 28.

Table 28. Summary list of published HRQOL studies

Study	Country	Population	Intervention	Sample size	Elicitation method	Health states	Utility score
GRID **Poole et al. (2015) (40)**	**58 years (SD 13.1)**	**Male: 64.3%** **Mean age (years): 58** **Metastatic** **Unresectable, associated with disease progression with imatinib and sunitinib (100%)**	**Regorafenib**	**185**	**EQ-5D index score**	**Mean at baseline (day 1 of cycle 1) from the combined data set**	**0.769**
						Mean at First progression-free state (Progression-free state represented by baseline observation, QoL observations made on day 1 of cycle 1 before commencing blinded treatment)	**0.767**
						Mean at First post-progression State (The first post progression health state suggesting significantly impaired health-related quality of life after confirmed disease progression showed a decrease of -0.120)	0.647

Source: Bayer submission, Table 43, p.174

5.3.8 Resources and costs

5.3.8.1 Drug acquisition costs

Drug acquisition costs make up the vast majority of costs in the regorafenib arm. The drug prices used in the economic model are based on the list price and separately, a confidential Patient Access Scheme (PAS).

Regorafenib comes in 40mg tablets and all patients in the trial took multiples of 40 mg/day up to 160 mg/day. The unit costs and full per cycle costs assuming the 160mg dosage are shown below in Table 29.

Table 29. Drug costs

Drug	Unit cost	Drug cost per 28-day cycle	Source
Regorafenib 160mg per day (without PAS)	£44.57/40mg tablet	£3,744.00	Bayer UK
Regorafenib 160mg per day (with PAS)	£[redacted]/40mg tablet	£[redacted]	Bayer UK

5.3.8.2 Treatment duration

Bayer's method of modelling treatment duration of regorafenib changed substantially from the time of their original report submission to the time of our report submission.

Regorafenib treatment in the regorafenib arm of GRID was continued after disease progression. However, originally, Bayer modelled regorafenib treatment only up to progression, as they claimed this would be as in clinical practice in England & Wales, citing surveys of physicians. Originally, Bayer also assumed a dose intensity of 84.1% during this period.

As reported above, Bayer originally used OS corresponding to the 2015 cut off. In response to our question for clarification, they then provided OS data corresponding to the 2017 cut off. We then asked whether they also had updated treatment duration corresponding to the 2017 cut off. In response, they completely changed their method of modelling treatment duration. In particular, they now model treatment with regorafenib for the entire duration as experienced in GRID RCT, see Figure 32 below.

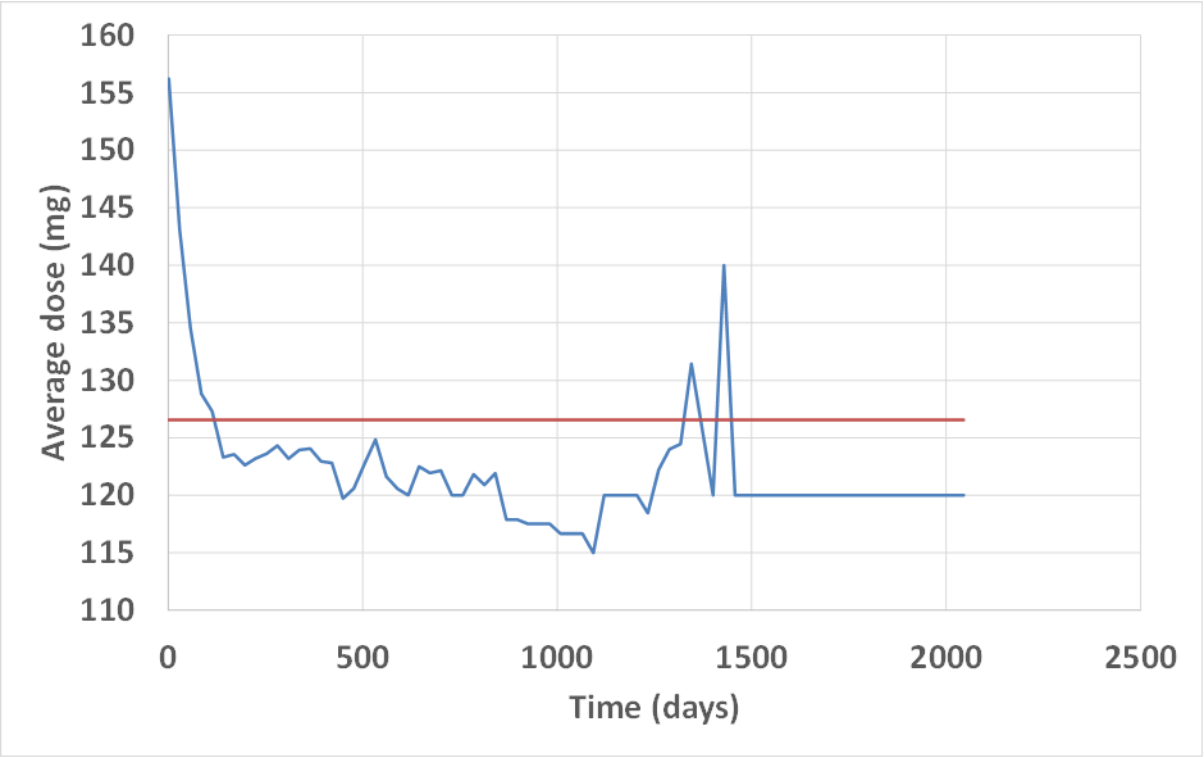
Figure 32. Time on regorafenib treatment in GRID RCT

We agree with this, their updated method of modelling treatment duration.

Bayer have also supplied different data for dose intensity of regorafenib (Figure 33). This is appropriate, because they now consider treatment with regorafenib over a different period, including post-progression. As explained above, previously, they assumed a dose intensity of 84%. By our calculations, the average dose, weighted for treatment duration is now 126.5mg, which gives a mean dose intensity of 79%. This dose intensity is implicit in Bayer's estimation of total cost of acquisition of regorafenib, and this is appropriate.

Notice that Bayer's updated method of modelling treatment duration acts to increase the ICER for regorafenib.

Figure 33. Average dose over time in GRID RCT



5.3.8.3 Health resources use and cost

Resource use information was gathered from a 2013 physician resource survey of 15 GIST medical oncologists with recent experience in managing GIST patients. Results were then updated and validated by two consultant oncologists in 2016 specialised in the management of metastatic or unresectable GIST. The physicians also showed that only 25.3% of patients receive TKIs post-progression, which informs Bayer's choice of only considering treatment costs during active progression.

The survey determined that the main tests for the patient population are CT scans, MRI scans, full blood counts and liver function tests. Table 30 below shows the proportion of patients taking each test *prior* to treatment. Fewer patients on BSC undergo tests compared to TKIs like regorafenib. The tests are continually performed, but CT and MRI scans are less common following disease progression, as shown in Table 31 and Table 32. Our clinical expert considers all estimates in Table 30, Table 31 and Table 32 reasonable, except that in the UK he estimates no MRI scans post-progression, and during PFS only for patients on a TKI, not BSC. Changing these values to those of our clinician increases the ICERs only marginally. Therefore, henceforth, we do not pursue this matter.

Table 30. Resource use prior to treatment

Test	Proportion of 3rd line patients receiving test prior to treatment with a TKI, Mean (SE)	Proportion of 3rd line patients receiving test prior to BSC, Mean (SE)
CT scan	0.85 (0.079)	0.24 (0.070)
MRI scan	0.12 (0.031)	0.01 (0.005)
Full blood count	0.92 (0.065)	0.56 (0.100)
Liver function test	0.92 (0.062)	0.49 (0.111)

Source: Bayer submission, Table 46, p.180

Table 31. Regular tests given to progression-free patients

Test	Patients on a TKI		Patients on BSC	
	Percentage of physicians responding that patients would be given the test regularly	**Average frequency (weeks between tests), Mean (SE)**	**Percentage of physicians responding that patients would be given the test regularly**	**Average frequency (weeks between tests), Mean (SE)**
CT scan	100%	12.1 (1.44)	60%	18.9 (3.26)
MRI scan	73%	19.9 (4.00)	27%	18.0 (2.58)
Full blood count	93%	6.4 (1.90)	67%	10.9 (2.36)
Liver function test	93%	6.4 (1.90)	60%	11.2 (2.61)

Source: Bayer submission, Table 47, p.180

Table 32. Regular tests given to patients in the post-progression state

Test	Percentage of physicians responding that patients would be given the test regularly, %	Average frequency (weeks between tests), Mean (SE)
CT scan	20%	14.5 (6.84)
MRI scan	7%	8.0 (-)
Full blood count	67%	8.8 (1.88)
Liver function test	60%	9.4 (2.03)

Source: Bayer submission, Table 48, p.180

All physicians consulted indicated that regular monitoring would be performed as an outpatient, as shown in Table 33. Our clinical expert estimates slightly different frequencies:

4 weeks between visits for patients on a TKI and 12 weeks for patients on BSC whilst in PFS and PD. Changing these values to those of our clinician increases the ICERs only marginally. Therefore, henceforth, we do not pursue this matter.

Table 33. Frequency of outpatient visits based on health state

Health state	Percentage of physicians responding that patients would be monitored on an outpatient basis	Average frequency (weeks between visits), Mean (SE)
Progression-free on a TKI	100%*	6.2 (0.86)
Progression-free on BSC	100%	7.9 (0.77)
Progressed disease on BSC	100%	6.9 (0.97)

Source: Bayer submission, Table 49, p.181

Average frequencies by health state for tests and monitoring were used to calculate per cycle (28) day probabilities.

Pain management medication is also common, and the physicians' responses to pain management usage are shown below in Table 34. Our clinical advisor considers these values reasonable. The physician survey also included the use of palliative surgical resection or palliative radiotherapy and indicated that this would not depend on whether a patient is on a TKI. These costs are shown below in Table 35. Our clinical advisor considers the data for radiotherapy reasonable, but consider the values for palliative surgical resection high. Instead, he advises proportions of 0.05 whilst in PFS (regardless of treatment) and 0.02 during progressed disease. Changing these values to those of our clinician increases the ICERs only marginally. Therefore, henceforth, we do not pursue this matter.

Table 34. Pain management resource use by health state

Treatment	Average proportion of patients treated with pain medication by health state and medicine	
	Progression-free Mean (SE)	**Progressed disease Mean (SE)**
Co-codamol, 2 tablets QDS (each containing 8mg codeine)	0.18 (0.039)	0.22 (0.043)
Tramadol, 100mg QDS	0.12 (0.028)	0.14 (0.036)
Paracetamol, 1g QDS	0.33 (0.074)	0.38 (0.085)
Morphine sulphate, 30mg immediate release every 4 hours	0.20 (0.057)	0.29 (0.065)
Dexamethasone, 4mg OD	0.11 (0.022)	0.19 (0.043)

Source: Bayer submission, Table 50, p.181

Table 35. Palliative care interventions by health state

Palliative intervention	Average proportion of patients who receive the palliative care intervention, Mean (SE)		
	Progression-free on a TKI	**Progression-free on BSC with no TKI**	**Progressed disease**
Palliative surgical resection	0.10 (0.024)	0.10 (0.031)	[redacted] (0.033)
Palliative radiotherapy	0.20 (0.053)	0.20 (0.061)	[redacted] (0.063)

Source: Bayer submission, Table 51, p.182

Full unit costs are given in Table 36 and full input costs per cycle associated with the intervention and the comparator in Table 37.

Table 36. Unit costs associated with health state resource use

Item	Cost (£)	Source	Assumption
Regular tests			
CT scan	40.23	NHS Reference costs 2015-16	Cost per scan (IMAG); code RD26Z - Computerised Tomography Scan of three areas, with contrast;
MRI scan	146.61	NHS Reference costs 2015-16	Cost per scan *(weighted average of all MRI – adult; codes: RD01A,*

			RD02A, RD03Z,RD04Z,RD05Z,RD06Z,RD07 Z)
Full blood count	3.10	NHS Reference costs 2015-16	Cost per test (DAPS); code DAPS05 - Haematology
Liver function test	1.18	NHS Reference costs 2015-16	Cost per test (DAPS); code DAPS04 - Clinical Biochemistry
Regular monitoring visit			
Outpatient visit (regular monitoring)	93.00	2016/17 National Tariff; OP	Cost of outpatient attendance Attendances - code 370 WF01A Follow Up Attendance - Single Professional
Pain management			
Co-codamol	0.89	MIMS, January 2017	Cost per 30-tab pack (non-proprietary), 8mg codeine phosphate per tab
Tramadol	2.87	MIMS, January 2017	Cost per 100-cap pack, 50mg per cap (non-proprietary)
Paracetamol	2.19	MIMS, January 2017	Cost per 100-tab pack, 500mg per tab (non-proprietary)
Morphine sulphate immediate release	5.31	MIMS, January 2017	Cost per 56-tab pack, 10mg per tab (Sevredol®)
Dexamethasone	42.85	MIMS, January 2017	Cost per 50-tab pack, 2mg per tab (non-proprietary)
Palliative care			
Palliative surgical resection	3,943.21	NHS Reference costs 2015-16	Single intervention for malignant GI Tract disorder *(weighted average; code: FZ92D, FZ92E, FZ92F)*
Palliative radiotherapy-	160.59	NHS Reference costs 2015-16	Cost per medical specialist palliative care attendance *(weighted average adult; code: SD01A, SD02A, SD03A, SD04A)*

Source: Bayer submission, Table 52, p.182

Table 37. Input costs per cycle in the economic model

Item	Regorafenib mean (CI)	Reference in submission	BSC mean (CI)	Reference in submission
Drug costs§	£3,271.09 (£2,616.87; £3,925.30)	Section 5.5.1	-	-
Management costs				
One-time costs for regorafenib	£55.72 (£44.58; £66.86)	Section 5.5.1	-	-
One-time costs post-progression	£[redacted] (£[redacted]; £[redacted])	Section 5.5.1	£[redacted] (£[redacted]; £[redacted])	Section 5.5.1
Regorafenib + BSC while progression-free	£124.21 (£99.37; £149.05)	Section 5.5.1	-	-
BSC while progression-free	-	-	£80.07 (£64.05; £96.08)	Section 5.5.1
BSC post-progression	£88.98 (£71.18; £106.78)	Section 5.5.1	£88.98 (£71.18; £106.78)	Section 5.5.1
End of life costs	£8,736.53 (£8,052.12; £9,422.00)	Section 5.5.8	£8,736.53 (£8,052.12; £9,422.00)	Section 5.5.8
Additional one-time costs for BSC	-	-	£13.82 (£11.05; £16.58)	Section 5.5.1
Adverse Events Costs				
Hand foot skin reaction	£0.00	Section 5.5.7	£0.00	Section 5.5.7
Diarrhoea	£7.02 (£5.62; £8.43)	Section 5.5.7	£7.02 (£5.62; £8.43)	Section 5.5.7

Hypertension	£11.86 (£9.48; £14.23)	Section 5.5.7	£11.86 (£9.48; £14.23)	Section 5.5.7

Source: Bayer submission, Table 53, p.185

5.3.8.4 Health state costs and resource use

Health state costs comprise one-time costs and per cycle costs, summarised in Table 38. The one-time costs consist of test costs prior to starting treatment, palliative surgical resection, and palliative radiotherapy. Palliative measures are only applied in the progressed disease state since resource use is zero for PFS regardless of treatment arm. One-off costs were estimated by unit cost of each test weighted by the proportion of patients undergoing each test/palliative measure, and then summed to get an expected one-off cost. Bayer made a minor error in modelling in their estimation of the number of new progressions in each cycle to which to apply the one-time costs. However, given that this error has a negligible effect on the ICERs per QALY, we pursue this no further.

Per-cycle costs consist of regular outpatient monitoring visits, regular tests and medication for pain management. Unit costs were weighted by the probabilities per cycle (see section 5.3.8.2). Standard errors are calculated assuming independence of variables – although this is unlikely, Bayer argue this results in larger standard errors and is a more conservative approach.

Table 38. Health state costs per cycle and one-off costs in the model

Cost component		Progression-free state on a TKI (£), Mean (SE)	Progression-free state on BSC with no TKI (£), Mean (SE)	Progressed disease (£), Mean (SE)
One-time costs	Tests	55.72 (5.53)	13.82 (2.93)	N/A
	Palliative resection	Not included	Not included	[redacted] (129.38)
	Palliative radiotherapy	Not included	Not included	[redacted] (10.11)
	Total one-time costs	55.72 (5.53)	13.82 (2.93)	[redacted] **(129.77)**
Regular per cycle costs	Regular tests	45.45 (5.46)	14.81 (4.08)	8.35 (36.00)
	Regular outpatient monitoring visits	60.49 (9.16)	46.91 (4.73)	53.68 (8.15)
	Pain management	18.27 (2.97)	18.35 (2.97)	26.95 (3.77)
	Total per cycle costs	124.21 (11.07)	80.07 (6.92)	**88.98 (37.11)**

Source: Bayer submission, Table 54, p.186

5.3.8.5 Adverse event costs and end-of-life criteria costs

Grade 3 and 4 adverse events were considered only if they were reported in at least 3% of patients and were: hand-foot skin reaction (HFRS), diarrhoea and hypertension. Bayer UK provides a free HFSR treatment kit and hence associate this AE with zero cost in the model.

Diarrhoea is treated with the drug loperamide. Hypertension is associated with an ACE inhibitor, and Bayer use the most common one according to their physician study, rampiril 10mg. Hypertension is also associated with 2 annual GP visits and two annual district nurse appointments. Treatments costs for both AEs and incidence rates are summarised in Table 39 to Table 42. We consider these values reasonable.

Table 39. AE incidence rates per cycle in the model

Adverse Event (Grade 3-4)	Estimated incidence rate per cycle (%)	
	Placebo	Regorafenib
Hypertension	1.35	5.16
Hand-foot skin reaction	0	4.25
Diarrhoea	0	1.07

Source: Bayer submission, Table 35, p. 162

Table 40. Diarrhoea drug treatment costs

Drug	Loperamide
Cost per pack	£2.15
No. tabs per pack	30.00
mg per tab	2.00
Cost per mg	£0.04
Average daily dose (mg)	7.00
Average weekly dose (mg)	49.00
Cost per cycle	**£7.02**

Source: Bayer submission, Table 55, p.187

Table 41. Hypertension drug treatment costs

Drug	Ramipril
Cost per pack*	£1.24
No. tabs per pack	28.00
mg per tab	10.00
Cost per mg	£0.004
Average daily dose (mg)	10.00
Average weekly dose (mg)	70.00
Cost per cycle	**£1.24**

Source: Bayer submission, Table 56, p.188

Table 42. Hypertension management costs

GP visit	£44	PSSRU Unit costs of Health & Social Care 2015, pg. 177 - Table 10.8b (62)
District nurse visit	£25	PSSRU Unit costs of Health & Social Care 2015, pg. 175 - Table 10.7 (62)

Source: Bayer submission, Table 57, p.188

End of life costs were taken from the study conducted by Abel et al [24], a UK hospice-based study. Costs were inflated to 2015/2016 level. The final EoL cost used is £8,736. Finally, Table 43 gives a complete summary of per-cycle variable costs and non-cost parameters.

