NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Regorafenib for previously treated unresectable hepatocellular carcinoma [ID991]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Bayer (company) – updated following ERG questions
   - National Clinical Research Institute, Association of Cancer Physicians, Royal College of Physicians and Royal College of Radiologists (joint response)

'No comments' received from Department of Health.

There were no comments received from clinical or patient experts.

There were no comments received through the NICE website consultation.

3. **Company response to ERG questions** – provided by Bayer (company)
   - Response received 30 November 2017
   - Response received 4 December 2017

4. **ERG critique of company ACD response,** provided by School of Health and Related Research

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Regorafenib for previously treated advanced hepatocellular carcinoma

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Bayer	***Issue 1 - The rate of hospitalisations in the economic model has a high level of uncertainty*** ***Summary of issue*** In our base case the proportion of patients hospitalised and the number of hospitalisations was derived from a survey conducted in 2015. NICE prefer to use resources pooling this survey with an earlier survey which was conducted in 2007. The main difference between the surveys which drives a higher ICER is the difference in the rate of hospitalisations. In addition, the ERG queried whether the respondents answered the survey as intended in relation to hospitalisations. **Response** We conducted a new survey to better understand the rate of hospitalisations and to address the ERGs concerns regarding how the original questions may have been interpreted (see Appendix 1 and Appendix 2). The results of this survey in respect of hospitalisations have been incorporated into the economic model as alternative values to those from the other surveys. Although we disagree (as documented in previous responses), all other estimates of resource use are from the pooled survey as per NICEs preference. The results of the survey show that the hospitalisation of patients is low - this aligns closely with the expert's statement in the ACD that "not many patients need to be admitted to hospital". All other model settings are as per NICEs preferred assumptions e.g. Weibull extrapolation, full dose per cycle and full extrapolation. The cost-effectiveness results are presented in Table 1. *[new evidence appendix 1 and 2 not reproduced here]*	Comment noted. At the second appraisal committee meeting, the committee discussed the new hospitalisation data. Section 3.14 of the final appraisal determination (FAD) has been updated to include hospital admission rate from the new survey.

<table>
<tr>
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Table 1. Scenario 1 - Cost-effectiveness results using updated hospitalisation
<table>
<tr><th></th><th>Incremental costs</th><th>Incremental QALYs</th><th>ICER</th><th>Changes to be made in the model</th></tr>
<tr><td>NICEs base case</td><td>£23,768</td><td>0.319</td><td>£74,559</td><td></td></tr>
<tr><td>Pooled survey with new hospitalisation estimates</td><td>£22,054</td><td>0.319</td><td>£69,182</td><td>On ‘model summary’ tab:
1) Change drop down in O42 from ‘yes’ to ‘no’
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<tr>
<td>Bayer</td>
<td>
Issue 2 – The ability of the NHS to manage wastage of oral medications

Summary of issue

In the RESORCE study, adverse events were proactively managed by reducing the dose (according to protocol defined steps) or interrupting treatment. As a consequence, the average daily dose received was lower than the maximum daily dose of 160mg, meaning that at the end of a treatment cycle some medication would not have been used. In Bayer’s economic model the cost of treatment was implemented according to the average daily dose as received in the trial. The assumption implied in this modelling approach is that any unused tablets for an individual patient in one cycle offsets the number of tablets that need to be dispensed for that same individual in the subsequent treatment cycle.
According to the clinical advisors (see ERG report) any unused medication from a completed cycle is destroyed and the patient is issued with a full pack of medication for the next cycle. The implication is that for costing purposes patients are assumed to receive 160mg per day as opposed to the lower average dose observed in the clinical trial.
In addition to the above we think there may be a misunderstanding regarding how the model works i.e. from the ERG report it appears as if it is believed that the model operates such that any medication not taken by a patient who has discontinued treatment is recovered for use by another patient.
</td>
<td>Comment noted. At the second appraisal committee meeting, the committee discussed the wastage of oral medication in the NHS. The committee has considered the inclusion of [redacted] of drug wastage and agreed that this value is arbitrary and associated with significant uncertainty. Section 3.12 of the FAD has been updated to reflect this.</td>
</tr>
</table>