Table 43. Summary of variables applied in the economic model (per cycle)

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Regorafenib cost	£[redacted]	(£[redacted]-£[redacted])	Table 45
One-time costs for regorafenib	£56	(£45-£67)	Table 54
Regorafenib + BSC while progression-free	£124	(£99-£149)	Table 54
BSC while progression-free	£80	(£64-£96)	Table 54
BSC post-progression	£89	(£71-£107)	Table 54
End of life costs	£8,736	(£8,052-£9,422)	Table 58
Diarrhoea costs	£7	(£6-£8)	Table 55
Hypertension costs	£12	(£9-£14)	Table 56
Progression-free state utility	0.767	(0.718-0.816)	Table 36
Post-progression state utility	0.647	(0.571-0.723)	Table 36
Discount rate (costs)	3.5%	(0-6%)	Table 29
Discount rate (benefits)	3.5%	(0-6%)	Table 29

Source: Bayer submission, Table 60, p.190

5.3.9 Cost-effectiveness results

Bayer's base case ICERs of regorafenib plus BSC compared to BSC alone are £[redacted]/QALY and £37,941/QALY without and with the PAS respectively. Table 44 and Table 45 below illustrate the base case results. Bayer present their base case as using the 2017 data cut off.

Table 44. Base case CE results. 2017 cut-off (no PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (LYs)	ICER (£) incremental (QALYs)
Placebo + BSC	10,395	1.154	0.761					
Regorafenib	[redacted]	2.546	1.733					
				[redacted]	1.393	0.971	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Source: Bayer response to clarification, Table 36, p. 47

Table 45. Base case CE results. 2017 cut-off (PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (LYs)	ICER (£) incremental (QALYs)
Placebo + BSC	10,395	1.154	0.761					
Regorafenib	47,249	2.546	1.733					
				36,854	1.393	0.971	26,465	37,941

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Source: Bayer response to clarification, Table 37, p. 47

Bayer argue that their model accurately reflects the trial data (Table 46).

Table 46. Summary of model results versus clinical data (2015 cut-off)

Outcome	Time horizon	Placebo + BSC		Regorafenib + BSC	
		Clinical trial result	Model result	Clinical trial result	Model result
Overall survival	1 year	0.38	0.42	0.65	0.66
	2 years	0.19	0.20	0.35	0.39
	3 years	0.15	0.12	0.26	0.26
Progression-free survival	168 days	n/a	n/a	0.43	0.44

5.3.9.1 Disaggregated base case cost-effectiveness results

Bayer provide disaggregated results for QALYs and predicted resource use (without and with the PAS) for the 2015 data cut-off, but not the 2017 cut-off. Given that the focus of our attention is now the 2017 data, we have recreated the disaggregated results from the Bayer model using the updated 2017 data, which are shown below.

Table 47. Summary of Bayer base case QALYs by health state, 2017 cut-off

Health state	QALY Regorafenib	QALY Placebo	Increment	Absolute increment	% absolute increment
Progression-free	0.566	0.095	0.471	0.471	40%
Post Progression	1.433	0.727	0.706	0.706	60%
Total	1.999	0.822	1.177	Total absolute increment	100%

QALY, quality-adjusted life year

*QALYs are undiscounted in line with the Bayer submission for 2015 results.

Table 48. Breakdown of Bayer base case costs, 2017 cut-off

	Component	Regorafenib + BSC	Placebo + BSC	Incremental
List price	Drug costs - progression-free	£[redacted]	£0	£[redacted]
	Drug costs - post-progression	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£3	£[redacted]
	Monitoring costs	£[redacted]	£1,418	£[redacted]
	End-of-life costs	£[redacted]	£8,503	-£[redacted]
	Total cost	**£[redacted]**	**£10,395**	**£[redacted]**
PAS price	Drug costs - progression-free	£[redacted]	£0	£[redacted]
	Drug costs - post-progression	£[redacted]	£0	£[redacted]
	Additional one-time cost post-progression	£[redacted]	£472	-£[redacted]
	Adverse event costs	£[redacted]	£3	£[redacted]
	Monitoring costs	£[redacted]	£1,418	£[redacted]
	End-of-life costs	£[redacted]	£8,503	-£[redacted]
	Total cost breakdown	**£47,249**	**£10,395**	**£36,854**

Source: Bayer response to clarification, Table 38, p.49

5.3.10 Sensitivity analyses

Bayer carried out both one-way sensitivity analyses (OWSA) and probabilistic sensitivity analyses to explore the effect of parameter uncertainty. Scenario analyses were also performed to explore the effects of assumptions in the model.

5.3.10.1 Probabilistic sensitivity analyses

Probabilistic sensitivity analysis (PSA) is a method of allowing all model parameters which are uncertain to vary simultaneously (for example, the exact HSUV for each state may be uncertain, but the list price of the drug is set by the company and is certain). Uncertain parameters were given suitable parametric distributions and repeatedly sampled 3,000 times and the ICERs recorded for each simulation. The probability of HFSR and diarrhoea were not varied in the PSA as there were 0 events in the GRID study making standard errors difficult to estimate. These probabilities were examined in the OWSA, but were found to have negligible effects on the ICERs per QALY. Table 49 shows the average of the simulated ICERs per QALY.

The base case PSA ICERs were £[redacted]/QALY without PAS and £38,494 with PAS. Results from the Monte Carlo simulations were also plotted in the (incremental cost QALY) space shown in Figure 34 and Figure 35 without and with PAS. The proportion of simulations which fall below the willingness-to-pay threshold (dotted line) gives the probability of the treatment being cost-effective. At a threshold of £50,000, regorafenib had a [redacted]% chance to be cost-effective without the PAS, and an 82% chance with the PAS.

Table 49. Average PSA ICER results. 2017 cut-off (with and without PAS)

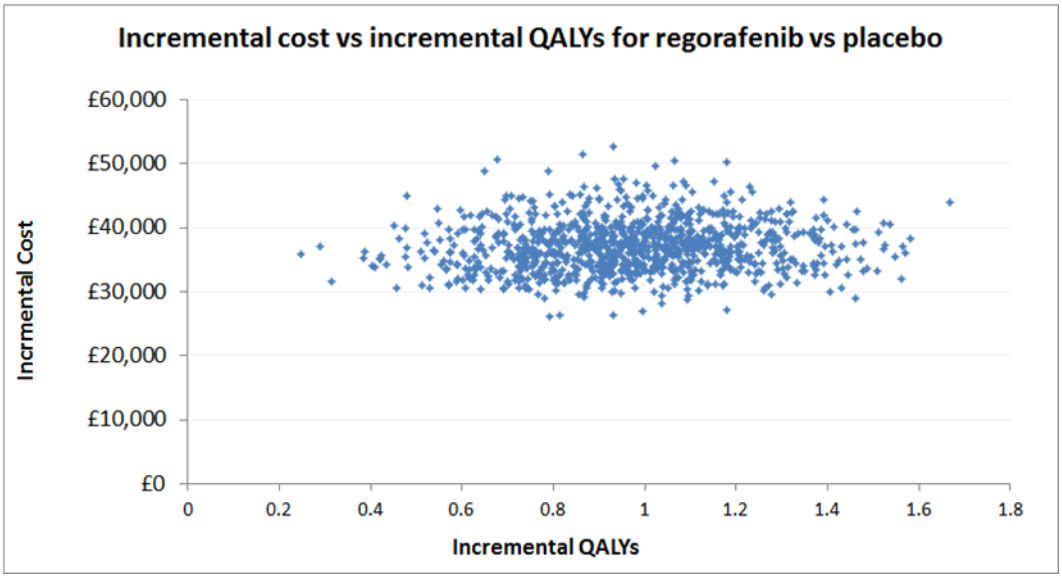
	Regorafenib + BSC			Placebo + BSC			Incremental			ICER (£/QALY)
	LYs	**QALYs**	**Costs**	**LYs**	**QALYs**	**Costs**	**LYs**	**QALYs**	**Costs**	
List Price	2.560	1.741	£[redacted]	1.178	0.776	£11,016	1.382	0.965	£[redacted]	£[redacted]
PAS price	2.533	1.745	£48,152	1.183	0.780	£11,021	1.380	0.965	£37,130	£38,494

Source: Bayer response to clarification, Table 39, p.47

Figure 34. PSA simulation results (no PAS)

Source: Bayer response to clarification, Figure 12, p. 52

Figure 35. PSA simulation results (with PAS)



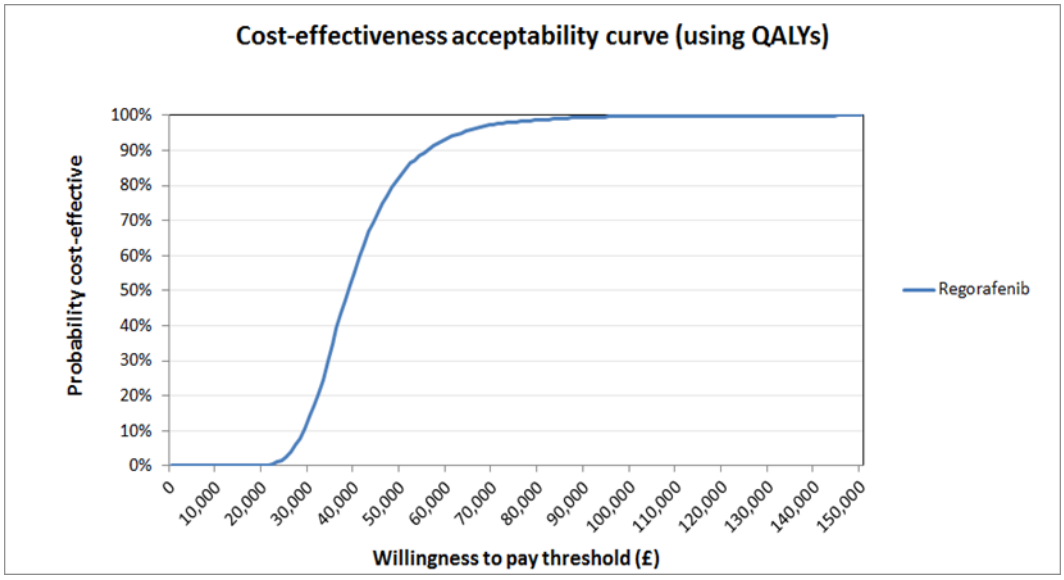
Source: Bayer response to clarification, Figure 14, p. 51

Cost-effectiveness acceptability curves (CEACs) show the probability of the treatment being cost-effective whilst varying the willingness to pay. CEACs without and with the PAS are shown below in Figure 36 and Figure 37.

Figure 36. Bayer base case CEAC (no PAS)

Source: Bayer addendum, Figure 13, p. 51

Figure 37. Bayer base case CEAC (with PAS)



Source: Bayer addendum, Figure 15, p. 52

5.3.10.2 Deterministic sensitivity analyses

The deterministic analyses carried out by Bayer are one-way sensitivity analyses. The input variables and their ranges are displayed below in Table 50, and the tornado diagrams for the top 15 drivers of the ICERs per QALY without and with the PAS are shown in Figure 38 and Figure 39. These variations resulted in ICERs per QALY varying between £[redacted]-£[redacted] at list price and £30,660-£45,222 with the PAS. See Tables 75 and 76 of Bayer's report for a full list of effects.

Table 50. Parameters varied in one-way sensitivity analyses

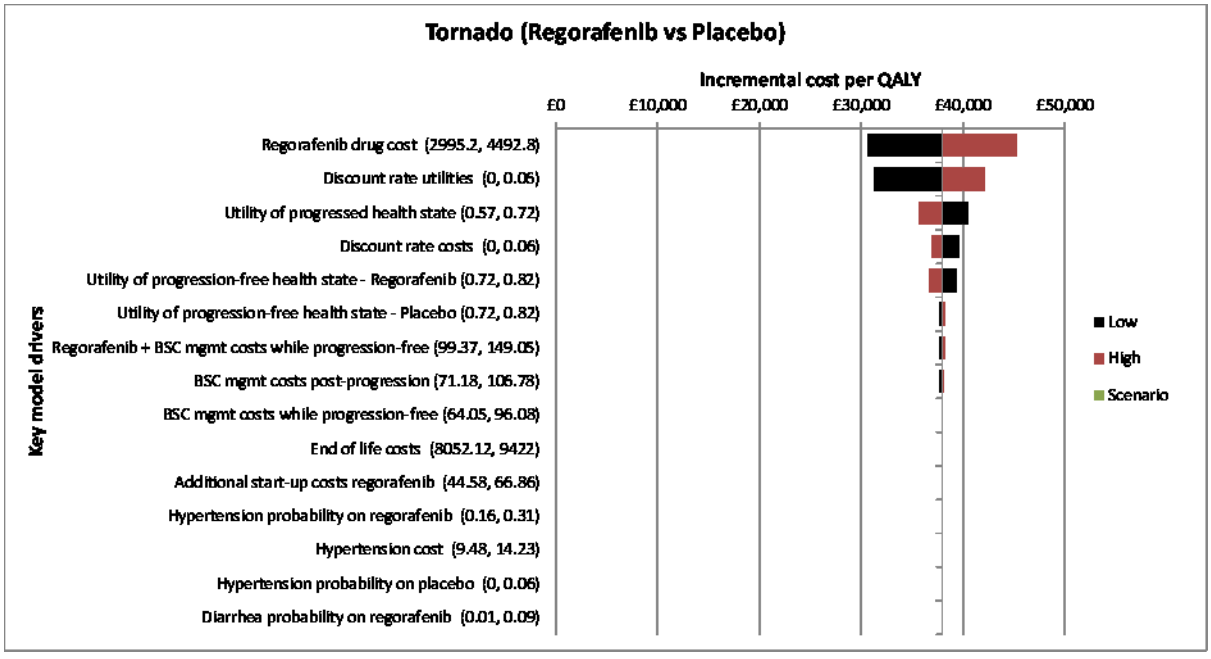
Variable	Input values used in OWSA		Source
	Lower input	**Upper input**	
Discount rate costs	0.00	0.06	Assumption
Discount rate utilities	0.00	0.06	Assumption
Additional one-time costs regorafenib	£44.58	£66.86	± 20% base case value
Regorafenib + BSC management costs while progression-free	£99.37	£149.05	± 20% base case value
BSC management costs while progression-free	£64.05	£96.08	± 20% base case value
BSC management costs post-progression	£71.18	£106.78	± 20% base case value
End of life costs	£8,052.12	£9,422	Abel et al (63)
Diarrhoea cost	£5.62	£8.43	± 20% base case value
Hypertension cost	£9.48	£14.23	± 20% base case value
HFSR probability on regorafenib	0.13	0.26	Base case ± 2 SE
Diarrhoea probability on regorafenib	0.01	0.09	Base case ± 2 SE
Hypertension probability on regorafenib	0.16	0.31	Base case ± 2 SE
Hypertension probability on placebo	0.00	0.06	Base case ± 2 SE
Utility of progression-free health state - Regorafenib	0.72	0.82	Base case ± 2 SE
Utility of progression-free health state - Placebo	0.72	0.82	Base case ± 2 SE
Utility of progressed health state	0.57	0.72	Base case ± 2 SE

Source: Bayer submission, Table 74, p. 208

Figure 38. Tornado diagram of top 15 model drivers, 2017 cut-off (no PAS)

Source: Bayer response to clarification, Figure 16, p. 57

Figure 39. Tornado diagram of top 15 model drivers, 2017 cut-off (with PAS)



Source: Bayer response to clarification, Figure 17, p. 57

5.3.10.3 Scenario analyses

Scenario analyses are designed to explore uncertainty around the structural assumptions of the model (see Table 18 in section 5.3.2 for a list of Bayer's assumptions). All scenario

analyses are reported here using the 2017 data cut-off. Bayer discuss 6 scenario analyses in their submission:

- OS extrapolation using Weibull and Gompertz curves;
- Using RPSFT crossover adjustment instead of IPE with loglogistic, Weibull and Gompertz curves;
- Changing resource use from the physician survey in line with clinical consultants' opinions;
- Costing for regorafenib post-progression in the regorafenib + BSC arm;
- Using repeated measures EQ-5D utility estimates over paired-samples;
- Using EORTC from GRID to derive utility estimates.

Bayer examined the effect of using Weibull and Gompertz parametric functions for OS data (for both placebo and regorafenib), although they argue that the statistical fit is worse than their base case (loglogistic). The Weibull curve caused both QALYs and costs to decrease, and the ICERs increased substantially: £[redacted]/£45,498 per QALY without and with PAS respectively.

The Gompertz model decreased both QALYs and incremental costs, and an increased ICERs of £[redacted]/£47,068 per QALY without and with the PAS respectively. Bayer also investigated the effect of using log-normal and exponential models, but argue that the effect was negligible and did not report results. We agree that the ICERs change only marginally when assuming log-normal distributions. However, using exponential distributions, we find that the ICERs increase substantially, to £[redacted] and £44,827 per QALY without and with the PAS respectively.

Bayer explore the effect of using the RPSFT method of crossover correction along with the loglogistic, Weibull and Gompertz parametric models for OS. The loglogistic case is still favoured using their AIC criterion. The resulting ICERs were:

- Loglogistic (no PAS/PAS): £[redacted]/£39,493 per QALY. These values are slightly higher than Bayer's base case, which use the IPE adjustment method: £[redacted]/ £37,941per QALY).
- Weibull(no PAS/PAS): £[redacted]/£46,996 per QALY
- Gompertz (no PAS/PAS): £[redacted]/£48,360 per QALY.

Bayer examine the effect of updating their resource use data from their physician survey in 2013 with suggestions from their clinical experts. The suggestions were:

- All patients should receive either a CT or a MRI scan prior to starting treatment.
- For progression-free patients on a TKI (i.e. regorafenib) a CT scan would be admitted about every 12 weeks.
- A lower frequency of outpatient visits (progression-free TKI patients from 6.2 weeks to 12 weeks, for BSC progression-free patients from 6.9 to 8-12 weeks).
- Reducing the proportion of progressed patients receiving either palliative resection or radiotherapy by 5%.

These changes resulted in the ICERs decreasing only very slightly: from £[redacted] / £37,941 to £[redacted]/£37,806 per QALY without and with the PAS respectively.

Bayer examine the use of utilities from repeated measures comparison (see Section 5.3.7, p95). Bayer maintain that this method is likely to be less reliable than paired-samples due to a heterogeneous progressed patient population. The ICERs decreased only very slightly, from £[redacted]/ £37,941 to £[redacted]/£36,765 per QALY without and with the PAS respectively.

Bayer also examine the use of the lower utility estimates from the GRID RCT for regorafenib in the PFS state to possibly account for disutility from AEs (see Section 5.3.7, p95). The resulting ICERs decrease only very slightly, to £[redacted]/£37,514 per QALY without and with the PAS respectively.

Finally, Bayer use utility values from the EORTC GRID data, using both repeated measures and paired-samples comparisons. The resulting ICERs were:

- Repeated measures (no PAS/PAS): £[redacted]/£34,281per QALY.
- Paired-samples (no PAS/PAS): £[redacted]/£33,964per QALY.

We agree with Bayer that these values are less relevant than those that underpin their base case, as the EQ-5D is the preferred instrument to measure health-related quality of life.

A summary of ICERs from the scenario analyses is presented below in Table 51.

Table 51. Summary of Bayer scenario analysis ICERs

Scenario analysis	ICER (list price)	ICER (PAS)
Bayer base case	[redacted]	£37,941
Weibull OS curve	[redacted]	£45,498
Gompertz OS curve	[redacted]	£47,068
RPSFT (loglogistic)	[redacted]	£39,493
RPSFT (Weibull)	[redacted]	£46,996
RPSFT (Gompertz)	[redacted]	£48,360
Resource use	[redacted]	£37,806
EQ-5D Repeated measures utility values	[redacted]	£36,765
EQ-5D repeated measures utility values by treatment arm (pre-progression)	[redacted]	£37,514
EORTC utility values (repeated measures)	[redacted]	£34,281
EORTC utility values (paired-samples)	[redacted]	£33,964

Bayer also initially submitted data from the 2015 cut-off. They do not present this as a scenario analysis in their updated report, but we consider it appropriate to present the cost-effectiveness results if only these data were available as a scenario analysis. Table 52 and Table 53 show the ICER per QALY without and with the PAS respectively. The ICERs per QALY were £[redacted]/£34,476 without and with the PAS respectively. This was also based on a different drug acquisition cost methodology; assuming that regorafenib was taken solely in PFS, which is superseded by their 2017 base case method of directly using the GRID data.

Table 52. Base case CE results. 2015 cut-off (no PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (LYs)	ICER (£) incremental (QALYs)
Placebo + BSC	10,671	1.474	0.969					
Regorafenib	[redacted]	2.521	1.717					
				[redacted]	1.047	0.748	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Source: Bayer submission, Table 62, p. 193

Table 53. Base case CE results 2015 cut-off (with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (LYs)	ICER (£) incremental (QALYs)
Placebo + BSC	10,671	1.474	0.969					
Regorafenib	36,457	2.521	1.717					
				25,786	1.047	0.748	24,623	34,476

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Source: Bayer submission, Table 63, p. 193

5.3.11 Model validation and face validity check

Bayer described their validation checks as follows: (source: Bayer submission, p.233):

> *In the course of model development an independent health economic expert, familiar with oncology modelling was consulted. The health economic expert agreed that the modelling approach including the crossover adjustment methods was reasonable and proposed no major changes.*
>
> *A check of validity was performed by the model developers using a quality control process, and a model audit which was performed by an experienced health economist external to the team who built the model. This involved calculation spot checks, cross checks against source data and extreme value scenarios to check if the model behaved logically.*

We consider these checks appropriate.

Bayer describe their clinical validation as follows: (source: Bayer submission, p.233)

The two clinical experts were asked to validate the model inputs and model assumptions. The key points raised by the clinical experts were explored in the scenario analysis. The key points raised were:

- Gompertz and Weibull functions should be explored to reflect alternative long term OS predictions (explored in scenario analyses).

- Some of the resource use assumptions taken from the physician survey conducted in 2013 do not reflect current/best practice. More plausible resource use assumptions should be explored (explored in scenario analyses).

- For patients who progress from BSC to regorafenib the common treatment effect is clinically plausible given the quick progression of patients on the BSC arm (median PFS = 0.9 months).

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

In this section we derive the PenTAG base case (Table 54 below). The impacts of the individual components of our base case on cost-effectiveness are shown, as well as selected combinations of components and finally the base case, which is composed of all relevant components applied simultaneously.

Total uncertainty in the cost-effectiveness of regorafenib versus BSC is high due to:

- Substantial uncertainty in the adjustment for widespread treatment switching on diseases progression, from BSC to regorafenib.
- Important uncertainty in the extrapolation of OS.

Table 54. Derivation of PenTAG base case ICERs Regorafenib vs. BSC (£ per QALY)

				Regorafenib price	
				PAS	List
	Bayer base case			**£38,000**	[redacted]
	PenTAG assumption	**Bayer assumption**			
1	OS from 2015 data-cut	OS from 2017 data-cut	(Section 5.3.6.2, p79)	£49,000	[redacted]
2	Include general mortality from UK population	Do not including general mortality from UK population	(Section 5.3.6.3, p87)	£41,000	[redacted]
3	OS average of Log-logistic / Weibull	OS average Log-logistic	(Section 5.3.6.3, p87)	£41,000	[redacted]
4	Utilities decrease with age	Utilities independent of age	(Section 5.3.7, p95)	£39,000	[redacted]
1 + 2				£52,000	[redacted]
1 + 3				£52,000	[redacted]
2 + 3				£43,000	[redacted]
1 + 2 + 3				£55,000	[redacted]
		ICER		**£56,000**	[redacted]
1+2+3+4	**PenTAG base case**	**Uncertainty**		**High, mostly due to switching adjustment, but also extrapolation.**	

Key: ICER = incremental cost-effectiveness ratio; OS = overall survival; PAS = patient access scheme; PFS= progression-free survival; QALYs = quality-adjusted life year(s);

Dark shading indicates ICER > £50,000 per QALY.

6.1 Key sensitivity analyses applied to PenTAG and Bayer base case

Here, we present key scenario analyses applied separately to the PenTAG and Bayer base cases. These scenarios were chosen either because they demonstrate key messages, e.g. the impact of adjustment for treatment switching (ITT analysis), or because they represent plausible alternatives (all other analyses).

Table 55. ICERs (£/QALY) for Regorafenib vs. BSC given important scenario analyses applied to Bayer base case

		PAS	List
Bayer base case		**£38,000**	[redacted]
ITT analysis	(Section 5.3.6.2, p79)	£149,000	[redacted]
Model costs and QALYs only up to progression	(Section 5.3.6.2, p79)	£52,000	[redacted]
OS from 2017 data cut	(Section 5.3.6.2, p79)	unchanged	unchanged
RPSFTM method (IPE method Bayer base case)	(Section 5.3.6.2, p79)	£39,000	[redacted]
Weibull distribution for OS (log-logistic base case)	(Section 5.3.6.3, p87)	£45,000	[redacted]
Gompertz distribution for OS (log-logistic base case)	(Section 5.3.6.3, p87)	£47,000	[redacted]

Key; PAS = patient access scheme; QALY, quality-adjusted life year
Dark shading indicates ICER > £50,000 per QALY.

Table 56. ICERs (£/QALY) for Regorafenib vs. BSC given important scenario analyses applied to PenTAG base case

		PAS	List
PenTAG base case		**£56,000**	[redacted]
ITT analysis	(Section 5.3.6.2, p79)	£235,000	[redacted]
Model costs and QALYs only up to progression	(Section 5.3.6.2, p79)	£51,000	[redacted]
OS from 2017 data cut	(Section 5.3.6.2, p79)	£44,000	[redacted]
RPSFTM method (IPE method Bayer base case)	(Section 5.3.6.2, p79)	£64,000	[redacted]
Weibull distribution for OS (log-logistic base case)	(Section 5.3.6.3, p87)	£59,000	[redacted]
Gompertz distribution for OS (log-logistic base case)	(Section 5.3.6.3, p87)	£64,000	[redacted]

Key; PAS = patient access scheme; QALY, quality-adjusted life year
Dark shading indicates ICER > £50,000 per QALY.

7 End of life

Bayer argues that their evidence supports inclusion into NICE's End of Life category; that the life expectancy for the patient population is under 24 months with the comparator and that there is sufficient evidence that regorafenib adds at least 3 months additional survival. They cite results from both their economic model and the GRID study. Bayer's model predicts a median OS for patients treated with BSC of about 7.5 months using the 2017 data cut, regardless of whether the crossover correction method is IPE or RPSFT. Using the 2015 data cut, median OS on BSC is between 11.1-11.9 months, depending on whether the crossover correction method is IPE or RPSFT respectively. Bayer also cite the crossover corrected median OS improvement from GRID for regorafenib to be at least 5.5 months, depending on whether IPE or RPSFT methods are used.

Under Bayer's base case, the mean OS for BSC, adjusted for treatment switching, is 1.25 years, substantially below the threshold of 2 years to quality for End of Life. Under our base case, mean OS on BSC is 1.37 years, again, clearly meeting the criterion.

Under Bayer's base case, the mean gain in OS for regorafenib over BSC, adjusted for treatment switching, is 20.5 months, substantially greater than the threshold of 3 months to quality for End of Life. Under our base case, mean OS benefit is 12.5 months, again, clearly meeting the criterion.

Considering all this, we agree with Bayer that regorafenib meets the End of Life criteria.

Based on the ITT data, i.e. without adjustment for treatment switching, Bayer estimate a mean survival benefit of regorafenib over BSC of just 1.4 months, clearly less than the 3 month threshold. So under the ITT analysis, regorafenib would not meet the End of Life criteria.

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Appendix 1. Baseline characteristic of trial participants

Table 57. Characteristics of participants in the studies across treatment groups (GRID study, ITT)

Characteristic	Regorafenib + BSC (n=133)	Placebo + BSC (n=66)
Median Age	60 (51-67)	61 (48-66)
Age group n (%)		
<65 years	90 (67.7)	46 (69.7)
≥65 years	43 (32.3)	20 (30.3)
Sex		
Men	85 (64%)	42 (64%)
Women	48 (36%)	24 (36%)
Ethnic Group		
White	90 (68%)	45 (68%)
Black or African American	0	1 (2%)
Asian	34 (26%)	16 (24%)
Not reported or missing	9 (7%)	4 (6%)
Geographic Region		
Asia	32 (24.1%)	15 (22.7%)
Rest of world	101 (75.9%)	51 (77.3%)
Geographic Region		
North America	22 (16.5%)	14 (21.2%)
USA	15 (11.3%)	11 (16.7%)
Canada	7 (5,3%)	3 (4.5%)
Non-North America	111 (83.5%)	52 (78.8%)
ECOG performance status		
0	73 (55%)	37 (56%)
1	60 (45%)	29 (44%)
Time since initial diagnosis to randomisation		
Mean (range), weeks	296.4 (32.3-774)	310.6 (47.0-657)
Median, weeks	256.0	272.2
Time since recent progression / relapse to randomisation		
Mean (range), weeks	13.29 (0.7-145)	16.7 (0.4-421)
Median, weeks	6.34	4.27
Extent of disease at baseline		
Metastatic	90 (67.7%)	38 (57.6%)
Unresectable	5 (3.8%)	10 (15.2%)
Metastatic and unresectable	35 (26.3%)	14 (21.2%)
Missing	3 (2.3%)	4 (6.1%)
Histology		
Missing	5 (3.8%)	4 (6.1%)
Spindle cells	66 (49.6%)	30 (45.5%)
Epithelioid	12 (9.0%)	4 (6.1%)
Mixed	18 (13.5%)	10 (15.2%)
Unknown	32 (24.1%)	18 (27.3%)
Number of tumour sites		
1	16 (12.0%)	9 (13.6%)
2	31 (23.3%)	20 (30.3%)
3	39 (29.3%)	13 (19.7%)
4	21 (15.8%)	9 (13.6%)
≥5	26 (19,5%)	15 (22.7%)
Previous systemic anti-cancer therapy		
2 lines	74 (56%)	39 (59%)
>2 lines	59 (44%)	27 (41%)
Duration of previous imatinib therapy		
≤ 6 months	18 (14%)	4 (6%)

Characteristic	Regorafenib + BSC (n=133)	Placebo + BSC (n=66)
6–18 months	26 (20%)	7 (11%)
> 18 months	89 (67%)	55 (83%)
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		

Source: Bayer submission, section 4.5, Table 20, p86.

Appendix 2. Adverse events

Table 58. TEAEs (all grade) occurring in ≥10% regorafenib patients during GRID study (NCI CTCAE; SAF)

	Double-blind treatment (data cut-off 26 January 2012)		Data cut-off 08 June 2015	
	Regorafenib + BSC	Placebo + BSC	Regorafenib-treated at any time during study	Subgroup treated with regorafenib for >1 year
	N=132 n (%)	N=66 n (%)	N=190 n (%)	N=75 n (%)
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Blood and Lymphatics Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac	[redacted]	[redacted]	[redacted]	[redacted]
Ear and Labyrinth	[redacted]	[redacted]	[redacted]	[redacted]
Endocrine Hypothyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal Abdominal pain Constipation Diarrhoea Dyspepsia Mucositis oral Nausea Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
General and Administrative Site Conditions Fatigue Fever Oedema limb Pain	[redacted]	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Infection and Infestations Bronchial infection Rash pustular Upper respiratory infection	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]
Investigations Alanine aminotransferase increased (ALT) Aspartate aminotransferase increased (AST) Blood bilirubin increased Platelet count decreased Weight Loss	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and Nutrition Anorexia Hyperglycaemia Hypokalaemia	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and Connective Tissue Arthralgia Back pain	[redacted]	[redacted]	[redacted]	[redacted]

	Double-blind treatment (data cut-off 26 January 2012)		Data cut-off 08 June 2015	
	Regorafenib + BSC	Placebo + BSC	Regorafenib-treated at any time during study	Subgroup treated with regorafenib for >1 year
	N=132 n (%)	N=66 n (%)	N=190 n (%)	N=75 n (%)
Myalgia Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]
Nervous System Dysgeusia Headache Paraesthesia	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders Insomnia			[redacted]	[redacted]
Renal and urinary Proteinuria	[redacted]	[redacted]	[redacted]	[redacted]
Reproductive system and breast disorders			[redacted]	[redacted]
Respiratory, Thoracic and Mediastinal Cough Dyspnoea Hoarseness Voice alteration	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue Alopecia Palmar-Plantar Erythrodysaesthesia Syndrome Pruritus Rash maculopapular	[redacted]	[redacted]	[redacted]	[redacted]
Vascular Hypertension	[redacted]	[redacted]	[redacted]	[redacted]

BSC=Best supportive care; TEAE=Treatment-emergent adverse event; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0; A patient may have experienced more than one TEAE.

Source: Bayer submission, Section 4.12, Table 25, p122

Appendix 3. AICs/BICs for parametric OS extrapolation

Table 59. AICs for parametric OS extrapolation (2015 data cut off)

Parametric Model	**Regorafenib**	**Placebo**		**Sum AIC (placebo + regorafenib)**	
		RPSFT	*IPE*	*RPSFT*	*IPE*
Exponential	390.96	196.66	195.24	587.62	586.21
Loglogistic	**388.92**	**195.74**	**193.24**	**584.66**	**582.16**
Weibull	391.25	198.43	196.92	589.67	588.17
Lognormal	393.24	197.25	194.77	590.49	588.01
Gompertz	392.85	198.39	196.89	591.23	589.74

Source: Bayer submission, Table 32, p.160

Table 60. AICs for parametric OS extrapolation (2017 data cut off)

Parametric Model	**Regorafenib**	**Placebo**			**Sum AIC (placebo + regorafenib)**		
		Un-adjusted	**RPSFT**	**IPE**	**Un-adjusted**	**RPSFT**	**IPE**
Exponential	394.12	**201.84**	192.53	192.00	595.96	586.65	586.12
Loglogistic	**391.08**	204.83	**188.99**	**187.78**	**595.92**	**580.08**	**578.86**
Weibull	394.93	203.80	193.89	193.32	598.73	588.82	588.25
Lognormal	395.36	206.53	190.64	189.48	601.89	586.00	584.84
Gompertz	396.12	203.80	194.21	193.60	599.92	590.33	589.72

Source: Bayer addendum, Table 4, p. 13

Table 61. BICs for parametric OS extrapolation (2015 data cut off)

Parametric Model	Regorafenib	Placebo		Sum BIC (placebo + regorafenib)	
		RPSFT	***IPE***	***RPSFT***	***IPE***
Exponential	**393.85**	**198.85**	**197.43**	**592.7**	**591.28**
Loglogistic	394.7	200.12	197.62	593.97	591.47
Weibull	397.03	202.81	201.3	596.66	595.15
Lognormal	399.02	201.63	199.14	595.48	592.99
Gompertz	398.63	202.77	201.27	596.62	595.12

Source: Bayer submission, table 33, p.160

Table 62. BICs for parametric OS extrapolation (2017 data cut off)

Parametric Model	Regorafenib	Placebo			Sum BIC (placebo + regorafenib)		
		Un-adjusted	**RPSFT**	**IPE**	**Un-adjusted**	**RPSFT**	**IPE**
Exponential	397.01	**204.03**	194.72	194.19	**601.04**	591.73	591.20
Loglogistic	**396.87**	209.21	**193.37**	**192.16**	606.08	**590.24**	**589.02**
Weibull	400.71	208.18	198.27	197.70	608.89	598.98	598.41
Lognormal	401.14	210.91	195.02	193.86	612.05	596.16	595.00
Gompertz	401.90	208.18	198.59	197.98	610.08	600.49	599.88

Erratum for

Title: Regorafenib for previously treated unresectable or metastatic gastrointestinal stromal tumours

Produced by	Peninsula Technology Assessment Group (PenTAG) University of Exeter Medical School South Cloisters St Luke's Campus Heavitree Road Exeter EX1 2LU
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Contributions of authors

Tracey Jones-Hughes	Led the critique of the company's decision problem and clinical effectiveness evidence. Wrote the Summary, Background, Decision problem, Clinical effectiveness and Overall conclusions. Compiled the report. Provided overall project management.
James Dunham	Contributed to the critique of the economic model and contributed to writing the Cost-effectiveness and End-of-life sections.
Sophie Robinson	Led the critique of the company's literature searching for this submission. Wrote the review of the literature searches for the report. Contributed to the writing and editing of the report.
Mark Napier	Provided clinical advice on soft tissue sarcoma and its management within the NHS. Reviewed and revised a draft version of the report.
Martin Hoyle	Contributed to writing the Cost-effectiveness and End-of-life sections. Contributed to the critique of the economic model and is the guarantor of the report.

for 16.8% of patients and distributed across all system organ classes. Five deaths were reported as related to regorafenib treatment by investigators (cardiac arrest, acute hepatic failure, acute kidney injury, colonic perforation, and thromboembolic event).

The most serious adverse drug reactions in patients receiving regorafenib were haemorrhage, severe liver injury, and gastrointestinal perforation and the most common adverse events included hand-foot skin reaction (HFSR), hypertension, diarrhoea, mucositis and fatigue

1.3 Summary of the ERG's critique of the clinical effectiveness evidence submitted

The methods for the searches and systematic review were adequate and well described, therefore, the ERG concluded that the company did not miss any evidence.

The primary focus of the company's submission was the GRID study. This was an appropriately-designed double-blinded, multi-centre RCT. The treatment arms were balanced and patients were representative of the UK population.

The crossover of 87.9% of placebo-treated patients to open-label regorafenib following disease progression may cause the OS to be overestimated, assuming regorafenib provides a clinical benefit for this outcome. Therefore Bayer applied two correction methods, which have been assessed as appropriate by the ERG, resulting in a statistically significant difference for OS in favour of regorafenib.

1.4 Summary of cost-effectiveness evidence submitted by the company

So far, we have received a total of three versions of Bayer's economic model and cost-effectiveness results.

We received Bayer's economic model and full report on 21st March 2017.

On 25th April 2017, after an earlier request for clarification from us, we received a second version of Bayer's economic model and cost-effectiveness results. This included some updated OS data, as discussed in Section **Error! Reference source not found.**, p**Error! Bookmark not defined.**.