	Response *Potential misunderstanding* In relation to the potential misunderstanding we can confirm that in the economic model there is no 'sharing' of unused medication between patients i.e. if a patient discontinues treatment and has some medication left the assumption is that the medication is wasted. In the model treatment costs are implemented at the start of each cycle (i.e. there is no half-cycle correction). Therefore, if a patient discontinues treatment at the start of a given cycle the whole of the treatment costs for that cycle are still accrued. ***New evidence – statements from the NHS*** In our response to the ERG report we presented two statements from oncology pharmacists which summarised the established processes to reduce wastage in relation to sorafenib and high-cost oral medications. In Appendix 3 these original statements have been updated by the same pharmacists and confirm that the processes to minimise wastage extend to regorafenib. A statement is also included from Healthcare at Home, which accounts for about [redacted] of the distribution of sorafenib in England, regarding their processes to reduce wastage of oral chemotherapy medicines. In summary there are consistent processes to reduce dispensing of new medicine accounting for medicines left over from the previous cycle. Some particularly 'high-risk' patients may only receive one weeks-worth of treatment at a time. We therefore do not believe that the current assumption of destroying a patients unused medicine and then dispensing a full pack to the same patient for the next treatment cycle is reflective of NHS practices and that this assumption leads to an unrealistic and high ICER. Whilst centres with poor practices may exist we don't believe this should be taken to be representative of the majority of NHS management - it is incumbent on these hospitals to do better. Basing the cost-effectiveness of a treatment on the avoidable and wasteful practices of a minority of centres is not appropriate and almost seems to be a tacit sanctioning of these practices. In relation to oral medicines the costing of reduced doses on an individual level basis is an established method of costing and has been rightly accepted on many previous occasions.	

[new evidence appendix 3 not reproduced here]

New evidence - scenario analysis

We believe, given the efforts of the NHS to minimise wastage, it is more appropriate to reflect costs aligning to the reduced doses as observed in the RESORCE study as opposed to using a full-dosing assumption. We recognise this assumes a high level of efficiency which may not be achievable in all circumstances and for all patients. Therefore, to capture an element of increased wastage we present below a scenario whereby the economic model incorporates the costs for the actual treatment taken (i.e. average doses as per our submission) but with an assumption that every patient wastes an additional [redacted] of medicine at the maximum daily dose ([redacted]) over the course of their treatment. The wastage is applied as a one-off cost to every patient. This scenario reflects an assumption between our original base case and that currently used by NICE. The results of this analysis are presented in table 2. All other model settings are as per NICEs preferred assumptions.

Table 2. Scenario 2: Cost-effectiveness results incorporating [redacted] of wastage

Incremental costs	Incremental QALYs	Incremental costs	ICER	Changes to be made in the model
NICE preferred Base case	*£23,768*	*0.319*	*£74,559*	
Retain average dosing but with the addition of [redacted] of wastage at the maximum daily dose i.e. [redacted]	£21,896	0.319	£68,685	**On 'model summary' tab:** 1) Change O41 from 'ERG discontinuation' to 'Original KM discontinuation' 2) Change O40 from 'no' to 'yes'

Bayer

Issue 3 - Duration of treatment

Comment noted. At the second appraisal committee meeting, the committee considered the scenario

Summary of issue

In the RESORCE study patients could receive treatment after progression. In the trial [redacted] of patients in the regorafenib arm who reached progression continued to receive regorafenib.
As stated in our submission we believe that in England most patients will discontinue treatment at progression and that less treatment will be received in practice compared to in the clinical trial. Statements in the ACD align with this i.e.
" the committee noted that the number of people continuing treatment with regorafenib despite disease progression was high in RESORCE and that time-to—treatment discontinuation did not equate to time to progression. The clinical expert explained that this did not represent clinical practice in England because 80% of patients would stop treatment at progression"

Response

As described earlier, a survey was conducted focused primarily to gather information on hospitalisation. One question in the survey investigated post-progression treatment with eight out of nine (89%) respondents stating treatment stops at progression (see Appendix 1).
To better reflect treatment practices in England we have presented a scenario reflecting 80% of patients stopping treatment at or before progression and 20% receiving treatment post-progression. Using an area-under-the-curve methodology it was estimated that approximately [redacted] cycles of treatment were post-progression (see Appendix 4 for more details). This mean number of post-progression treatment cycles was adjusted to reflect 20% of patients receiving treatment after progression rather that [redacted] i.e. [redacted] cycles x 20/[redacted] equals approximately [redacted] cycle of post-progression treatment.
The mean number of pre- and post-progression treatment cycles were summed and multiplied by the cost per pack (based on a full dose) to estimate the overall drug costs. Cost-effectiveness results are shown in [new *evidence appendix 1 and 4 not reproduced here]*
Table 3.

[new evidence appendix 1 and 4 not reproduced here]

Table 3: Scenario 3: cost-effectiveness results assuming 20% post-progression treatment

	Incremental costs	Incremental QALYs	ICER	Changes to be made in the model

reflecting 80% of patients stopping treatment at or before progression and 20% receiving treatment post-progression. It considered including survival benefits associated with post-progression treatment but excluding the costs associated with this treatment was inappropriate. See section 3.11 of the FAD.