On 16th May 2017, in response to another request for clarification from us, we received a third version of Bayer's economic model and cost-effectiveness results. In addition to the updated OS data, this also included some updated data on treatment duration and mean

observed dose of regorafenib (excluding those with a dose of 0 mg) by cycle, as discussed in Section 5.3.8.1, p102.

censoring date within the crossover adjustment calculation" (Bayer response to clarification, p11). This reduction in mean OS substantially improves the cost-effectiveness of regorafenib. For example, assuming the PAS, the ICER for regorafenib vs. BSC decreases from £49,000 to £38,000 per QALY.

However, we have several important concerns with the switching adjustment applied to the 2017 data. Given these concerns, we use the 2015 data-cut for OS in our base case.

We turn now to the extrapolation of OS. Two consultant oncologists, who specialised in the disease area, validated the fittings of various parametric models, on behalf of Bayer. They argued that the loglogistic, Weibull and Gompertz models all looked clinically plausible. However, in their base case, Bayer chose the log-logistic distribution for OS based on the accuracy of the fit the data from GRID.

We surveyed the literature for studies that could help to inform the extrapolation of OS. We found just one relevant study, which suggested, if anything, a reasonably long tail for OS. However, we caution not to rely solely on this study to inform extrapolation, due to limitations in comparability with the GRID study. On balance, in our base case, we model OS as the average of the shorter-tailed Weibull and longer-tailed log-logistic distributions.

Bayer do not explicitly model background general population mortality. In our base case, we include this additional mortality.

1.4.2.3 End of Life criteria

We agree with Bayer that regorafenib meets the End of Life criteria.

1.4.3 Results

In Bayer's base case analysis (without/with PAS), treatment with regorafenib resulted in 1.7333 QALYs at a cost of [redacted]/£47,249, while treatment with the placebo resulted in 0.761 QALYs at a cost of £10,395. The QALY differential was 0.971 and the cost differential was £[redacted]/£36,854. The corresponding ICERs per QALY were £[redacted]/£37,941.

Regorafenib was predicted to result in QALY gains in both PFS and OS, with the benefits roughly similar in both health states. The overall QALY gain depends heavily on the treatment switching adjustments.

Drug acquisition costs were by far the largest cost in the regorafenib arm at £[redacted]/£35,363 which was also the incremental cost as the placebo arm had zero drug costs. Other cost differentials were much smaller; the next largest incremental cost was +£[redacted] for monitoring costs in the regorafenib arm. Remaining costs were very similar between the two treatment arms.

In the probabilistic sensitivity analysis, the ICERs per QALY were similar to the deterministic case at £[redacted]/£38,494 without and with the PAS. Both costs and QALYs were very similar to the base case. At a willingness to pay threshold of £50,000 per QALY, regorafenib had a [redacted]/82% chance of being cost-effective.

Univariate sensitivity analyses were also carried out, indicating that results were sensitive to a number of parameters. Regorafenib drug costs and utility discount rates were the most impactful parameters, with HSUVs and cost discount rates also being significant.

Bayer also carried scenario analyses looking at assumptions for: OS extrapolation, treatment switching, resource use, and utility elicitation method. The most impactful of these were the choice of OS extrapolation, and the method of treatment switching adjustment.

1.5 Summary of the ERG's critique of the cost-effectiveness evidence submitted

The derivation of the PenTAG base case is shown in **Table 1** below.

Total uncertainty in the cost-effectiveness of regorafenib versus BSC is high due to:

Substantial uncertainty in the adjustment for widespread treatment switching on diseases progression, from BSC to regorafenib.

Important uncertainty in the extrapolation of OS.

In key plausible scenario analyses, we suggest alternative plausible methods of extrapolating OS, and of modelling costs and QALYs only whilst patients are in PFS.

Table 1. Derivation of PenTAG base case ICERs Regorafenib vs. BSC (£ per QALY)

				Regorafenib price	
				PAS	List
	Bayer base case			**£38,000**	[redacted]
	PenTAG assumption	**Bayer assumption**			
1	OS from 2015 data-cut	OS from 2017 data-cut	(Section **Error! Reference source not found.**, p**Error! Bookmark**	£49,000	[redacted]

			not defined.)		
2	Include general mortality from UK population	Do not including general mortality from UK population	(Section **Error! Reference source not found.**, p**Error! Bookmark not defined.**)	£41,000	[redacted]

Following adjustment for crossover, both the 2015 and 2017 data indicate a statistically significant difference in overall survival favouring regorafenib. The RPSFT method, based on 2015 data, gave a median OS 17.4 months over the placebo median OS of 11.9 months. Based on 2017 data, the RPSFT method for placebo gave a median OS of 8.4 months. Using the IPE method, placebo gave a median OS of 11.1 months based on 2015 data and 8 months based on 2017 data. The 2017 data show a longer OS benefit compared to placebo (varying from 9 to 9.4 months) than when considering the 2015 data (varying from 5.5 to 6.3 months).

Time to progression

For the cut-off date of 26th January 2012, 57.1% of participants in the regorafenib group experienced disease progression and 93.9% in the placebo group. Median TTP was reported as 165 days in the regorafenib group and 28 days in the placebo group (HR 0.248, [95% CI: 0.170-0.364, p<0.000001]). Therefore, there is a statistically significant difference between arms, in favour of regorafenib for TTP.

Objective Response Rate, Disease Control Rate and Duration of Response

For ORR, although numerically in favour of regorafenib, there was no statistically significant difference between the two arms: 4.5% with regorafenib (PR n= 6/133) vs. 1.5% with placebo (PR n=1/66) and there were no cases reported of complete response.

[redacted]

The disease control rate (DCR) reflects the percentage of patients with metastatic cancer who have achieved complete response, partial response and stable disease, as opposed to ORR which only includes CR or PR. Stable disease was reported by the company to be 71.4% (95/133 patients) in the regorafenib arm as compared to 33.3% (22/66 patients) in the placebo arm. Therefore, DCR for the regorafenib group was 52.6% (n=70/133) compared with 9.1% (n=6/66) in the placebo group (95% CI: –54.72, –32.49; p<0.0001). Bayer suggest this outcome indicates the clinically meaningful tumour control of regorafenib as a third-line treatment in patients with advanced GIST.

With regard to median duration of response, only one patient in the placebo group reported PR, which was 30 days, whereas the median duration of response for patients receiving regorafenib was 99 days.

Maximum percent reduction in the size of target lesions

[redacted]

4.2.2.4.3 Exploratory endpoints

Secondary PFS (SPFS)

Bayer investigated secondary PFS for participants who crossed over from placebo to regorafenib (n=56; 151 days) and for participants who continued on open label regorafenib,

Figure 1. Overall survival by subgroup, IPE correction (data cut-off 08 June 2015)

Source: Bayer submission, Section 4.8, p108

4.2.2.4.5 Adverse events

The GRID study included 198 participants in the safety population, which included 132 in the regorafenib arm and 66 participants in the placebo arm who received at least one dose of regorafenib. The analysis included treatment-emergent adverse events (TEAEs) occurring up to the primary efficacy analysis cut-off date of 26th January 2012.

Secondary analyses included patients who crossed over to regorafenib from placebo (n=132+58) and a subgroup of patients who received regorafenib for over 1 year (n=75).

A summary for all grade adverse events (AEs) is presented in **Error! Reference source not found.** which reports the incidences of AEs for > 10 % of people in any treatment arm. The main groups are included, with further detail on individual conditions provided in **Error! Reference source not found.**.

End of life costs were taken from the study conducted by Abel et al [24], a UK hospice-based study. Costs were inflated to 2015/2016 level. The final EoL cost used is £8,736. Finally, **Table 2** gives a complete summary of per-cycle variable costs and non-cost parameters.

Table 2. Summary of variables applied in the economic model (per cycle)

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Regorafenib cost	£[redacted]	(£[redacted]-£[redacted])	Table 45
One-time costs for regorafenib	£56	(£45-£67)	Table 54
Regorafenib + BSC while progression-free	£124	(£99-£149)	Table 54
BSC while progression-free	£80	(£64-£96)	Table 54
BSC post-progression	£89	(£71-£107)	Table 54
End of life costs	£8,736	(£8,052-£9,422)	Table 58
Diarrhoea costs	£7	(£6-£8)	Table 55
Hypertension costs	£12	(£9-£14)	Table 56
Progression-free state utility	0.767	(0.718-0.816)	Table 36
Post-progression state utility	0.647	(0.571-0.723)	Table 36
Discount rate (costs)	3.5%	(0-6%)	Table 29
Discount rate (benefits)	3.5%	(0-6%)	Table 29

Source: Bayer submission, Table 60, p.190

5.3.9 Cost-effectiveness results

Bayer's base case ICERs of regorafenib plus BSC compared to BSC alone are £[redacted]QALY and £37,941/QALY without and with the PAS respectively. **Error! Reference source not found.** and

5.3.10 Sensitivity analyses

Bayer carried out both one-way sensitivity analyses (OWSA) and probabilistic sensitivity analyses to explore the effect of parameter uncertainty. Scenario analyses were also performed to explore the effects of assumptions in the model.

5.3.10.1 Probabilistic sensitivity analyses

Probabilistic sensitivity analysis (PSA) is a method of allowing all model parameters which are uncertain to vary simultaneously (for example, the exact HSUV for each state may be uncertain, but the list price of the drug is set by the company and is certain). Uncertain parameters were given suitable parametric distributions and repeatedly sampled 3,000 times and the ICERs recorded for each simulation. The probability of HFSR and diarrhoea were not varied in the PSA as there were 0 events in the GRID study making standard errors difficult to estimate. These probabilities were examined in the OWSA, but were found to have negligible effects on the ICERs per QALY. **Error! Reference source not found.** shows the average of the simulated ICERs per QALY.

The base case PSA ICERs were £[redacted]/QALY without PAS and £38,494 with PAS. Results from the Monte Carlo simulations were also plotted in the (incremental cost QALY) space shown in **Error! Reference source not found.** and **Error! Reference source not found.** without and with PAS. The proportion of simulations which fall below the willingness-to-pay threshold (dotted line) gives the probability of the treatment being cost-effective. At a threshold of £50,000, regorafenib had a [redacted]% chance to be cost-effective without the PAS, and an 82% chance with the PAS.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Regorafenib for treating advanced gastrointestinal stromal tumours [ID1056]

You are asked to check the ERG report from Peninsula Technology Assessment Group (PenTAG) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on 12 June 2017** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
"…*this also included some updated data on treatment duration of regorafenib as discussed in Section 5.3.8.1, p102*." (ERG report, page 14) Updated data also included the mean observed dose of regorafenib (excluding those with a dose of 0mg) by cycle. This important detail is not mentioned in the report.	"…*this also included some updated data on treatment duration* ***and mean observed dose of regorafenib (excluding those with a dose of 0mg) by cycle***"	This is an important detail as the mean observed dose of regorafenib by cycle has an impact on the total acquisition costs of regorafenib. The exclusion of doses of 0mg represents a conservative scenario implying a higher mean observed dose of regorafenib and, as a consequence, a higher estimate of its acquisition cost.	We accept the proposed change.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
"*The QALY differential was 0.971 and the cost differential was £[redacted]/£36,864*." (ERG report, page 16) The cost differential when considering the PAS is £36,854.	"The QALY differential was 0.971 and the cost differential was £[redacted]**/£36,854**."	The cost differential reported in this sentence of the ERG report when considering the PAS price is not the same as the one reported in Bayer's submission.	We accept the proposed change.

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
"*Drug acquisition costs were by far the largest cost in the regorafenib arm at £[redacted]/£35,636, which was also the incremental cost as the placebo arm had zero drug…"* (ERG report, page 16) The cost differential when considering the PAS is £35,363.	"Drug acquisition costs were by far the largest cost in the regorafenib arm at £[redacted]**/£35,363**, which was also the incremental cost as the placebo arm had zero drug…"	The cost differential reported in this sentence of the ERG report when considering the PAS price is not the same as the one reported in the Bayer's submission.	We accept the proposed change.

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
"*In the probabilistic sensitivity analysis, the ICERs per QALY were similar to the deterministic case at £[redacted]/£38,949 without and with the PAS.*" (ERG report, page 17) The ICER with the PAS is £38,494.	"*In the probabilistic sensitivity analysis, the ICERs per QALY were similar to the deterministic case at £[redacted]**/£38,494** without and with the PAS.*" (ERG report, page 17)	The ICER with PAS reported in this sentence of the ERG report is not the same as the one reported in Bayer's submission.	We accept the proposed change.

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
"*Following adjustment for crossover, both the 2015 and 2017 data, indicate a*	"*Following adjustment for crossover, both the 2015 and 2017 data, indicate*	Median OS for placebo when considering the 2017 data is	We accept the proposed change, but have re-worded

statistically significant difference in overall survival favouring regorafenib (median OS 17.4 months) over placebo (median OS 11.9 months using RPSFT method or 11.1 months using IPE method)." (ERG report, page 55) Median OS for placebo when considering the 2017 data is 8.4 months using RPSFT method or 8 months using IPE method.	*a statistically significant difference in overall survival favouring regorafenib (median OS 17.4 months) over placebo (median OS 11.9 months* ***(based on 2015 data) and 8.4 months (based on 2017 data)*** *using RPSFT method or 11.1 months* ***(based on 2015 data) and 8 months (based on 2017 data)*** *using IPE method). The 2017 data show a longer OS benefit compared to placebo (varying from 9 to 9.4 months) than when considering the 2015 data (varying from 5.5 to 6.3 months) "*	different from median OS when considering the 2015 data	slightly for clarity.

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
"The GRID study included 198 participants in the safety population, which included 162 in the regorafenib arm and 66 participants in the placebo arm who received at least one dose of regorafenib." (ERG report, page 61) Participant in the safety population in the regorafenib arm were 132.	*"The GRID study included 198 participants in the safety population, which included* ***132*** *in the regorafenib arm and 66 participants in the placebo arm who received at least one dose of regorafenib."*	In the GRID trial, the safety population in the regorafenib arm included 132 participants.	We accept the proposed change.

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
"*Only the 2015 data cut appears in Bayer's Clinical Study Report. The 2017 data does not appear in this document.*" (ERG report, page 82)	"*Only the 2015 data cut appears in Bayer's Clinical Study Report.*"	The 2017 OS data are reported in a different clinical study report addendum. This clinical study report was not ready at the time of the ERG request for the availability of more recent OS data.	This is not a factual inaccuracy, because at the time of our report submission, we had not been provided with the CSR Addendum. However, after submission of our report, we have now received the CSR Addendum reporting the 2017 data cut. We find the information in this Addendum to be consistent with the information that Bayer have previously reported about the 2017 data.

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
"*Given all these concerns, we use the 2015 data-cut for OS in our base case.*" (ERG report, page 83)	The base case analysis should be conducted using the most up-to-date data available.	The 2017 OS data was gathered and implemented in the model in response to an ERG request for more up-to-date evidence on OS.	This is not a factual inaccuracy. As explained in our report, all others things being equal, of course we should use the most up to date data, in this case, the 2017 data. However, in our report, p82, Section 5.3.6.2, we list 5 concerns we have with the 2017 data. Bayer have addressed only the

			first these, concerning the availability of the CSR for the 2017 data. Therefore, we still prefer to assume the 2015 OS data in the economic model.

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
"*We believe essential to incorporate background mortality. This is because mortality in GRID will be due almost exclusively to causes related to GIST*" (ERG report, page 90) Double counting of the background mortality.	Inclusion of background mortality for the general population is not essential because this is included in the Kaplan-Meier curves for the overall survival since the trial already captures death due to any cause. Inclusion of background mortality would be double counting.	At page 53 of the GRID study protocol, overall survival is defined as a study outcome measured from the date of randomization until the date of death due to any cause. Hence, background mortality is already captured in the overall survival function considered in Bayer's model and submission.	We agree that inclusion of background mortality does amount to double counting of background mortality during the follow-up of the GRID RCT. Despite this, we maintain that our approach constitutes a more accurate way to model OS than the approach taken by Bayer. First, the extent of double counting during the trial follow-up period is extremely small. For example, half way to maximum trial follow up, at 2.4 years, with patients aged 62.4 years, predicted OS for regorafenib based on Bayer's log-logistic is 0.327, versus 0.321 using the log-logistic and background mortality combined, a difference of just 2%. At maximum trial follow-up of 4.7 years, with patient aged 64.7, predicted OS based on Bayer's log-logistic is 0.148, versus 0.142 using the log-logistic and background mortality combined, a difference of 4%. Whereas in the extrapolated period, at 10 years, with patients aged 70, OS is 0.052 and 0.047, with a difference of 10%. At 20 years when patients are aged 80, OS is 0.019 and 0.012, a

			difference 33%. It is important to independently model background mortality because this is relatively minor during the trial follow-up period, but much more substantial in the extrapolated period. This is not captured in Bayer's approach of simply extrapolating OS from the RCT. It would be possible to perform a more exact analysis, by adjusting the statistical curve fit, e.g. log-logistic ore Weibull, in such a way that the combination of the adjusted curve plus background mortality fits the trial data more exactly than our approach of modelling the unadjusted curve plus background mortality. Due to time constraints, we have not done this and besides, to do precisely, would require use of the individual patient data, to which we do not have access. However, it is likely that such an adjustment would result in only a minimal change in modelled OS, because, as discussed above, our modelled OS fits the clinical data nearly as well as Bayer's fit.

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
"*Therefore, in our base case, we model OS as the average of the Weibull and log-logistic distributions, adjusted for general background mortality*". (ERG	The base case analysis should be based on the selection of the best fitting distribution. This distribution should be selected according to the approach recommended in the NICE DSU TECHNICAL SUPPORT DOCUMENT	As reported in the NICE DSU technical support document 14, the selection of the best fitting model should be based on a systematic assessment of different distributions. This approach includes also the AIC/BIC tests (or other suitable tests of	We do not consider this a factual inaccuracy. We agree that, as explained in the TSD, the closeness of fit to the clinical data is a factor in the

report, page 94)	14.	internal validity), where a lower AIC/BIC value indicates a better fitting distribution. On the basis of this criterion, the average of the Weibull and log-logistic distributions would still result in having a higher AIC/BIC value as compared to the log-logistic distribution alone. The log-logistic function should still be used in the ERG base case analysis.	choice of curve. However, the TSD also recommends consideration of external data to inform the tail of the curve fit, e.g. clinical expert opinion, observational data with longer follow up.

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
"*Bayer's base case ICERs of regorafenib plus BSC compared to BSC alone are £[redacted]/QALY and £37,941/QALY without and with the PAS respectively*" (ERG report, page 113)	Bayer's base case ICERs of regorafenib plus BSC compared to BSC alone are £[redacted]/QALY and £37,941/QALY without and with the PAS respectively	In Bayer's submission, the base case ICER when considering the list price of regorafenib is £[redacted]/QALY.	We accept the proposed change.

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
"*The base case PSA ICERs were £[redacted]/QALY without PAS and £38,494 with PAS.*" (ERG report, page 117)	*The base case PSA ICERs were £[redacted]/QALY without PAS and £38,494 with PAS*	In the Bayer's submission, the base case PSA ICER when considering the list price of regorafenib is £[redacted]/QALY.	We accept the proposed change.

15/06/2017

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Single Technology Appraisal

Regorafenib for treating advanced gastrointestinal stromal tumours [ID1056]

Dear [redacted]

We have a few queries ahead of the committee meeting that we would like to discuss in order to allow as full a discussion as possible at the committee meeting. It would be helpful if we could have a teleconference to help us answer the following:

1. The company did not report a change in the maximum follow up time from 2015 to 2017 (both reported as 1,397 days) please could you clarify that this is correct when we would expect maximum follow up time for 2017 data to be greater?
2. The KM curves for 2015 and 2017 look similar but the company report a 24% reduction in mean OS in the placebo arm (see page 83 of the ERG report for more detail) - can the company confirm if this is correct and explain how a small increase in maturity can result in a large reduction?
3. The p-values differ for uncorrected and corrected OS hazard ratios for the 2015 and 2017 data (see table 22 of company submission and table 13 of the ERG report) - can the company explain why this is the case when we would expect the uncorrected and corrected values under the RPSFT and IPE methods for treatment switching to be identical to the ITT p-values?
4. In the company's submission (table 61 on page 195) it states that patients discontinuing treatment prior to progression are not assigned a cost of active treatment. Can the company confirm whether this stands for the new company base case?
5. In the new company base case, time to discontinuation is used directly from the GRID trial but how are the costs of regorafenib adjusted for dose intensity?
6. Could the company provide further explanation for using fully parametric extrapolation for PFS instead of using the trial data alone?

Please let us know your availability for a teleconference tomorrow or Monday 19th June and we will arrange this.

Thanks

[redacted] [redacted]
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Responses

1. Apologies for this error, the maximum follow-up time was 1,708 and 1,397 days for the 2017 and 2015 OS data, respectively.
2. We are unable to replicate the ERGs figures of 24% and did not find a description of this calculation in the text. We observed an increase of around 40 days in median OS difference between arms when moving from the 2015 to 2017 data and extending maximum follow up by around 300 days. This is associated with a change in the unstratified HR from 0.551 to 0.456. We note that the two datasets were dealt with using the same methodology and following DSU advice.

   The observed difference in outcomes between the 2015 and 2017 data comes from a combination of two effects as a result of updating the data:

   - Differences in events (additional deaths or changes to censoring times) due to increased certainty in the tail of the survival curve
   - Increase in follow-up affecting algorithm applied in the crossover correction

   Differences in events There are some differences in outcomes between 2015 and 2017 data as there is greater certainty in the tail with the more recent data and this difference favours the active (regorafenib) arm. We tested the effect of this difference by analysing the impact of updating the data but disabling any recensoring. When recensoring is disabled (and the follow-up duration is not directly applicable to the crossover calculation) the difference (measured by HRs) between the 2015 and 2017 results is around half the observed difference (2015 unstratified HR: [redacted] vs 2017 unstratified HR: 0.544).

   Increase in follow up The second key of the difference is due to application of recensoring. In line with NICE DSU guidance patients in the adjusted placebo arm are recensored – not all their data is used – at the end of the observed period, in order to avoid bias associated with informative censoring. With the extended follow-up period, the amount of information lost in this way is reduced and the difference between treated and untreated patients is increased.

   We examined the impact of applying the same increase in follow-up to the 2015 data, leaving the data unchanged, altering only the potential censoring time in the *strbee* command. A decrease in the hazard ratio of around 0.05 was observed, again accounting for approximately half the difference (measured by HRs) observed between the 2015 and 2017 data.
3. ERG is correct that following DSU guidance the p-values should be unchanged. The values in the company evidence submission comparing the adjusted placebo and unadjusted regorafenib arms should be removed. This will not impact the cost-effectiveness results. Note that the 2015 HRs

(table 22 of the company submission) are not recensored and should not be compared with the recensored 2017 HRs (table 13 of the ERG report).

4. The new company base case does not distinguish between costs of active treatment encountered in the pre and post progression health states. Instead, total drug acquisition costs of regorafenib are calculated based on the GRID Kaplan Meier time to treatment discontinuation curve (Figure 22 of the ERG report). This curve presents the proportion of patients on regorafenib treatment in the GRID trial for each day on treatment since randomisation.
5. Dose intensity is captured in the new company base case by including the GRID mean observed dose of regorafenib (excluding those with a dose of 0mg) by model cycle in line with the safety analysis set excluding time off drug/interruptions (GRID Amended CSR No. A59137). This conservative approach generates a greater average dose of regorafenib per cycle compared to when the 0mg dose is included in the calculations. If those with a dose of 0mg but who then resume treatment later (e.g. due to interruptions) are included within the analysis (using company model based on the 2017 data cut) the resulting ICER per QALY decreases from £[redacted] to £[redacted] (list price) and from £37,941 to £36,357 (PAS). When implementing the same calculation within the ERG base case analysis (based on the 2015 data cut) the resulting ICER per QALY decreases from £[redacted] to £[redacted] (list price) and from £55,672 to £53,323 (PAS).
6. Full parametric PFS was selected because of the following main reasons:
    - The final analysis for the primary endpoint PFS was performed at primary completion (26 January 2012 data cut-off date). Because no further PFS data were collected after primary completion of the GRID study the data are not complete. In order to directly use the KM data additional assumptions would have to be made (e.g. that all patients progress at end of follow-up)
    - Implementation of the full parametric curve for PFS is consistent with the methodology used for the OS data
    - The use of parametric PFS is consistent with previous company submissions

    Additionally, the trial data is very similar to the parametric curve and therefore we would expect little difference in outcomes.

Regorafenib for previously treated unresectable or metastatic gastrointestinal stromal tumours

PenTAG response to Bayer replies to questions from NICE

26th June 2017

Recently, NICE asked Bayer the following questions:

1. The company did not report a change in the maximum follow up time from 2015 to 2017 (both reported as [redacted] days) please could you clarify that this is correct when we would expect maximum follow up time for 2017 data to be greater?

2. The KM curves for 2015 and 2017 look similar but the company report a 24% reduction in mean OS in the placebo arm (see page 83 of the ERG report for more detail) - can the company confirm if this is correct and explain how a small increase in maturity can result in a large reduction?

3. The p-values differ for uncorrected and corrected OS hazard ratios for the 2015 and 2017 data (see table 22 of company submission and table 13 of the ERG report) - can the company explain why this is the case when we would expect the uncorrected and corrected values under the RPSFT and IPE methods for treatment switching to be identical to the ITT p-values?

4. In the company's submission (table 61 on page 195) it states that patients discontinuing treatment prior to progression are not assigned a cost of active treatment. Can the company confirm whether this stands for the new company base case?

5. In the new company base case, time to discontinuation is used directly from the GRID trial but how are the costs of regorafenib adjusted for dose intensity?

6. Could the company provide further explanation for using fully parametric extrapolation for PFS instead of using the trial data alone?

On 21st June 2017, NICE sent us Bayer's responses to these questions. We now comment on Bayer's responses.

Question 1

We raised this concern in our report.

Bayer apologised for the error, and said the maximum follow-up times were [redacted] and [redacted] days for the 2017 and 2015 OS data respectively.

As stated in our report, we assumed that the maximum follow-up time shown in the Kaplan-Meier graph for the switching-adjusted placebo OS data would be greater for the 2017 data-cut compared to the 2015 cut, given that the 2017 data is more mature. However, as can be seen in Figure 23 in our report, the maximum follow up times are equal, at [redacted] days.

Indeed, this is reflected in the two versions of Bayer's model, using the 2015 and 2017 data cuts for OS KM data IPE switching adjusted for placebo. Specifically the maximum follow-up is given in worksheet "OS Kaplan Meier GRID".

But this contradicts Bayer's statement above.

So we still consider this matter unresolved.

Question 2

We raised this concern in our report.

First, Bayer say they are unable to replicate our calculated 24% decrease in mean OS for the placebo arm. So we now explain the derivation of our 24% figure. In Bayer's original model, which used the 2015 data, mean survival in the placebo arm is 1.640 years, given in cell G7 sheet "Summary Results", whilst setting the discount rate for benefits to 0%. In Bayer's latest model, which uses the 2017 data, this figure is 1.249 years, a decrease of 24%.

Next, Bayer claim that the fall in mean OS is due to a combination of:

- "*Differences in events (additional deaths or changes to censoring times) due to increased certainty in the tail of the survival curve*
- *Increase in follow-up affecting algorithm applied in the crossover correction*"

Bayer's first bullet point concerns the relative OS treatment effect of regorafenib versus placebo. However, our concern about the 24% reduction in mean OS refers to the placebo arm only.

The unadjusted (ITT) OS Kaplan-Meier curves for the placebo arm for the 2015 and 2017 data cuts are virtually identical (Figure 23 our report). The only difference is that the tail for the 2017 data cut appears to be about 200 days longer. But given that the additional tail in the 2017 Kaplan-Meier is flat (from about 1,420 to 1,650 days), if anything, we would expect the tail of the extrapolated OS to be longer using the 2017 data compared to the 2015 data. This contradicts Bayer's estimated 24% reduction in mean OS for the placebo arm.

The second bullet point builds on Bayer's argument about recensoring in their original report. Now they also quantify the impact of recensoring alone.

Question 3

We raised this concern in our report.

Bayer acknowledge that the p-values are incorrect in their original report corresponding to OS HRs for regorafenib versus adjusted placebo. They claim that these errors will not affect the estimated cost-effectiveness. We agree. However, the error leads us to question whether other aspects of the switching adjustment have been implemented correctly.

Question 4

This question was raised by NICE. We have no concerns with Bayer's response.

Question 5

This question was raised by NICE.

Bayer's estimate of dose intensity, by model cycle, used in their model was taken directly from the GRID RCT. They say their estimates of dose intensities were calculated omitting values of 0mg.

We understand that in their calculation of mean dose per cycle, Bayer exclude 0mg doses, so that, for example, if a patient is given regorafenib in Cycle 1, then that dose is included in the calculation of the mean dose in Cycle 1, but if he/she then has a dose of 0mg in Cycle 2, but then again receives regorafenib in subsequent cycles, then the 0mg is *not* included in the calculation of the mean dose in

Cycle 2. If our understanding is correct, then we agree with Bayer that their method of disallowing 0mg doses is conservative. Indeed, we prefer their revised method of including 0mg doses in the average calculations. In this case, and assuming Bayer have correctly implemented the revised dose intensity calculations, then we are happy to revise down our base case ICERs:

- List price: from [redacted] to [redacted] per QALY.
- PAS price: from £56,000 to £53,000 per QALY.

Question 6

This question was raised by NICE. We have no concerns with Bayer's response.

Revised PenTAG base case

As explained in our answers to Questions 1 and 2, we still have concerns about Bayer's method of adjusting for treatment switching using the 2017 data. For this reason, we retain the 2015 data cut for OS in the economic model. However, if our remaining concerns above can be satisfactorily addressed, then we would be happy to reconsider our choice of OS data.

As explained in answer to Question 5, assuming Bayer have correctly implemented the revised dose intensity calculations, we are happy to revise down our base case ICERs:

- List price: from [redacted] to [redacted] per QALY.
- PAS price: from £56,000 to £53,000 per QALY.

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Single technology appraisal

Regorafenib for treating advanced gastrointestinal stromal tumours [ID1056]

Dear Lesley,

Questions for Bayer (after Appraisal Committee 1)
The appraisal committee require more information about the treatment switching adjustment used in the 2017 analysis for overall survival. Any cost effectiveness analyses for regorafenib should include the committee's preferred assumptions:

- additional background mortality and
- inclusion of age-related utility decrements

Please provide the following information by Friday 28 July, uploading your response documents to NICE Docs.

1. The appraisal committee was unclear whether the treatment switching adjustment met the pivotal assumptions for IPE and RPSFTM (that it, a common treatment effect. Please discuss the reasonableness of the common treatment effect assumption (see Latimer et al 2015 and 2016 for more details). The committee also identified uncertainty in the use of recensoring. Please provide the following:

    a. An assessment of the impact of recensoring on the adjusted overall survival hazard ratios and cost effectiveness of regorafenib. Please provide sensitivity analyses including ICERs with and without recensoring.

    b. A comparison of standard IPE results to results obtained "on treatment" (analysis that adjusts for treatment switching and assumes that the treatment effect is only present while a patient remains on treatment) and "treatment group" (adjusts for treatment switching and assumes that the treatment effect could continue until death).

    c. A counterfactual comparison of survival times in the regorafenib and placebo arms (this is an estimate of overall survival if no patients in either group had received regorafenib treatment). A HR value close to 1 indicates that the estimation procedure has worked well, reflecting that the method has produced a treatment effect that results in counterfactual survival independent of the randomised groups. Please also provide a visual comparison of the complete counterfactual survival curves.

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d. A detailed explanation of the cause of the 24% reduction in overall survival in the placebo arm after adjustment for treatment switching and the impact on the Life Years and QALYs used in the company's model.

2. The appraisal committee noted that the p-values associated with the 2017 adjusted analyses for overall survival are incorrect. Please provide the updated adjusted hazard ratios (stratified and unstratified analyses), 95% confidence intervals and associated p-values using both IPE and RPSFT methods.

3. The appraisal committee heard an additional concern from the ERG that, whilst the Weibull distribution was assumed in the implementation of the IPE method, the company then extrapolated the adjusted OS data using a different distribution, the log-logistic. The ERG noted this inconsistency. Related to this, the committee considered extrapolation with the Weibull as more appropriate than the log-logistic, based on the estimated proportions of patients alive after several years. Use of the Weibull for extrapolation then removes the inconsistency referred to above. Please provide ICERs using a Weibull extrapolation for overall survival.

4. The appraisal committee noted that maximum follow up in the placebo adjusted arms were the same in the 2015 and 2017 analyses please complete the table below for maximum follow up.

	Maximum follow up time (days)			
Data cut	Placebo unadjusted	Placebo RPSFT adjusted	Placebo IPE adjusted	Regorafenib
2015				
2017				

5. Please provide all relevant log files for the treatment switching analysis for both 2015 and 2017 data for overall survival. This should be provided as a text file and will be used by the ERG to validate the treatment switching methods used.

References

Latimer, N. R. et al. (2016). Adjusting for treatment switching in the METRIC study shows further improved overall survival with trametinib compared with chemotherapy. Cancer medicine, 5(5), 806-815. (This reference has been used as part of question1)

Latimer, N. R. et al. (2015). Adjusting for the Confounding Effects of Treatment Switching—The BREAK-3 Trial: Dabrafenib Versus Dacarbazine. The oncologist, 20(7), 798-805. (This reference has been used as part of question1)

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Latimer NR and Abrams KR. (2014) NICE DSU Technical Support Document 16: Adjusting survival time estimates in the presence of treatment switching.

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UPDATED VERSION OF THE DOCUMENT IN RESPONSE TO THE NICE QUESTIONS RECEIVED AFTER THE FIRST APPRAISAL COMMITTEE MEETING INCLUDING RESPONSE TO QUESTION 1.b

This document presents the response to question 1.b based on the results of the analysis conducted in line with Latimer et al. 2015 and guidance received from Dr. Latimer on the methods used in that paper.

While providing guidance on the methods implemented in response to question 1.b, Dr. Latimer also confirmed that the selection of the distribution used for the extrapolation of the adjusted OS is independent from the distribution used for the implementation of the IPE method. Our response to question 3 has been expanded to reflect his view.

All the other responses have been kept unchanged, except for the addition of footnotes indicating the references cited in responses 1, 1.a, and 1.d. Formatting of the document has also been carried out and Figure 5 marked as AIC.

This document should replace the one submitted on July 27th, 2017 entitled "ID1056 regorafenib Questions post ACM1 for Bayer to PM [ACIC]_v1.0"

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Single technology appraisal

Regorafenib for treating advanced gastrointestinal stromal tumours [ID1056]

Dear [redacted],

Questions for Bayer (after Appraisal Committee 1)

The appraisal committee require more information about the treatment switching adjustment used in the 2017 analysis for overall survival. Any cost effectiveness analyses for regorafenib should include the committee's preferred assumptions:

- additional background mortality and
- inclusion of age-related utility decrements

Please provide the following information by Friday 28 July, uploading your response documents to NICE Docs.

1. The appraisal committee was unclear whether the treatment switching adjustment met the pivotal assumptions for IPE and RPSFTM (that it, a common treatment effect. Please discuss the reasonableness of the common treatment effect assumption (see Latimer et al 2015 and 2016 for more details). The committee also identified uncertainty in the use of recensoring. Please provide the following:

The common treatment effect assumption states that the treatment effect received by switching patients must be equal to that received by patients initially randomised to the active treatment group, or else the crossover-adjustment will produce biased results. Methodology to test the common treatment effect assumption is particularly limited in this case due to the small number of patients in the study (for example it is not possible to perform a regression analysis to compare the survival times of BSC patients who did and did not switch [as in Latimer et al 2015[1]] as only 8 patients did not switch). An analysis of the counterfactual survival times (presented in 1c) indicated that the adjustment methods worked well, producing HRs close to 1, providing evidence that the common treatment effect assumption holds.

[1] Latimer, N. R. et al. (2015). Adjusting for the Confounding Effects of Treatment Switching—The BREAK-3 Trial: Dabrafenib Versus Dacarbazine. The oncologist, 20(7), 798-805.

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a. An assessment of the impact of recensoring on the adjusted overall survival hazard ratios and cost effectiveness of regorafenib. Please provide sensitivity analyses including ICERs with and without recensoring.

Hazard ratios from the 2017 overall survival analysis including and excluding recensoring are provided in Table 1 below. The exclusion of recensoring results in an increase in HR of approximately 0.05 for RPSFT and 0.1 for IPE.

Table 1: HRs from overall survival analysis (2017 data)

HRs	Recensored	No recensoring
Unadjusted	0.898	
RPSFT	0.483	0.537
IPE	0.454	0.555

** 2017 data cut, stratified HRs*

The impact of recensoring on cost-effectiveness results is presented below. This analysis includes the ERG assumptions for age-related utility decrements, additional background mortality and a 50% Weibull 50% Loglogistic extrapolation, as well as the updated dosing analysis. However, given that the age of patients in the GRID trial[2] ranged from 18 to 87 years, we believe that age-related utility decrements are already captured in the EQ-5D data collected during the trial. For this reason, we believe the cost-effectiveness analysis should not be including age-related utility decrements.

The exclusion of recensoring results in a decrease in QALYs associated with BSC of around 0.15 for IPE and 0.10 for RPSFT. This results in an increase in ICER of around £9,000/QALY for IPE and £6,000/QALY for RPSFT (with PAS).