	NICE preferred Base case	*£23,768*	*0.319*	*£74,559*		
	Daily dose: 160mg	£20,120	0.319	£63,115	**On 'model summary' tab:** 1) Change O41 from 'ERG discontinuation' to 'Discontinuation with 20% post-progression treatment'.	
Bayer	***Issue 4 - Choice of extrapolation curve for Overall survival*** **Summary of issue** In our base case we used the lognormal curve to extrapolate overall survival. The lognormal curve is statistically the best-fitting curve to the data which, in terms of events, is 87% mature for best supportive care and 77% mature for regorafenib. However, the clinical advisors favoured the Weibull curve as it was felt to be more clinically plausible in the tail. It is our understanding, from the ERG report, that the preference for the Weibull curve was not absolute as the Gompertz and Exponential curves were also considered to be clinically plausible by the clinical advisors. **Response** In Table 4 we report cost-effectiveness results using a) the Weibull overall survival function but with the combined assumptions used in scenarios 1 and 2 b) the Weibull overall survival function but combined with the combined assumptions used in scenarios 1, 2 & 3 The above two analyses are repeated replacing the Weibull with the Gompertz and exponential functions instead of the Weibull function. As can be seen, regorafenib has an ICER below the 50K threshold when the 3 scenarios are combined. We believe that any of the ICERs combining scenarios 1-3 could be considered a plausible base-case for decision making purposes. **Table 4: Cost-effectiveness results**					Comment noted. At the second appraisal committee meeting, the committee considered all updated analyses for the Weibull, Gompertz and exponential overall survival curves. As no further information was provided to support the use of an exponential or Gompertz curve, the committee's preference for the Weibull remained unchanged. Please see section 3.9 of the FAD.

	Incremental costs	Incremental QALYs	ICER	Changes to be made in the model
NICE Base Case	*£23,768*	*0.319*	*£74,559*	
Weibull OS + assumptions from Scenarios 1 and 2*	£20,427	0.319	£64,077	**On 'model summary' tab:** 1) Change drop down in O42 from 'yes' to 'no'. 2) Change drop down in O43 from 'no' to 'yes'. 3) Change O41 from 'ERG discontinuation' to 'Original KM discontinuation' 4) Change O40 from 'no' to 'yes'.
Weibull OS + assumptions from Scenarios 1, 2† and 3	£16,085	0.319	£50,456	**On 'model summary' tab:** 1) Change drop down in O42 from 'yes' to 'no'. 2) Change drop down in O43 from 'no' to 'yes'. 3) Change O41 from 'ERG discontinuation' to 'Discontinuation with 20% post-progression treatment' 4) Change O40 from 'no' to 'yes'.
Gompertz + assumptions from Scenarios 1 and 2*	£19,091	0.343	£55,589	**On 'model summary' tab**: 1) Change drop down in O42 from 'yes' to 'no'. 2) Change drop down in O43 from 'no' to 'yes'. 3) Change O41 from 'ERG discontinuation' to 'Original KM discontinuation' 4) Change O40 from 'no' to 'yes'. **On the 'effect' tab:** 1) Change F25 from 'weibull' to 'gompertz'.

	Gompertz + assumptions from Scenarios 1, 2† and 3	£14,748	0.343	£42,944	**On 'model summary' tab:** 1) Change drop down in O42 from 'yes' to 'no'. 2) Change drop down in O43 from 'no' to 'yes'. 3) Change O41 from 'ERG discontinuation' to 'Discontinuation with 20% post-progression treatment' 4) Change O40 from 'no' to 'yes' **On the 'effect' tab:** 1) Change F25 from 'weibull' to 'gompertz'.	
	Exponential + assumptions from Scenarios 1 and 2*	£19,240	0.348	£55,260	**On 'model summary' tab:** 1) Change drop down in O42 from 'yes' to 'no' 2) Change drop down in O43 from 'no' to 'yes' 3) Change O41 from 'ERG discontinuation' to 'Original KM discontinuation' 4) Change O40 from 'no' to 'yes' **On the 'effect' tab:** 1) Change F25 from 'weibull' to 'exponential'.	
	Exponential + assumptions from Scenarios 1, 2† and 3	£14,897	0.348	£42,788	**On 'model summary' tab:** 1) Change drop down in O42 from 'yes' to 'no' 2) Change drop down in O43 from 'no' to 'yes' 3) Change O41 from 'ERG discontinuation' to 'Discontinuation	

					with 20% post-progression treatment' 4) Change O40 from 'no' to 'yes' **On the 'effect' tab:** 1) Change F25 from 'weibull' to 'exponential'.	
	* uses cycle specific average dose information from the KM discontinuation tab of the economic model (column D); † assumes a constant average per cycle dose of [redacted]mg i.e. the average pre-progression dose in the originally submitted model – see Appendix 4 *[appendix 4 not reproduced here]*					
Bayer	We note the concern expressed in several places throughout the ACD that evidence is lacking from the RESORCE study for patients with Child Pugh B or ECOG performance status 2. These patients are not excluded from the licensed indication and would therefore be eligible to receive treatment with regorafenib. We believe the recent restrictions to sorafenib (only Child Pugh A) will manifest in a predominantly healthier population being eligible for regorafenib in England therefore we consider that applying the same restriction to regorafenib as for sorafenib would remove the stated uncertainty.					Comment noted. Please see section 3.4 and 3.5 of the FAD
Bayer	It is stated that "Regorafenib is not recommended through the cancer drugs fund because it does not have the plausible potential to be cost-effective" We consider this statement to be wrong as the base-case ICER from the ERG is founded on a combination of worst-case assumptions leading to an inflated 'most plausible ICER'. We have presented new evidence in our response and shown that regorafenib is likely to be cost-effective.					Thank you for your comment. The appraisal committee has considered the new evidence presented and the related range of ICERs. See sections 3.9, 3.11, 3.12, 3.14, 3.16 and 3.17 of the FAD
Bayer	Utility values – concern is expressed over the validity of the utility values The utility values used in the economic evaluation are derived from the EQ-5D questionnaire that was administered during the RESORCE study. Utility values were based on UK tariffs and as such the utility values align with the reference case. There are uncertainties in the utility values but these are no different to those observed in the majority of oncology studies. The values presented are the best values available and are suitable for use in the economic evaluation.					Comment noted. The committee's view that the high utility values used in the model did not seem clinically plausible despite EQ-5D data from the trial being used remains unchanged.

Comments received from consultees

submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
Royal College of Physicians	There are currently no funded systemic therapy options for patients with advanced HCC who have failed sorafenib therapy, and the RESORCE trial demonstrated that regorafenib provides a significant and clinically-meaningful improvement in survival compared to placebo in patients who previously tolerated sorafenib. Hence, as acknowledged in the appraisal consultation document, regorafenib meets an important unmet need.	Comment noted.
Royal College of Physicians	Whilst there is disappointment that the appraisal committee has not recommended the use of regorafenib in patients with previously-treated advanced HCC, it is noted that the application was based on the marketing authorisation for regorafenib in this indication, and hence includes patients that would not have been eligible for recruitment to the RESORCE trial. In the interest of patients with HCC, we would encourage the committee to recommend that Bayer consider a revised application based on the eligibility criteria applied within the RESORCE trial. This would restrict the use of regorafenib to those that have shown benefit from treatment, and improve outcomes for patients with HCC in the UK.	Thank you for your comment. The committee considered this restricted population during their decision-making and when considering all evidence. Please see section 3.4 and 3.5 of the FAD

Comments received from commentators- Department of Health (no comments)

Comments received from members of the public-None

6 December 2017

ERG questions received 5 & 6 December 2017:

Question: 5 December

Following on from the updated ACD response submitted by yourself in response to the ERG's query, the ERG have noted another potential typo/error. The ERG note that when the changes to the model are made to amend the errors in the survey data, the ICER obtained is £69,137/QALY. However, in Table 2 of your response, this is reported as £69,454.

Question: 6 December

The ERG have further identified that the first two ICERS reported in Table 4 also don't match the value produced by the model (they have not checked the values for Gompertz or exponential). Could you also re-check all the values in Table 4 and confirm if they are correct.

PART 1

Response

On receipt of the question received on 5 December we initiated a review with our modelling agency but using individuals without prior exposure to the model. It has been brought to our attention that further to the two corrections notified to the ERG on the 4th December there were 3 other incorrect formula identified which had also been corrected (Table A corrections 3 to 5) – these were not notified to us and subsequently not to the ERG which is why we think they have understandably not been able to replicate our results. If the ERG implements corrections 1 – 5 in the model sent on 27th November they will be able to replicate the results sent on 4 December 2017.

Unfortunately the review of the economic model has led to other errors being identified. These are listed in Table A below (6-12). We can only apologise for the additional work this causes.

All of the corrections listed have been implemented in the model – updated results are presented in part 2 which is an update to the response sent on 4 December. If the ERG implements the corrections listed in the table in the model sent on 27th November they will get the results presented in part 2. We have attached an updated model with all the corrections implemented. Please note, that the new corrections have been made directly in the cells and not as dropdown options. The ERG basecase ICER with the corrections is £73,790.

Table A. Changes made to model 'Regorafenib_ID991_ACIC_EconomicModel_ACD Response_27Nov17_Final'