[2] Bayer Health Care. Amended Clinical Study Report No. A59137. Clinical study report; 2012 Oct 5

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Table 2: Cost-effectiveness results with PAS, IPE-adjustment, recensoring (ERG assumptions and new dosing analysis)

Technologies	Total costs	Total LY	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/LYGs)	ICER incremental (£/QALYs)
BSC	£10,295	1.036	0.681					
Regorafenib	£45,459	2.238	1.515					
				£35,164	1.202	0.834	£29,262	£42,156

Table 3: Cost-effectiveness results with PAS, IPE-adjustment, no recensoring (ERG assumptions and new dosing analysis)

Technologies	Total costs	Total LY	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/LYGs)	ICER incremental (£/QALYs)
BSC	£10,511	1.283	0.838					
Regorafenib	£45,459	2.238	1.515					
				£34,948	0.955	0.677	£36,601	£51,629

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Table 4: Cost-effectiveness results with PAS, RPSFT-adjustment, recensoring (ERG assumptions and new dosing analysis)

Technologies	Total costs	Total LY	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/LYGs)	ICER incremental (£/QALYs)
BSC	£10,338	1.085	0.712					
Regorafenib	£45,459	2.238	1.515					
				£35,121	1.153	0.803	£30,464	£43,737

Table 5: Cost-effectiveness results with PAS, RPSFT-adjustment, no recensoring (ERG assumptions and new dosing analysis)

Technologies	Total costs	Total LY	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/LYGs)	ICER incremental (£/QALYs)
BSC	£10,471	1.238	0.809					
Regorafenib	£45,459	2.238	1.515					
				£34,988	1.000	0.706	£34,980	£49,573

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Table 6: Cost-effectiveness results without PAS, IPE-adjustment, recensoring (ERG assumptions and new dosing analysis)

Technologies	Total costs	Total LY	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/LYGs)	ICER incremental (£/QALYs)
BSC	£10,295	1.036	0.681					
Regorafenib	£[redacted]	2.238	1.515					
				£[redacted]	1.202	0.834	£[redacted]	£[redacted]

Table 7: Cost-effectiveness results without PAS, IPE-adjustment, no recensoring (ERG assumptions and new dosing analysis)

Technologies	Total costs	Total LY	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/LYGs)	ICER incremental (£/QALYs)
BSC	£10,511	1.283	0.838					
Regorafenib	£[redacted]	2.238	1.515					
				£[redacted]	0.955	0.677	£[redacted]	£[redacted]

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Table 8: Cost-effectiveness results without PAS, RPSFT-adjustment, recensoring (ERG assumptions and new dosing analysis)

Technologies	Total costs	Total LY	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/LYGs)	ICER incremental (£/QALYs)
BSC	£10,338	1.085	0.712					
Regorafenib	£[redacted]	2.238	1.515					
				£[redacted]	1.153	0.803	£[redacted]	£[redacted]

Table 9: Cost-effectiveness results without PAS, RPSFT-adjustment, no recensoring (ERG assumptions and new dosing analysis)

Technologies	Total costs	Total LY	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/LYGs)	ICER incremental (£/QALYs)
BSC	£10,471	1.238	0.809					
Regorafenib	£[redacted]	2.238	1.515					
				£[redacted]	1.000	0.706	£[redacted]	£[redacted]

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In addition the cost-effectiveness results both with and without PAS excluding age-related utility decrements are presented (but including other ERG assumptions and updated dosing analysis).

Table 10: Cost-effectiveness results with PAS, IPE-adjustment, recensoring (ERG assumptions and new dosing analysis)

Technologies	Total costs	Total LY	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/LYGs)	ICER incremental (£/QALYs)
BSC	£10,295	1.036	0.685					
Regorafenib	£45,459	2.238	1.533					
				£35,164	1.202	0.848	£29,262	£41,473

Table 11: Cost-effectiveness results with PAS, IPE-adjustment, no recensoring (ERG assumptions and new dosing analysis)

Technologies	Total costs	Total LY	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/LYGs)	ICER incremental (£/QALYs)
BSC	£10,511	1.283	0.845					
Regorafenib	£45,459	2.238	1.533					
				£34,948	0.955	0.688	£36,601	£50,786

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Table 12: Cost-effectiveness results with PAS, RPSFT-adjustment, recensoring (ERG assumptions and new dosing analysis)

Technologies	Total costs	Total LY	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/LYGs)	ICER incremental (£/QALYs)
BSC	£10,338	1.085	0.717					
Regorafenib	£45,459	2.238	1.533					
				£35,121	1.153	0.816	£30,464	£43,026

Table 13: Cost-effectiveness results with PAS, RPSFT-adjustment, no recensoring (ERG assumptions and new dosing analysis)

Technologies	Total costs	Total LY	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/LYGs)	ICER incremental (£/QALYs)
BSC	£10,471	1.238	0.816					
Regorafenib	£45,459	2.238	1.533					
				£34,988	1.000	0.718	£34,980	£48,763

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Table 14: Cost-effectiveness results without PAS, IPE-adjustment, recensoring (ERG assumptions and new dosing analysis)

Technologies	Total costs	Total LY	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/LYGs)	ICER incremental (£/QALYs)
BSC	£10,295	1.036	0.685					
Regorafenib	£[redacted]	2.238	1.533					
				£[redacted]	1.202	0.848	£[redacted]	£[redacted]

Table 15: Cost-effectiveness results without PAS, IPE-adjustment, no recensoring (ERG assumptions and new dosing analysis)

Technologies	Total costs	Total LY	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/LYGs)	ICER incremental (£/QALYs)
BSC	£10,511	1.283	0.845					
Regorafenib	£[redacted]	2.238	1.533					
				£[redacted]	0.955	0.688	£[redacted]	£[redacted]

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Table 16: Cost-effectiveness results without PAS, RPSFT-adjustment, recensoring (ERG assumptions and new dosing analysis)

Technologies	Total costs	Total LY	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/LYGs)	ICER incremental (£/QALYs)
BSC	£10,338	1.085	0.717					
Regorafenib	£[redacted]	2.238	1.533					
				£[redacted]	1.153	0.816	£[redacted]	£[redacted]

Table 17: Cost-effectiveness results without PAS, RPSFT-adjustment, no recensoring (ERG assumptions and new dosing analysis)

Technologies	Total costs	Total LY	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/LYGs)	ICER incremental (£/QALYs)
BSC	£10,471	1.238	0.816					
Regorafenib	£[redacted]	2.238	1.533					
				£[redacted]	1.000	0.718	£[redacted]	£[redacted]

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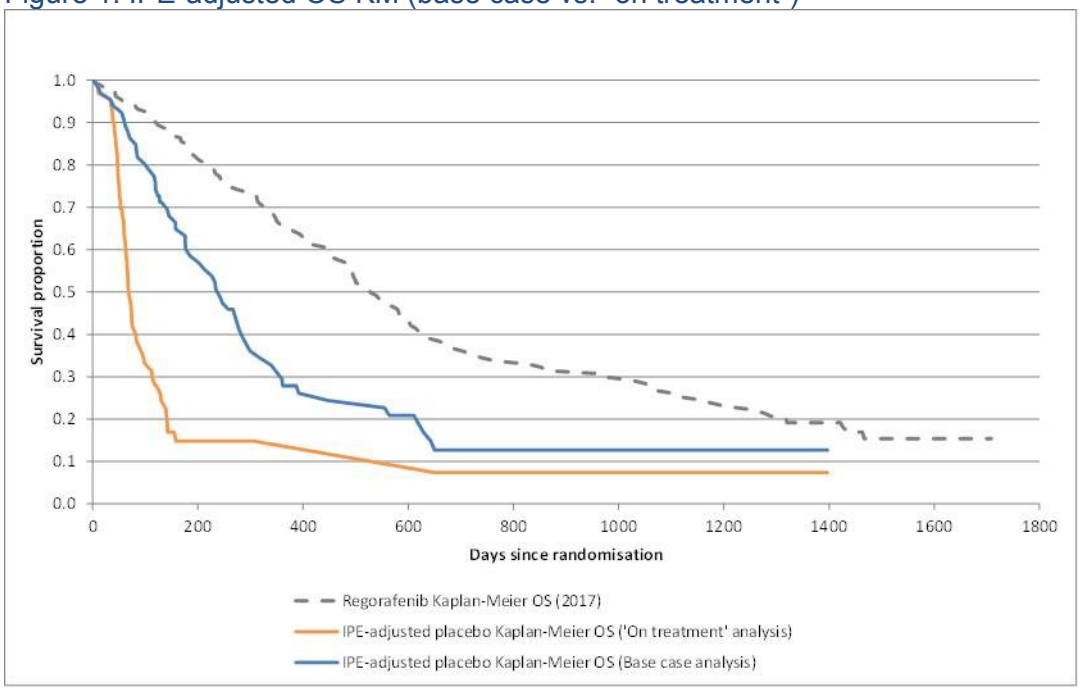
b. A comparison of standard IPE results to results obtained "on treatment" (analysis that adjusts for treatment switching and assumes that the treatment effect is only present while a patient remains on treatment) and "treatment group" (adjusts for treatment switching and assumes that the treatment effect could continue until death).

The "on treatment" analysis was conducted in line with Latimer et al. 2015[1], with guidance on the methods used in that paper received from Dr. Latimer on July 29th, 2017. The analysis assumed that the treatment effect of regorafenib was only present when patients were on treatment. This means assuming that regorafenib patients discontinue therapy crossover to the BSC arm, and therefore crossover is occurring in both directions in the trial (regorafenib to BSC and BSC to regorafenib). During the course of the analysis it became apparent that due to the small sample sizes and large number of patients switching treatment (or discontinuing) the output may not be reliable.

A comparison of the Kaplan-Meier curves produced using the base case and "on treatment" IPE crossover corrections is presented in Figure 1 below.

Figure 1: IPE-adjusted OS KM (base case vs. "on treatment")



In the "on treatment" analysis, median overall survival for placebo was substantially reduced compared to the base case from 242 to 69 days, this is also reflected in the HRs (reducing from 0.454 in the base case to 0.166 in the "on treatment" analysis). We also conducted the analysis using RPSFT crossover

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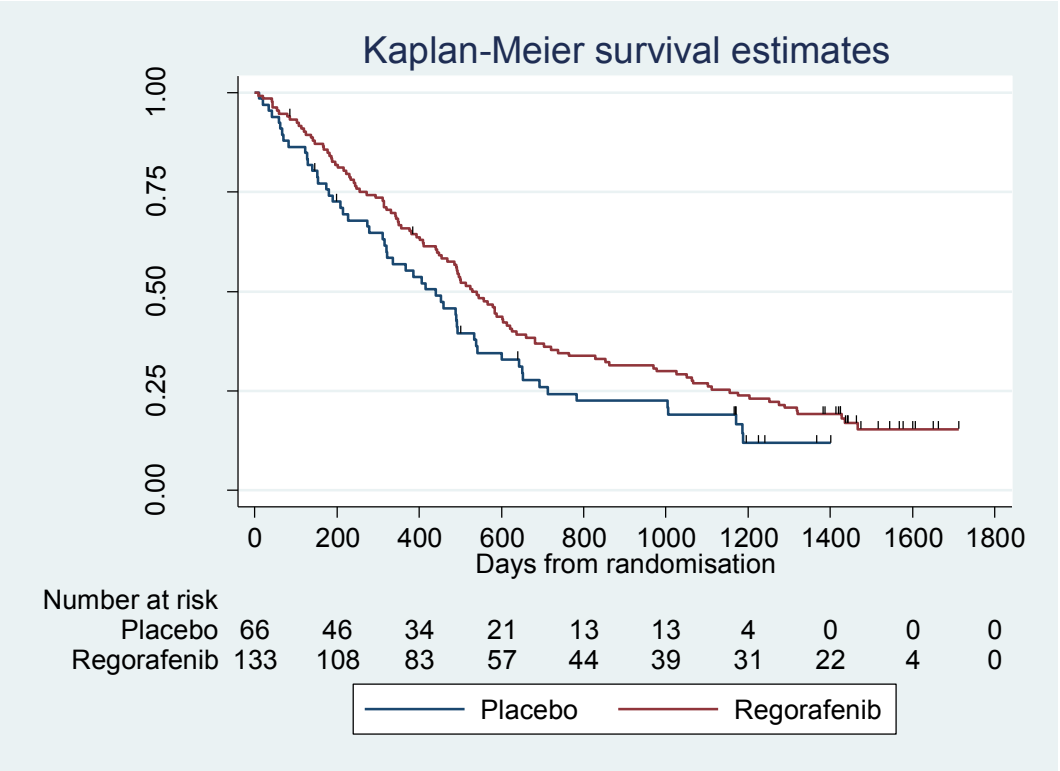
correction and produced similar results; however, the analysis also produced a non-linear Z(psi) function, indicating that the results may not be reliable.

A further exploratory analysis was undertaken only adjusting for the discontinuation of regorafenib (crossover from regorafenib to BSC) in order to verify the outcomes of the analysis. This analysis included no correction for BSC patients crossing over to regorafenib and simply investigated the difference in outcomes due to the inclusion of a correction for regorafenib discontinuation. The analysis resulted in a HR indicating greater regorafenib treatment effect than the unadjusted analysis (0.757 vs. 0.898). This signifies that the "on treatment" analysis will likely produce results more favourable for regorafenib than the base case. The resulting Kaplan-Meier plot for this exploratory analysis is presented in Figure 2 below.

Figure 2: Kaplan-Meier plot (exploratory analysis)



The "treatment group" analysis corresponds to the Intention to treat (ITT) analysis already presented in the full collection of responses to the clarification questions submitted in May 2017 and presented during the Appraisal Committee meeting held on June 28th, 2017.

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Because of the short time frame it was not possible to implement a further analysis based on the suggestions made by Dr. Latimer in the email he sent to us on August 3rd, 2017.

Stata log files for both the "on treatment" and exploratory analyses are attached to this document. Please, also note that neither the results of the analysis presented above nor the Stata code have been seen by Dr. Latimer.

c. A counterfactual comparison of survival times in the regorafenib and placebo arms (this is an estimate of overall survival if no patients in either group had received regorafenib treatment). A HR value close to 1 indicates that the estimation procedure has worked well, reflecting that the method has produced a treatment effect that results in counterfactual survival independent of the randomised groups. Please also provide a visual comparison of the complete counterfactual survival curves.

An analysis of the counterfactual survival times associated with the IPE and RPSFT crossover corrections was undertaken in line with Latimer et al 2015[1]. In both cases hazard ratios close to 1 were produced (1.065 [95% CI: 0.768-1.479] for IPE, and 1.046 [95% CI: 0.754-1.451] for RPSFT), indicating that the estimation procedure has worked well. Kaplan-Meier survival curves for the counterfactual survival are provided in Figure 3 and Figure 4 for IPE and RPSFT respectively. Note that analyses were conducted using the 2017 survival data.

Figure 3: Counterfactual survival (IPE-adjusted, with recensoring, 2017 data cut)

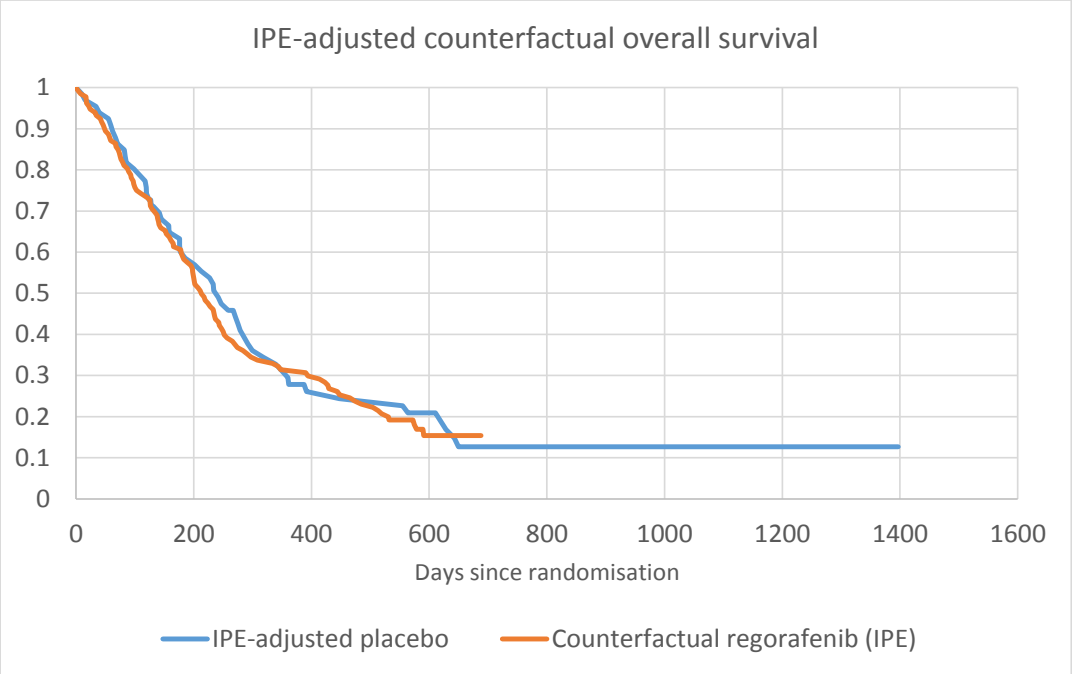

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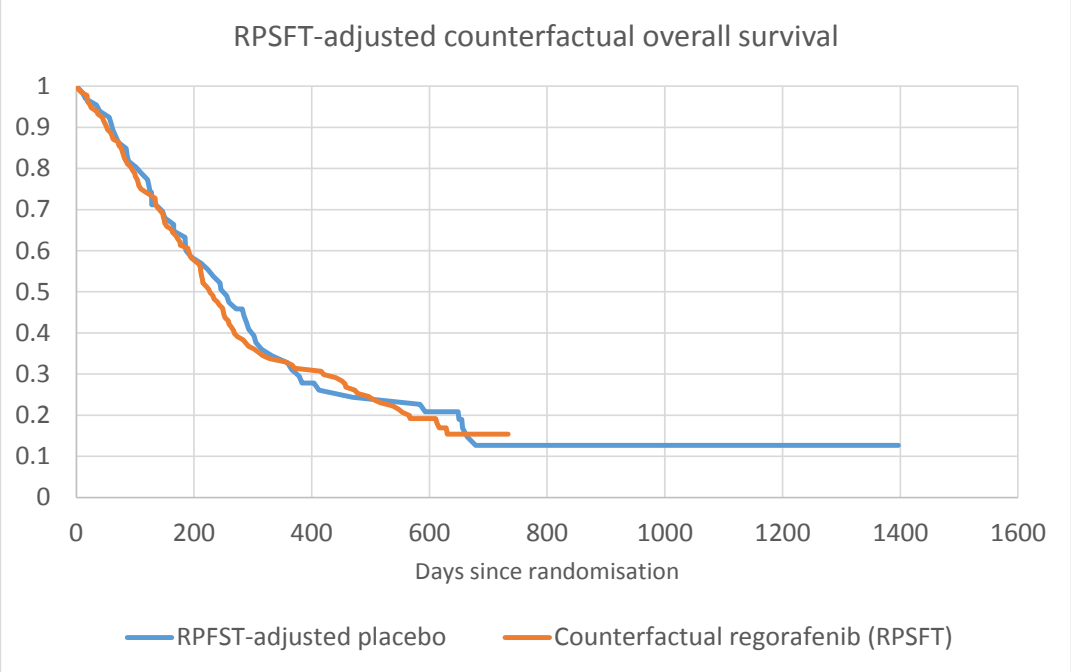
Figure 4: Counterfactual survival (RPSFT-adjusted, with recensoring, 2017 data cut)



d. A detailed explanation of the cause of the 24% reduction in overall survival in the placebo arm after adjustment for treatment switching and the impact on the Life Years and QALYs used in the company's model.