Number	Cell on 'costs' tab	Correction	Original formula	Corrected formula
1	K69	Day in hospital incorrectly listed as 6% rather than 6	=IF(AND(ResUse="YES",UPresuse="YES"),6,IF(AND(ResUse="YES"=1,UPresuse="NO"),5.25,IF(AND(ResUse="NO",UPresuse="YES"),**6%**,5.42)))	=IF(AND(ResUse="YES",UPresuse="YES"),6,IF(AND(ResUse="YES"=1,UPresuse="NO"),5.25,IF(AND(ResUse="NO",UPresuse="YES"),**6**,5.42)))
2	G69	Days in hospital listed as 3.93 instead of 4.40 when the 2017 survey results is selected on the Model Summary tab	=IF(AND(ResUse="YES",UPresuse="YES"),4.4,IF(AND(ResUse="YES",UPresuse="NO"),5.83,IF(AND(ResUse**="NO"=2**,UPresuse="YES"),4.4,3.93)))	=IF(AND(ResUse="YES",UPresuse="YES"),4.4,IF(AND(ResUse="YES",UPresuse="NO"),5.83,IF(AND(ResUse**="NO"**,UPresuse="YES"),4.4,3.93)))
3	F103	Incorrectly linked to cell F38; link to F37	=costs!F**38***(costs!F70*costs!G70*costs!H70)	=costs!F**37***(costs!F70*costs!G70*costs!H70)
4	H103	Incorrectly linked to cell F38; link to F37	=costs!F**38***(costs!J70*costs!K70*costs!L70)	=costs!F**37***(costs!J70*costs!K70*costs!L70)
5	K103	Incorrectly linked to cell F38; link to F37	=costs!F**38***(costs!Q70*costs!R70*costs!S70)	=costs!F**37***(costs!Q70*costs!R70*costs!S70)
6	I103	Incorrectly linked to cell F38; link to F37	=costs!F**38***(costs!M70*costs!N70*costs!O70)	=costs!F**37***(costs!M70*costs!N70*costs!O70)
7	F104	Incorrectly excluded number of hospitalisations/visits; include number of hospitalisations/visits in calculation	=costs!F38*costs!F71	=costs!F38*(costs!F71***H71)**
8	H104	Incorrectly excluded number of hospitalisatio	=costs!F38*costs!J71	=costs!F38*(costs!J71***L71)**

		ns/visits; include number of hospitalisations/visits in calculation		
9	I104	Incorrectly excluded number of hospitalisations/visits; include number of hospitalisations/visits in calculation	=costs!F38*costs!M71	=costs!F38*(costs!M71***O71)**
10	K104	Incorrectly excluded number of hospitalisations/visits; include number of hospitalisations/visits in calculation	=costs!F38*costs!Q71	=costs!F38*(costs!Q71***S71)**
	Cell on 'KM discontinuation' tab	**Description**	**Original formula**	**Corrected formula**
11	J3659	Drag formula down to J3658	Blank	=K3659/28
12	K3659	Include an additional day	Blank	=1+K3658

PART 2: NICE Appraisal Consultation Document – Company Response

Thank you for the opportunity to respond to the draft guidance for regorafenib in HCC.

Overview

Our base case ICER was £36,050 which is substantially lower than NICEs preferred ICER of £74,559. The divergence between the two estimates of cost-effectiveness is driven predominantly by different assumptions in four key areas. These differences relate to:

1) The proportion of patients who are hospitalised and how often
2) The ability of the NHS to manage wastage of oral medications
3) The average duration of treatment
4) The choice of extrapolation curve for overall survival

In our response we summarise each of these key differences and present new evidence and economic analyses.

After incorporation of the new evidence the ICER using the Weibull overall survival extrapolation reduces to £50,456. Using other survival functions considered by the clinical experts to be plausible the ICER reduces further to £42,788.

Issue 1 - The rate of hospitalisations in the economic model has a high level of uncertainty

Summary of issue

In our base case the proportion of patients hospitalised and the number of hospitalisations was derived from a survey conducted in 2015. NICE prefer to use resources pooling this survey with an earlier survey which was conducted in 2007. The main difference between the surveys which drives a higher ICER is the difference in the rate of hospitalisations. In addition, the ERG queried whether the respondents answered the survey as intended in relation to hospitalisations.

Response

We conducted a new survey to better understand the rate of hospitalisations and to address the ERGs concerns regarding how the original questions may have been interpreted (see Appendix 1 and Appendix 2). The results of this survey in respect of hospitalisations have been incorporated into the economic model as alternative values to those from the other surveys.

Although we disagree (as documented in previous responses), all other estimates of resource use are from the pooled survey as per NICEs preference.

The results of the survey show that the hospitalisation of patients is low - this aligns closely with the expert's statement in the ACD that "not many patients need to be admitted to hospital".

All other model settings are as per NICEs preferred assumptions e.g. Weibull extrapolation, full dose per cycle and full extrapolation. The cost-effectiveness results are presented in Table 1.

Table 1. Scenario 1 - Cost-effectiveness results using updated hospitalisation

	Incremental costs	Incremental QALYs	ICER	Changes to be made in the model
NICEs base case	*£23,768*	*0.319*	*£74,559*	
Pooled survey with new hospitalisation estimates	£22,054	0.319	£69,182	**On 'model summary' tab:** 1) Change drop down in O42 from 'yes' to 'no' 2) Change drop down in O43 from 'no' to 'yes'

Issue 2 – The ability of the NHS to manage wastage of oral medications

Summary of issue

In the RESORCE study, adverse events were proactively managed by reducing the dose (according to protocol defined steps) or interrupting treatment. As a consequence, the average daily dose received was lower than the maximum daily dose of 160mg, meaning that at the end of a treatment cycle some medication would not have been used. In Bayer's economic model the cost of treatment was implemented according to the average daily dose as received in the trial. The assumption implied in this modelling approach is that any unused tablets for an individual patient in one cycle offsets the number of tablets that need to be dispensed for that same individual in the subsequent treatment cycle.