As described in a previous response, the observed difference in outcomes between the 2015 and 2017 data comes from a combination of two effects as a result of updating the data:

- Differences in events (additional deaths or changes to censoring times) due to increased certainty in the tail of the survival curve
- Increase in follow-up affecting algorithm applied in the crossover correction

Differences in events

There are some differences in outcomes between 2015 and 2017 data as there is greater certainty in the tail with the more recent data and this difference favours the active (regorafenib) arm. In the 2015 data by day 1,467 the survival in both the unadjusted placebo and regorafenib arms was equal to 13% (no further events then take place in either arm), whereas in the 2017 data there is a sustained difference in survival after day 1,400 (10.9% survival in the unadjusted placebo arm vs. 15.4% in the regorafenib arm), additionally this difference is maintained for longer (over 200 days) due to the increased follow-up. A graphical comparison of the data is presented in Figure 5 below. We tested the effect of this difference on the crossover correction by analysing the impact of updating the data but disabling

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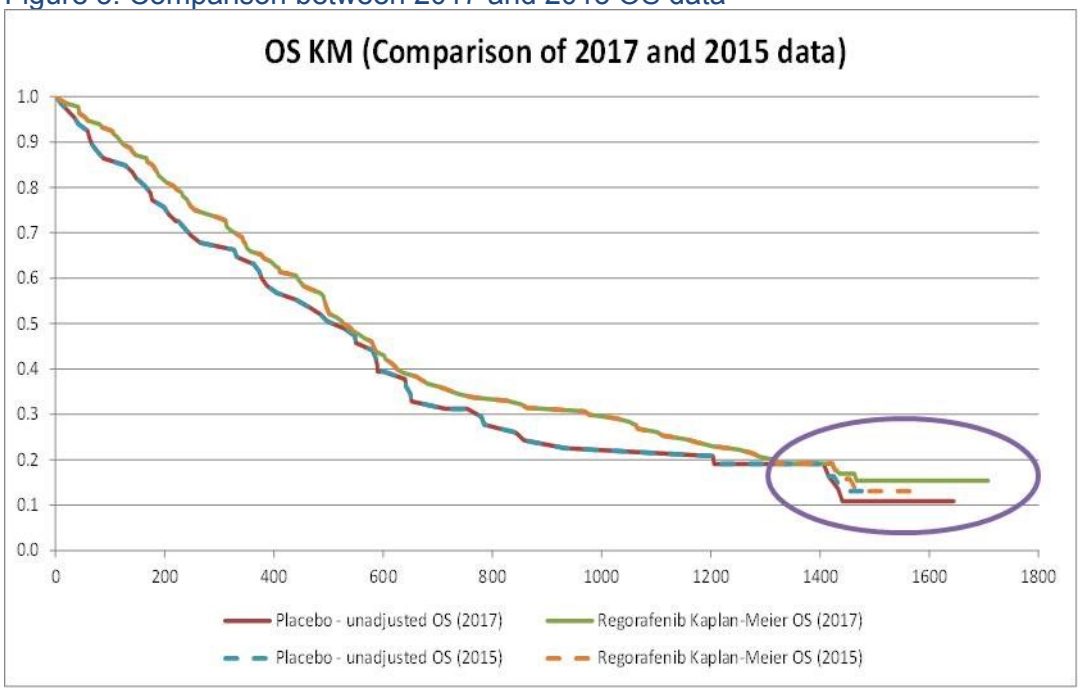
any recensoring (in both the 2015 and 2017 analyses), this change means that follow-up duration is not directly applicable to the crossover calculation. The results of this analysis showed that around half of the observed difference is due to the change in the underlying data - 2015 unstratified HR: 0.[redacted] vs 2017 unstratified HR: 0.544.

Figure 5: Comparison between 2017 and 2015 OS data



Increase in follow up

The second key of the difference is due to application of recensoring. In line with NICE DSU Technical Support Document 16[3] patients in the adjusted placebo arm are recensored – not all their data is used – at the end of the observed period, in order to avoid bias associated with informative censoring. With the extended follow-up period, the amount of information lost in this way is reduced and the difference between treated and untreated patients is increased.

We examined the impact of applying the same increase in follow-up to the 2015 data, leaving the data unchanged, altering only the potential censoring time in the *strbee* command. A decrease in the hazard ratio of around 0.05 was observed, again accounting for approximately half the difference (measured by HRs) observed between the 2015 and 2017 data. This was discussed at the NICE committee meeting, the ERG mentioned they had contacted Nicholas Latimer to ask about this difference and he agreed it was possible.

[3] Latimer NR and Abrams KR. (2014) NICE DSU Technical Support Document 16: Adjusting survival time estimates in the presence of treatment switching

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The impact on Life Years (LYs) and QALYs within the model is consistent with the differences observed in the survival analysis. Table 18 and Table 19 present the LY and QALY outcomes from the model for the 2015 and 2017 analyses using IPE and RPSFT crossover correction. LYs and QALYs in the regorafenib arm are increased (by 0.027 and 0.017 respectively), this is due to the difference in underlying data as regorafenib is unaltered by the crossover correction. The differences in the BSC arm are greater due to the observed decrease in adjusted placebo survival (LYs and QALYs are reduced by 0.255 and 0.162 for IPE and 0.343 and 0.218 for RPSFT). The combination of these two effects results in a total difference-in-difference in LYs of 0.282 (IPE) and 0.370 (RPSFT) and a total difference-in-difference in QALYs of 0.179 (IPE) and 0.235 (RPSFT).

Table 18: Differences in LYs and QALYs between 2015 and 2017 analyses (IPE-adjustment, ERG assumptions)

IPE	2015		2017		*Incremental*	
	Total LY	Total QALYs	Total LY	Total QALYs	*Total LY*	*Total QALYs*
BSC	1.291	0.843	1.036	0.681	*-0.255*	*-0.162*
Regorafenib	2.211	1.498	2.238	1.515	*0.027*	*0.017*
Incremental	*0.920*	*0.655*	*1.202*	*0.834*	*0.282*	*0.179*

Table 19: Differences in LYs and QALYs between 2015 and 2017 analyses (RPSFT-adjustment, ERG assumptions)

RPSFT	2015		2017		*Incremental*	
	Total LY	Total QALYs	Total LY	Total QALYs	*Total LY*	*Total QALYs*
BSC	1.428	0.930	1.085	0.712	*-0.343*	*-0.218*
Regorafenib	2.211	1.498	2.238	1.515	*0.027*	*0.017*
Incremental	*0.782*	*0.568*	*1.153*	*0.803*	*0.370*	*0.235*

2. The appraisal committee noted that the p-values associated with the 2017 adjusted analyses for overall survival are incorrect. Please provide the updated adjusted hazard ratios (stratified and unstratified analyses), 95% confidence intervals and associated p-values using both IPE and RPSFT methods.

Table 20 presents the updated hazard ratios, and accompanying CIs for both the unstratified and stratified analyses.

Note that the confidence intervals around the adjusted HRs are estimated based on the ITT p-values presented below. The wide confidence intervals are to be expected given the

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usage of the ITT p-value. Use of these confidence intervals would not alter the base case results.

Table 20: Hazard ratios update based on both stratified and unstratified analyses

	Data cut-off 2017 Unstratified analysis		Data cut-off 2017 Stratified analysis	
	Regorafenib + BSC (N=133)	Placebo + BSC (N=66)	Regorafenib + BSC (N=133)	Placebo + BSC (N=66)
Hazard ratio: uncorrected	0.884		0.898	
95% CI for hazard ratio: uncorrected	(0.638, 1.226)		(0.676, 1.194)	
p-value (one-sided) from log rank test: uncorrected	0.23		0.262	
Hazard ratio: corrected RPSFT	0.477		0.483	
Estimated 95% CI for hazard ratio given p-value fixed to ITT: corrected RPSFT	(0.067, 3.392)		(0.070, 3.329)	
Hazard ratio: corrected IPE	0.456		0.454	
Estimated 95% CI for hazard ratio given p-value fixed to ITT: corrected RPSFT	(0.057, 3.658)		(0.056, 3.688)	

* All analyses performed on 2017 data set. Crossover adjustments include recensoring.

3. The appraisal committee heard an additional concern from the ERG that, whilst the Weibull distribution was assumed in the implementation of the IPE method, the company then extrapolated the adjusted OS data using a different distribution, the log-logistic. The ERG noted this inconsistency. Related to this, the committee considered extrapolation with the Weibull as more appropriate than the log-logistic, based on the estimated proportions of patients alive after several years. Use of the Weibull for extrapolation then removes the inconsistency referred to above. Please provide ICERs using a Weibull extrapolation for overall survival.

Results using the Weibull extrapolation for overall survival are shown below. This analysis includes the ERG assumptions for age-related utility decrements and additional background mortality, as well as the updated dosing analysis. However, we found no public evidence showing that the parametric model used for the extrapolation of the adjusted OS data must be same used in the implementation of the IPE method - i.e. Weibull.

Moreover, in the email we received from Dr. Latimer on July 29th, 2017 he also agreed that the function used in the likelihood test when using the IPE method does not necessarily need to be the same as the survival extrapolation function.

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Table 21: Cost-effectiveness results with PAS (ERG assumptions, new dosing analysis and Weibull OS)

Technologies	Total costs	Total LY	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER incr. (£/LYGs)	ICER incr. (£/QALYs)
BSC	£10,404	1.162	0.763					
Regorafenib	£45,274	2.027	1.385					
				£34,870	0.865	0.622	£40,295	£56,037

Table 22: Cost-effectiveness results without PAS (ERG assumptions, new dosing analysis and Weibull OS)

Technologies	Total costs	Total LY	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER incr. (£/LYGs)	ICER incr. (£/QALYs)
BSC	£10,404	1.162	0.763					
Regorafenib	£[redacted]	2.027	1.385					
				£[redacted]	0.865	0.622	£[redacted]	£[redacted]

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4. The appraisal committee noted that maximum follow up in the placebo adjusted arms were the same in the 2015 and 2017 analyses please complete the table below for maximum follow up.

	Maximum follow up time (days)			
Data cut	Placebo unadjusted	Placebo RPSFT adjusted	Placebo IPE adjusted	Regorafenib
2015	1,477	1,397	1,397	[redacted]
2017	1,645	1,397	1,397	1,708

As requested, the maximum follow-up times have been added to the table above. Note that the maximum follow-up for placebo patients who do not crossover (N=8) is 1,397 days. As the counterfactual survival for all crossover placebo patients is estimated to be less than this, and patients who do not crossover are not affected by the crossover adjustment this results in the maximum follow-up for the adjusted analysis with both data cuts being equal.

5. Please provide all relevant log files for the treatment switching analysis for both 2015 and 2017 data for overall survival. This should be provided as a text file and will be used by the ERG to validate the treatment switching methods used.

Please find the requested log files attached. This analysis was run in Stata 11.

References

Latimer, N. R. et al. (2016). Adjusting for treatment switching in the METRIC study shows further improved overall survival with trametinib compared with chemotherapy. Cancer medicine, 5(5), 806-815. (This reference has been used as part of question1)

Latimer, N. R. et al. (2015). Adjusting for the Confounding Effects of Treatment Switching—The BREAK-3 Trial: Dabrafenib Versus Dacarbazine. The oncologist, 20(7), 798-805. (This reference has been used as part of question1)

Latimer NR and Abrams KR. (2014) NICE DSU Technical Support Document 16: Adjusting survival time estimates in the presence of treatment switching.

[redacted]

Subject: FW: Clarification regarding 2015 paper on the BREAK-3 trial

From: Nicholas R Latimer [redacted]
Sent: 03 August 2017 16:03
To: [redacted]
Subject: RE: Clarification regarding 2015 paper on the BREAK-3 trial

Hi [redacted],

The small sample size could be a problem. However, it's still unusual to get a non-unique value for psi. Can you rule one of them out as being extreme? Are you using a sensible range? I would certainly also test a "treatment group" analysis, where discontinuation is ignored (hence no switching in the control group, and discontinuation in switchers also ignored). Often I find that a more reliable analysis. I'd also do all the analyses with and without recensoring, which can make a huge difference if you are losing much information (if you are losing much information not recensoring may be better - see my poster from ispor Boston). It's also worth trying the IPE algorithm to see if you get the same issue with that, and for the RPSFTM consider whether you're using interval bisection or a step estimation procedure. And also check whether the HR comparing counterfactual survival times in each randomised group make sense. Finally, if you suspect the common treatment effect doesn't hold, do sensitivity analysis around that.

There are quite a lot of things to check and try if the analysis doesn't seem to be working well! And of course there is the two-stage adjustment method and ipcw too. Ipcw may not be good if you have a very small sample or very few non-switchers, but the two-stage method is more robust to those issues (though can still have problems).

Best wishes,

[redacted]

Sent from my telephone

On 1 Aug 2017 13:23, [redacted] wrote:

> Hi Nick,
>
> Thanks so much for the response. For the problem I'm working on we assumed that discontinuers essentially switch to the placebo arm (so that we have switching in both directions); however, we ended up with a nonlinear Z(psi) vs psi plot so the acceleration factor was not actually unique. In our problem we have a very small number of patients which I'm wondering may be an issue here? Have you had any experience with nonuniqueness in any of the problems you've worked on? You've already been a huge help, but any insight on possible nonuniqueness of solutions would be great!
>
> Kind regards,
>
> [redacted]

From: Nicholas R Latimer [redacted]
Sent: 29 July 2017 21:31
To: [redacted]
Subject: Re: Clarification regarding 2015 paper on the BREAK-3 trial

Hi [redacted],

Thanks for your interest and email.

For your first question: it is quite a simplistic approach, basically assuming that upon discontinuation people switch onto the control. Really this only makes much sense if the control is placebo or best supportive care. If another treatment group was added the method probably wouldn't work well - several papers report the RPSFTM not working at all well when you try to estimate more than one treatment effect.

For your second question: I agree with you really, because one is about finding a model that exclusively fits the observed data well, whereas the other is about a model that fits the data but that also extrapolates credibly. Often several models fit the data similarly well but extrapolate very differently so you could decide that one is best for fitting to the data and another is best for extrapolation.

Hope this helps,

Nick

On 25 July 2017 at 15:16, [redacted] wrote:

> Hi Dr Latimer,
>
> [redacted]

I'm emailing you to ask for clarification regarding the methodology used in your 2015 paper on the BREAK-3 trial. One of your analyses was the "on-treatment observed" analysis. For this analysis, you estimated "a causal treatment effect under the assumption that the benefits are only accrued while treatment is being received." I had a look at the supplementary material for this paper but it doesn't describe how you do this in more detail. Is it that equation (1) in the supplemental appendix will change so that instead of:

$$U_i = T_{Ai} + e^{(psi_0)} * T_{Bi}$$

we will have an additional acceleration factor and additional treatment group for discontinuers, i.e.:

$$U_i = T_{Ai} + e^{(psi_0_1)} * T_{Bi} + e^{(psi_0_2)} * T_{Ci}$$

Or does the method essentially assume that the discontinuers switch to the control arm? Did you implement this with strbee in Stata?

That was my main question. Any clarification you could provide would be invaluable.

I also have one other question. Is there any reason why you would want to ensure that the likelihood test when using the IPE method with the strbee function in Stata should be the same as the survival extrapolation function? Is there any need for consistency there? In my mind these two things are separate and different.

Thanks for your time – I hope to hear from you but completely understand if your schedule doesn't permit it.

Kind regards,

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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Regorafenib for previously treated unresectable or metastatic gastrointestinal stromal tumours:

NICE STA

Addendum:

Between 1st and 2nd NICE Appraisal Committee meetings

11th August 2017

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Confidential information that is academic-in-confidence is highlighted and underlined.

Contents

1 Critique of Bayer responses to questions from NICE

The first NICE committee meeting for this STA was held on 28th June 2017. Afterwards, NICE reported that the appraisal committee require more information about Bayer's treatment switching adjustment for overall survival used in the 2017 data cut analysis. NICE asked Bayer to assume the following in all analyses:

- additional background mortality and
- age-related utility decrements

1.1 Question 1 (Introduction)

NICE asked for more justification for the assumptions underlying the RPSFTM and IPE methods of adjusting for treatment switching.

Bayer replied that the common treatment effect assumption states that the treatment effect received by switching patients must be equal to that received by patients initially randomised to the active treatment group, otherwise the crossover adjustment will produce biased results. We agree, and note that this assumption applies to both methods.

Bayer said that the ability to test the common treatment effect assumption is particularly limited in this case due to the small number of patients in the study. They continued that analysis of the counterfactual survival times (presented in 1c) indicated that the adjustment methods worked well, producing hazard ratios close to 1, providing evidence that the common treatment effect assumption holds.

We consider this response reasonable.

Bayer and we have previously agreed that the IPCW method is inappropriate due to the high proportion of placebo patients that switched treatment.

Therefore, we consider it reasonable to use the RPSFTM or IPE methods.

However, as discussed in our original report, we are not convinced by Bayer's rationale for choosing the IPE method over the RPSFT method in the base case. We consider both methods equally plausible. For example, Latimer et al (2016) preferred the RPSFT method

over the IPE method to adjust for treatment switching in a trail of metastatic melanoma. For this reason, in Section 2, p14, we now give equal credibility to these two methods.

1.2 Question 1a

NICE asked for an assessment of the impact of recensoring on the adjusted overall survival hazard ratios and cost effectiveness of regorafenib, specifically ICERs with and without recensoring.

In response, Bayer provided the hazard ratios below. The ITT and recensored values are the same as those previous reported by Bayer. The "no recensoring" values in the table below are new information.

Table 1. OS HRs (2017 data)

HRs	Recensored	No recensoring
Unadjusted		[redacted]
RPSFT	[redacted]	[redacted]
IPE	[redacted]	[redacted]

For completeness, we show the corresponding, higher, hazard ratios corresponding to the 2015 data.

Table 2. OS HRs (2015 data)

HRs	Recensored	No recensoring
Unadjusted		[redacted]
RPSFT	[redacted]	[redacted]
IPE	[redacted]	[redacted]

These values are summarised in Figure 1 below. This shows that in general hazard ratios are lower, and hence the estimated cost-effectiveness of regorafenib is better:

- For the IPE method compared to the RPSFT method,

- For the 2017 data compared to the 2015 data.
- Allowing for recensoring.

Recensoring reduces the hazard ratios more for the:

- 2017 data than the 2015 data.
- IPE method than the RPSFT method.

Figure 1 OS hazard ratio by data cut and whether data recensored

Next, Bayer present the impact of recensoring on cost-effectiveness (Table 3, Table 4) on the following basis:

- age-related utilities.
- additional background mortality.
- OS extrapolated as a 50%:50% average of the Weibull and log-logistic distributions (our original assumption).

- “updated dosing analysis”.
- 2017 data cut.

Although they apply the correction for age-related disutility, they claim this is unnecessary, as they believe this is already captured in the EQ-5D data from the GRID trial. We disagree. Age-related utility adjustment is standard practice in cost-utility analyses in general, and is certainly relevant in this case, given that some patients are predicted to survive far beyond the maximum follow up time of the trial.

Before the first NICE committee meeting, we also modelled OS as a 50%:50% average of the Weibull and log-logistic distributions. However, NICE stated that the committee preferred the Weibull distribution (Question 3). Therefore, this limits the relevance of the ICERs Bayer present in this section.