According to the clinical advisors (see ERG report) any unused medication from a completed cycle is destroyed and the patient is issued with a full pack of medication for the next cycle. The implication is that for costing purposes patients are assumed to receive 160mg per day as opposed to the lower average dose observed in the clinical trial.

In addition to the above we think there may be a misunderstanding regarding how the model works i.e. from the ERG report it appears as if it is believed that the model operates such that any medication not taken by a patient who has discontinued treatment is recovered for use by another patient.

Response

Potential misunderstanding

In relation to the potential misunderstanding we can confirm that in the economic model there is no 'sharing' of unused medication between patients i.e. if a patient discontinues treatment and has some medication left the assumption is that the medication is wasted. In the model

treatment costs are implemented at the start of each cycle (i.e. there is no half-cycle correction). Therefore, if a patient discontinues treatment at the start of a given cycle the whole of the treatment costs for that cycle are still accrued.

New evidence – statements from the NHS

In our response to the ERG report we presented two statements from oncology pharmacists which summarised the established processes to reduce wastage in relation to sorafenib and high-cost oral medications. In Appendix 3 these original statements have been updated by the same pharmacists and confirm that the processes to minimise wastage extend to regorafenib. A statement is also included from Healthcare at Home, which accounts for about [redacted] of the distribution of sorafenib in England, regarding their processes to reduce wastage of oral chemotherapy medicines. In summary there are consistent processes to reduce dispensing of new medicine accounting for medicines left over from the previous cycle. Some particularly 'high-risk' patients may only receive one weeks-worth of treatment at a time. We therefore do not believe that the current assumption of destroying a patients unused medicine and then dispensing a full pack to the same patient for the next treatment cycle is reflective of NHS practices and that this assumption leads to an unrealistic and high ICER.

Whilst centres with poor practices may exist we don't believe this should be taken to be representative of the majority of NHS management - it is incumbent on these hospitals to do better. Basing the cost-effectiveness of a treatment on the avoidable and wasteful practices of a minority of centres is not appropriate and almost seems to be a tacit sanctioning of these practices.

In relation to oral medicines the costing of reduced doses on an individual level basis is an established method of costing and has been rightly accepted on many previous occasions.

New evidence - scenario analysis

We believe, given the efforts of the NHS to minimise wastage, it is more appropriate to reflect costs aligning to the reduced doses as observed in the RESORCE study as opposed to using a full-dosing assumption. We recognise this assumes a high level of efficiency which may not be achievable in all circumstances and for all patients. Therefore, to capture an element of increased wastage we present below a scenario whereby the economic model incorporates the costs for the actual treatment taken (i.e. average doses as per our submission) but with an assumption that every patient wastes an additional [redacted] days of medicine at the maximum daily dose ([redacted] tablets) over the course of their treatment. The wastage is applied as a one-off cost to every patient. This scenario reflects an assumption between our original base case and that currently used by NICE. The results of this analysis are presented in table 2. All other model settings are as per NICEs preferred assumptions.

Table 2. Scenario 2: Cost-effectiveness results incorporating [redacted] days of wastage

Incremental costs	Incremental QALYs	Incremental costs	ICER	Changes to be made in the model
NICE preferred Base case	*£23,768*	*0.319*	*£74,559*	
Retain average dosing but with the addition of [redacted] days of wastage at the maximum daily dose i.e. [redacted] tablets	£21,896	0.319	£68,685	**On 'model summary' tab:** 1) Change O41 from 'ERG discontinuation' to 'Original KM discontinuation' 2) Change O40 from 'no' to 'yes'

Issue 3 - Duration of treatment

Summary of issue

In the RESORCE study patients could receive treatment after progression. In the trial [redacted] of patients in the regorafenib arm who reached progression continued to receive regorafenib.

As stated in our submission we believe that in England most patients will discontinue treatment at progression and that less treatment will be received in practice compared to in the clinical trial. Statements in the ACD align with this i.e.

> *" the committee noted that the number of people continuing treatment with regorafenib despite disease progression was high in RESORCE and that time-to—treatment discontinuation did not equate to time to progression. The clinical expert explained that this did not represent clinical practice in England because 80% of patients would stop treatment at progression"*

Response

As described earlier, a survey was conducted focused primarily to gather information on hospitalisation. One question in the survey investigated post-progression treatment with eight out of nine (89%) respondents stating treatment stops at progression (see Appendix 1).

To better reflect treatment practices in England we have presented a scenario reflecting 80% of patients stopping treatment at or before progression and 20% receiving treatment post-progression. Using an area-under-the-curve methodology it was estimated that approximately [redacted] cycles of treatment were post-progression (see Appendix 4 for more details). This mean number of post-progression treatment cycles was adjusted to reflect 20% of patients receiving treatment after progression rather that [redacted] i.e.[redacted] cycles x 20/[redacted] equals approximately [redacted] cycle of post-progression treatment.

The mean number of pre- and post-progression treatment cycles were summed and multiplied by the cost per pack (based on a full dose) to estimate the overall drug costs. Cost-effectiveness results are shown in Table 3.

Table 3: Scenario 3: cost-effectiveness results assuming 20% post-progression treatment

	Incremental costs	Incremental QALYs	ICER	Changes to be made in the model
NICE preferred Base case	*£23,768*	*0.319*	*£74,559*	
Daily dose: 160mg	£20,120	0.319	£63,115	**On 'model summary' tab:** 1) Change O41 from 'ERG discontinuation' to 'Discontinuation with 20% post-progression treatment'.

Issue 4 - Choice of extrapolation curve for Overall survival

Summary of issue

In our base case we used the lognormal curve to extrapolate overall survival. The lognormal curve is statistically the best-fitting curve to the data which, in terms of events, is 87% mature for best supportive care and 77% mature for regorafenib.

However, the clinical advisors favoured the Weibull curve as it was felt to be more clinically plausible in the tail. It is our understanding, from the ERG report, that the preference for the Weibull curve was not absolute as the Gompertz and Exponential curves were also considered to be clinically plausible by the clinical advisors.

Response

In Table 4 we report cost-effectiveness results using

a) the Weibull overall survival function but with the combined assumptions used in scenarios 1 and 2
b) the Weibull overall survival function but combined with the combined assumptions used in scenarios 1, 2 & 3

The above two analyses are repeated replacing the Weibull with the Gompertz and exponential functions instead of the Weibull function.

As can be seen, regorafenib has an ICER below the 50K threshold when the 3 scenarios are combined. We believe that any of the ICERs combining scenarios 1-3 could be considered a plausible basecase for decision making purposes.

Table 4: Cost-effectiveness results

	Incremental costs	Incremental QALYs	ICER	Changes to be made in the model
NICE Base Case	*£23,768*	*0.319*	*£74,559*	
Weibull OS + assumptions from Scenarios 1 and 2*	£20,427	0.319	£64,077	**On 'model summary' tab:** 1) Change drop down in O42 from 'yes' to 'no'. 2) Change drop down in O43 from 'no' to 'yes'. 3) Change O41 from 'ERG discontinuation' to 'Original KM discontinuation' 4) Change O40 from 'no' to 'yes'.
Weibull OS + assumptions from Scenarios 1, 2† and 3	£16,085	0.319	£50,456	**On 'model summary' tab:** 1) Change drop down in O42 from 'yes' to 'no'. 2) Change drop down in O43 from 'no' to 'yes'. 3) Change O41 from 'ERG discontinuation' to 'Discontinuation with 20% post-progression treatment' 4) Change O40 from 'no' to 'yes'.
Gompertz + assumptions from Scenarios 1 and 2*	£19,091	0.343	£55,589	**On 'model summary' tab**: 1) Change drop down in O42 from 'yes' to 'no'. 2) Change drop down in O43 from 'no' to 'yes'. 3) Change O41 from 'ERG discontinuation' to 'Original KM discontinuation' 4) Change O40 from 'no' to 'yes'. **On the 'effect' tab:** 1) Change F25 from 'weibull' to 'gompertz'.
Gompertz + assumptions from Scenarios 1, 2† and 3	£14,748	0.343	£42,944	**On 'model summary' tab:** 1) Change drop down in O42 from 'yes' to 'no'. 2) Change drop down in O43 from 'no' to 'yes'. 3) Change O41 from 'ERG discontinuation' to 'Discontinuation with 20% post-progression treatment' 4) Change O40 from 'no' to 'yes' **On the 'effect' tab:** 1) Change F25 from 'weibull' to 'gompertz'.

Exponential + assumptions from Scenarios 1 and 2*	£19,240	0.348	£55,260	**On 'model summary' tab:** 1) Change drop down in O42 from 'yes' to 'no' 2) Change drop down in O43 from 'no' to 'yes' 3) Change O41 from 'ERG discontinuation' to 'Original KM discontinuation' 4) Change O40 from 'no' to 'yes' **On the 'effect' tab:** 1) Change F25 from 'weibull' to 'exponential'.
Exponential + assumptions from Scenarios 1, 2† and 3	£14,897	0.348	£42,788	**On 'model summary' tab:** 1) Change drop down in O42 from 'yes' to 'no' 2) Change drop down in O43 from 'no' to 'yes' 3) Change O41 from 'ERG discontinuation' to 'Discontinuation with 20% post-progression treatment' 4) Change O40 from 'no' to 'yes' **On the 'effect' tab:** 1) Change F25 from 'weibull' to 'exponential'.

* uses cycle specific average dose information from the KM discontinuation tab of the economic model (column D); † assumes a constant average per cycle dose of [redacted]mg i.e. the average preprogression dose in the originally submitted model – see Appendix 4

Other comments

1) We note the concern expressed in several places throughout the ACD that evidence is lacking from the RESORCE study for patients with Child Pugh B or ECOG performance status 2. These patients are not excluded from the licensed indication and would therefore be eligible to receive treatment with regorafenib.