Originally, we did not understand the meaning of “updated dosing analysis”. On 10th August 2017, Bayer clarified as follows:

“*we refer to the revised dose intensity calculation of regorafenib including doses of 0 mg. Cost effectiveness analysis results based on the “updated dosing analysis” were already presented in our response to clarification question 5 from NICE received on June 15th, 2017. The inclusion of the revised dose intensity calculation in the ERG’s revised base case analysis was accepted by the Appraisal Committee on June 28th, 2017 (please see Cost Effectiveness slide 22). We agree with the ERG and the Appraisal Committee that cost effectiveness analyses should be based on the mean observed dose of regorafenib by cycle including 0 mg doses.*

When considering the actual doses from the GRID trial (including those of 0 mg), the mean observed dose of regorafenib by cycle is lower compared to when 0 mg doses are excluded from the calculation of the average. As shown during the first Appraisal Committee Meeting, the inclusion of the revised dose intensity calculation or “updated dosing analysis” had an impact on the ICER of approximately £2,000.”

As we have previously stated, we accept the logic of this argument. However, we caution that we do not have the underlying data to verify the change in the ICER. In other words, our version of Bayer’s economic model does not reflect the updated dosing analysis.

Table 3. Bayer ICERs with and without recensoring (with PAS, 2017 data)

	No recensoring	Recensoring
IPE	£51,629	£42,156
RPSFT	£49,573	£43,737

Table 4. Bayer ICERs with and without recensoring (without PAS, 2017 data)

	No recensoring	Recensoring
IPE	[redacted]	[redacted]
RPSFT	[redacted]	[redacted]

Bayer also present the analogous ICERs without the age-related utility adjustment. This reduces all ICERs by about £1,000 per QALY.

We attempted to recreate Bayer's ICERs in the tables above. We find the ICERs given in the tables below, on the same basis as used Bayer, but without the "updated dosing analysis". We are unable to calculate the ICERs in the absence of recensoring because we do not have the relevant OS data, although we make approximations in Section 2. Assuming the PAS, these ICERs are about £2,000 per QALY higher than those presented by Bayer, and without the PAS, about £3,000 per QALY higher. We agree with Bayer's estimates of total costs, life years and QALYs for BSC, and total life years and QALYs for regorafenib. However, we estimate slightly higher total costs of regorafenib. For example assuming the PAS, we estimate £46,997 versus Bayer's £45,459. We assume this difference is due to Bayer's "updated dosing analysis".

Table 5. PenTAG ICERs with and without recensoring (with PAS, 2017 data)

	No recensoring	Recensoring
IPE	unknown	£44,000
RPSFT	unknown	£45,652

Table 6. PenTAG ICERs with and without recensoring (without PAS, 2017 data)

	No recensoring	Recensoring
IPE	unknown	[redacted]
RPSFT	unknown	[redacted]

Our ICERs above are 4% higher than Bayer's ICER.

Relevance of recensoring

As stated in our original report, recensoring may lead to biased estimates of the average treatment effect when the proportional treatment effect assumptions do not hold, because longer term data on the effect of treatment may be lost. We understand that, whilst the relevant NICE Technical Support Document recommends recensoring, whether to perform recensoring remains a subject of academic debate. Indeed recent research recommends performing the adjustment both with and without recensoring (Latimer & Abrams 2017, Latimer et al 2016). This was confirmed in the email of 3rd August 2017 from Dr. Latimer to Bayer. The estimated treatment effect is generally greater when recensoring is performed compared to the analysis without recensoring (Latimer & Abrams 2017). Adjustment without recensoring was favoured in one recent dataset by Latimer et al 2016.

For these reasons, in our base case (Section 2, p14), we now consider analyses both with and without recensoring to be equally valid.

1.3 Question 1b

NICE asked for a comparison of results obtained with the IPE method under two distinct bases: (a) "on treatment" which assumes that the treatment effect applies only while a patient is on treatment and (b) "treatment group" which assumes that the treatment effect applies from the time of initiation of the drug until death.

In all analyses so far, Bayer have assumed the "treatment group" analysis. In response to NICE's request for further information, Bayer now present the results of the "on treatment" analysis. Bayer say they implemented this analysis based on an academic paper and

advice from Dr. Latimer. They estimated a much shorter tailed OS for placebo than using their base case "treatment group" analysis: median OS 69 days vs. [redacted] days. However they caution that the "on treatment" method "may not be reliable" due to the small sample size and large numbers of patients switching treatment. Using the RPSFT method, they found similar results with the same concerns about reliability.

Bayer then say they performed an exploratory analysis "adjusting only for discontinuation of regorafenib (crossover from regorafenib to BSC)". They claim this analysis suggests that the "on treatment" analysis will likely produce results more favourable for regorafenib than the "treatment group" analysis. In response, first, we do not understand this exploratory analysis. Second, Bayer already claim that the "on treatment" analysis yields a greater estimated treatment benefit for regorafenib than the "treatment group" analysis (e.g. median OS values quoted above). Therefore, we do not see the relevance of this exploratory analysis.

Bayer then say that due to time constraints, it was not possible to implement a further analysis suggested by Dr. Latimer. We assume Bayer refer here to Dr. Latimer's suggestion in his email of 3rd August 2017 to try the two-stage method of adjustment for treatment switching. We sympathise with Bayer's reason for not using this technique and we consider that they have considered a reasonable range of adjustment methods.

We believe that all this uncertainty further highlights the uncertainty in the results of switching adjustments in general.

1.4 Question 1c

NICE asked for a comparison of counterfactual survival times in the regorafenib and placebo arms (estimate of overall survival if no patients in either treatment arm had received regorafenib). NICE also requested a visual comparison of the counterfactual survival curves. They noted that a hazard ratio close to 1 would indicate that the estimation procedure had worked well.

In response, Bayer now present the counterfactual OS survival curves with recensoring applied to the 2017 data cut. They considered separately the IPE and RPSFT methods. In both cases, they found that the counterfactual OS survival curves were very similar, with OS hazard ratios close to 1.

We agree that this provides some evidence to support use of these methods. However, importantly, this does not necessarily mean that the assumptions associated with the method are justified, or that the data fit the model (Latimer et al 2016).

1.5 Question 1d

NICE asked for a detailed explanation of the cause of the 24% reduction in mean overall survival in the placebo arm after adjustment for treatment switching using the 2017 data compared to the 2015 data.

In response, Bayer again account for the reduction as a combination of (a) difference in events i.e. change in the Kaplan-Meier curves during the follow up period of the 2015 data cut and (b) increase in follow up using the 2017 data.

Concerning (a), we agree that the estimated benefit of regorafenib during the follow up period of the 2015 data cut has increased. However, this increase appears very small on inspection of the relevant Kaplan-Meier curves in Figure 5 of Bayer's response document.

Concerning (b), we agree that there is some further follow up for both treatment arms. But this is only small.

Overall, we are surprised that together these small effects can yield rather a substantial reduction of 24% in mean OS for the adjusted placebo arm. However, given that we have no conclusive evidence that Bayer have not performed the IPE method correctly, we accept Bayer's justification.

In our original base case, we preferred the 2015 data cut over the 2017 data cut, because of our concerns about the 24% reduction in OS.

In our revised base case (Section 2), we now prefer the 2017 data cut.

In their Tables 18 and 19, Bayer report total life years and QALYs for each treatment arm, separately for the 2015 and 2017 data cuts. We agree with the data they present in these tables.

1.6 Question 2

The appraisal committee noted that the p-values associated with the 2017 adjusted analyses for overall survival are incorrect. NICE requested the updated adjusted hazard ratios (stratified and unstratified analyses), 95% confidence intervals and associated p-values using both IPE and RPSFT methods.

Bayer have now provided the data requested in Table 20 of their response document. They provide hazard ratios separately for the unstratified and stratified analyses. We are unable to check the unstratified hazard ratios. For the stratified analysis, the mean hazard ratios for the ITT, RPSFT and IPE methods are appropriately the same as those given in Bayer's Clinical Study Report Addendum 2 (2017 data cut) at [redacted], [redacted] and [redacted] respectively. We expected the confidence interval for the ITT analysis quoted by Bayer to be the same as that given in Clinical Study Report Addendum 2. However, these differ: (0.676, 1.194) and (0.645, 1.250) respectively. Nonetheless, we do not dwell on this issue, as we believe this will not materially affect the committee's decisions.

1.7 Question 3

The appraisal committee heard an additional concern from us, the ERG that, whilst the Weibull distribution was assumed in the implementation of the IPE method, Bayer then extrapolated the adjusted OS data using a different distribution, the log-logistic. Related to this, the committee considered extrapolation of overall survival with the Weibull as more appropriate than the log-logistic, based on the estimated proportions of patients alive after several years. NICE asked Bayer to provide ICERs assuming a Weibull extrapolation for overall survival.

In response, Bayer estimate ICERs of £56,000 with the PAS and [redacted] without the PAS on the following basis, which is the same as that given in Section 1.2, p4, but assuming OS Weibull:

- age-related utilities.
- additional background mortality.
- OS extrapolated Weibull.
- updated dosing analysis.
- 2017 data cut.

When we try to create these ICERs, without the "updated dosing analysis", we estimate £47,000 with the PAS and [redacted] without the PAS. Applying the 4% reduction in ICERs corresponding to the "updating dosing analysis", these ICERs decrease to £45,000 with the PAS and [redacted] without the PAS. Our ICERs are substantially lower than those given by Bayer. Also, we estimate different total costs, life years and QALYs compared for both treatment arms to Bayer. We are unable to account for these differences. We believe that Bayer's ICERs are incorrect.

Based on Bayer's analysis, when we select the Weibull distribution over the 50% Weibull: 50% log-logistic, the ICERs increase substantially, from:

- £42,000 to £56,000 assuming the PAS and
- [redacted] to [redacted] without the PAS.

On the other hand, we estimate that the ICERs increase less, from:

- £42,000 to £45,000 with updated dosed, and £44,000 to £47,000 without updated dosing assuming the PAS and
- [redacted] to [redacted] with updated dosed and [redacted] to [redacted] without updated dosing without the PAS.

Next, Bayer cite advice from Dr. Latimer that the function used for the IPE method, namely the Weibull, does not necessarily need to be the same as the function used to extrapolate OS. We now have some sympathy for this argument. However, we note that Bayer chose the log-logistic distribution because it gave the best fit to the trial data. This would suggest that they should have used the log-logistic, rather than the Weibull, as part of the IPE method. Nonetheless, we do not dwell on this issue, as we have no evidence for the impact of using the log-logistic function in the IPE method.

The NICE appraisal committee favoured the Weibull, partly on advice from the clinical experts at the meeting. **Therefore, we now change our base case assumption for OS extrapolation from a 50%:50% average of the Weibull and log-logistic to 100% Weibull.**

1.8 Question 4

The appraisal committee noted that maximum follow up in the placebo adjusted arms were the same in the 2015 and 2017 analyses. NICE asked Bayer to complete a table summarising maximum follow up times.

In response, Bayer provide the required follow up times. The maximum follow up time for the placebo RPSFT-adjusted and IPE-adjusted data was [redacted] days for both the 2015 and 2017 data cuts. In our report, we noted that we expected the maximum follow up to be greater for the 2017 data cut compared to the 2015 cut, given that the 2017 data is more mature.

Bayer accounted for this as follows: "*Note that the maximum follow-up for placebo patients who do not crossover (N=8) is [redacted] days. As the counterfactual survival for all crossover placebo patients is estimated to be less than this, and patients who do not crossover are not affected by the crossover adjustment this results in the maximum follow-up for the adjusted analysis with both data cuts being equal*.".

It seems surprising to us that the counterfactual survival for all crossover placebo patients is estimated to be less than the maximum follow-up for placebo patients who do not crossover. Nonetheless, given no evidence to the contrary, we accept Bayer's explanation.

1.9 Question 5

NICE asked Bayer to provide all relevant log files for the treatment switching analysis for both 2015 and 2017 data for overall survival. This should be provided as a text file.

In response, Bayer have provided STATA log files for the 2015 and 2017 data separately for the ITT, IPE and RPSFT methods.

Due to time constraints, we have not had checked the STATA logs in detail. However, they do at least appear reasonable.

2 PenTAG revised base case

In our original report, we favoured:

- OS Weibull 50%, log-logistic 50%.
- Age-related utilities.
- IPE method.
- Analyses with recensoring.
- 2015 data cut.

We have now revised our preferred assumptions, in the light of (a) the committee discussion at the first NICE committee meeting and (b) Bayer responses above, to the following:

- OS Weibull (Section 1.7, p11).
- Age-related utilities (unchanged) (Section 1.2, p4).
- IPE and RPSFT methods equally plausible (Section 1.1, p3).
- Analyses with and without recensoring equally plausible (Section 1.2, p4).
- 2017 data cut (Section 1.5, p10).
- With or without Bayer's "updated dosing analysis" equally plausible (Section 1.2, p4).

Our corresponding ICERs are given in the Tables below. We consider all ICERs within each table equally valid. ICERs above NICE's £50,000 per QALY willingness to pay threshold for End of Life treatments are shown in grey shading.

The ICERs corresponding to no recensoring are approximations, because we do not have access to the relevant OS data. These are estimated by multiplying our relevant ICER in Table 7, Table 8, Table 9 or Table 10 corresponding to recensoring by the ratio of Bayer's relevant ICER from Table 3 or Table 4 on p7 without recensoring to their relevant ICER with recensoring. For example, our ICER of £55,230 (rounded to £55,000 in Table 9) = £45,096 (Table 9) x (£51,629 / £42,156).

We repeat from our original report that total uncertainty in the cost-effectiveness of regorafenib versus BSC is high due to:

- Substantial uncertainty in the adjustment for widespread treatment switching.
- Important uncertainty in the extrapolation of OS.

Table 7. PenTAG revised preferred ICERs without updated dosing, with PAS

	No recensoring	Recensoring
IPE	£57,000#	£47,000
RPSFT	£55,000#	£49,000

approximation, see text

Table 8. PenTAG revised preferred ICERs without updated dosing, without PAS

	No recensoring	Recensoring
IPE	[redacted]#	[redacted]
RPSFT	[redacted]#	[redacted]

approximation, see text

Applying the updated dosing, all ICERs are estimated to be 4% lower, as shown in the tables below. But we repeat our concern that we are unable to use Bayer's model to check these figures, because we have not been provided with the updated dosing data.

Table 9. PenTAG revised preferred ICERs with updated dosing, with PAS

	No recensoring	Recensoring
IPE	£55,000#	£45,000
RPSFT	£53,000#	£47,000

approximation, see text

Table 10. PenTAG revised preferred ICERs with updated dosing, without PAS

	No recensoring	Recensoring
IPE	[redacted]#	[redacted]

	No recensoring	Recensoring
RPSFT	[redacted]#	[redacted]

approximation, see text

3 References

Latimer NR & Abrams KR (2017). To re-censor, or not to re-censor, that is the question: critical considerations when applying statistical methods to adjust for treatment switching in clinical trials. Poster for ISPOR conference Boston. https://www.ispor.org/ScientificPresentationsDatabase/Presentation/73257?pdfid=50852

Latimer N, Bell, H, Abrams K, Amonkar M, Casey M. (2016) Adjusting for treatment switching in the METRIC study shows further improved overall survival with trametinib compared with chemotherapy. Cancer Medicine, 5(5):806–815.

Analyses based on PAS price = £[redacted] per pack

The following settings are used in the tables below:

- Includes PAS
- Age-related utility decrements
- Additional background mortality
- Weibull OS extrapolation
- Updated dosing analysis
- 2017 OS data

Table 1 CE results with IPE adjustment and recensoring

Technologies	Total costs	Total LY	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/LYGs)	ICER incremental (£/QALYs)
BSC	£10,218	0.949	0.627					
Regorafenib	£41,679	2.061	1.406					
				£31,461	1.111	0.780	£28,310	£40,353

Table 2 CE results with IPE adjustment and no recensoring

Technologies	Total costs	Total LY	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/LYGs)	ICER incremental (£/QALYs)
BSC	£10,399	1.155	0.759					
Regorafenib	£41,679	2.061	1.406					
				£31,280	0.905	0.648	£34,548	£48,298

Table 3 CE results with RPSFT adjustment and recensoring

Technologies	Total costs	Total LY	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/LYGs)	ICER incremental (£/QALYs)
BSC	£10,254	0.990	0.653					
Regorafenib	£41,679	2.061	1.406					
				£31,426	1.071	0.754	£29,343	£41,691

Table 4 CE results with RPSFT adjustment and no recensoring

Technologies	Total costs	Total LY	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/LYGs)	ICER incremental (£/QALYs)
BSC	£10,365	1.117	0.734					
Regorafenib	£41,679	2.061	1.406					
				£31,314	0.944	0.672	£33,184	£46,588

Regorafenib for previously treated unresectable or metastatic gastrointestinal stromal tumours:

NICE STA

Addendum #2:

Between 1st and 2nd NICE Appraisal Committee meetings

29th August 2017

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1 Background

The first NICE committee meeting for this STA was held on 28th June 2017. Afterwards, NICE asked Bayer to provide some additional information and new analyses. Our critique of Bayer's response is given in our Addendum of 11th August 2017. Our Addendum also contained our revised base case.

On 29th August 2017, NICE presented us, the ERG, with Bayer's model which was revised in two ways:

- Include the option of assuming no recensoring in the implementation of treatment switching. Previously, recensoring was assumed in all analyses.
- Include the "revised dosing assumption" for regorafenib. Here, the mean doses of regorafenib per treatment cycles were amended to include 0mg doses. Previously, 0mg doses were excluded.

On 29th August 2017, NICE also sent us two documents from Bayer. The first presented their revised ICER with no PAS, and the second contained their revised ICERs under their new revised PAS.

Originally, Bayer submitted a PAS of a [redacted] reduction in the price of regorafenib. This corresponds to a mean cost per pack of regorafenib of [redacted], compared to the list price of £3,744. Bayer now offer regorafenib for a price of [redacted] per pack, which we calculate equates to a PAS price reduction of [redacted].

2 Bayer's revised ICERs

Bayer now estimate the ICERs for regorafenib vs. placebo below. They assume the following basis:

- Age-related utility decrements.
- Additional background mortality.
- Weibull OS extrapolation.
- Updated dosing analysis.
- 2017 OS data.

Table 1. Bayer ICERs (revised [redacted] PAS)

	No recensoring	Recensoring
IPE	£48,000	£40,000
RPSFT	£47,000	£42,000

Table 2. Bayer ICERs with no PAS

	No recensoring	Recensoring
IPE	[redacted]	[redacted]
RPSFT	[redacted]	[redacted]

We can recreate the ICERs above using Bayer's revised model.

3 PenTAG revised base case

In our previous Addendum, we cautioned that we had not been presented with the mean doses corresponded to Bayer's "updated dosing analysis" for regorafenib. Bayer have now provided this data. We now accept the use of the "updated dosing analysis".

We now agree with Bayer's revised basis given in the section above. Therefore our base case ICERs are given in Tables 1 and 2 above. As mentioned in our previous Addendum, we consider all ICERs within each Table equally likely.

In our previous Addendum, we estimated our base case ICERs without allowing for recensoring. It is reassuring to observe that the relevant ICERs in the Tables above are very similar to those we estimated.

We repeat from our original report that total uncertainty in the cost-effectiveness of regorafenib versus BSC is high due to:

- Substantial uncertainty in the adjustment for widespread treatment switching.
- Important uncertainty in the extrapolation of OS.