We believe the recent restrictions to sorafenib (only Child Pugh A) will manifest in a predominantly healthier population being eligible for regorafenib in England therefore we consider that applying the same restriction to regorafenib as for sorafenib would remove the stated uncertainty.

2) It is stated that "Regorafenib is not recommended through the cancer drugs fund because it does not have the plausible potential to be cost-effective"

We consider this statement to be wrong as the basecase ICER from the ERG is founded on a combination of worst-case assumptions leading to an inflated 'most plausible ICER'. We have presented new evidence in our response and shown that regorafenib is likely to be cost-effective.

3) Utility values – concern is expressed over the validity of the utility values

The utility values used in the economic evaluation are derived from the EQ-5D questionnaire that was administered during the RESORCE study. Utility values were based on UK tariffs and as such the utility values align with the reference case.

There are uncertainties in the utility values but these are no different to those observed in the majority of oncology studies. The values presented are the best values available and are suitable for use in the economic evaluation.

Conclusion

We have presented new evidence and analyses which we believe reduce the main areas of uncertainty and show regorafenib is likely to be a cost-effective use of NHS resources. We hope the committee will be open to the new evidence and will reconsider its draft advice.

New Evidence Appendices

Appendix 1 – Resource use survey

Report Title :	UK Resource Use Physician Questionnaire – sorafenib in HCC
Report Number :	
Report to :	[redacted]
Submitted on :	6th October 2017
Document Version :	1.1
Document Status :	

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1. Ethical undertaking

IMS works under the rules of the EphMRA International Code of Conduct.

We are currently undertaking an investigation into resource use due to acute (non-elective) hospitalisations that occur during the treatment of advanced hepatocellular carcinoma (HCC). The patients we are interested in are those who are either unsuitable for surgical or loco-regional treatments or their HCC has progressed after surgery or loco-regional therapies. These patients are referred to as **advanced HCC** hereafter. We would very much appreciate your co-operation.

Our intention is not to sell you anything.

We will comply with all UK laws protecting your personal data and the British Healthcare Business Intelligence Association guidelines. Your responses will be used by us and the sponsoring pharmaceutical company for future and ongoing UK technology appraisals (where there is uncertainty regarding resource use). Your responses will be collated with other respondents and presented to the sponsor in aggregated or anonymised form.

Please be informed that we use your personal data limited to contact details and information about your specialization in order to conduct market research. We will send you written information about this use.

You can withdraw from the market research at any time, and you have the right to withhold information, i.e. not answer a question should you wish

All answers that you provide will be treated in the strictest confidence and your identity will not be revealed to any third parties. The results from your interview will be aggregated with those provided by other respondents.

You are about to enter a market research interview. We are now required to pass on to our client details of adverse events that are raised during the course of market research interviews. Should you raise an adverse event in a specific patient or group of patients, we will need to report this, even if it has already been reported by you directly to the company or the regulatory authorities using the MHRA's 'Yellow Card' system. In such a situation you will be contacted to ask whether or not you are willing to waive the confidentiality given to you under the Market Research Codes of conduct specifically in relation to that adverse event. Everything else you contribute during the course of the interview will continue to remain confidential. Are you happy to proceed with the interview on this basis?

Yes [ ] No [ ]

Should we need to contact you again regarding clarification for any of your answers would we be able to do so?

Yes [ ] No [ ]

2. Screening

Please answer the following questions to confirm you are eligible to participate in this questionnaire:

a) You have treated 10 or more advanced HCC patients in the past year?

Yes [ ] No [ ]

b) You have experience prescribing or have been involved in managing patients treated with sorafenib

c) Yes [ ] No [ ]

A1.

If you do not meet both of these criteria please do not continue with the questionnaire.

3. Objectives

To obtain data about acute (non-elective) hospitalisations in patients with non-curative advanced HCC actively treated with sorafenib or managed with best supportive care only.

4. Background

This questionnaire relates to patients with advanced HCC that are either unsuitable for surgical or loco-regional treatments or their HCC has progressed after surgical or loco-regional therapies. We would like you to have this patient group in mind throughout all the questions .

We are interested in rate of acute (non-elective) hospitalisations according to the next phase of treatment (i.e. sorafenib or best supportive care alone) and the progression status of the patient (i.e. pre-progression or post-progression). In this questionnaire we define “pre-progression” as not experiencing further progression whilst receiving either sorafenib or best supportive care alone. We define “post-progression” as experiencing progression whilst on either of these treatments.

Distinguishing between progression status and treatment leads to 4 groups of patients for which we are interested in the rate of acute hospitalisations. This will allow us to estimate how resource use varies as a patient's condition and cancer treatment changes.

Group 1	Pre-progression: treated with sorafenib
Group 2	Pre-progression: treatment with BSC alone
Group 3	Post-progression: treated with sorafenib
Group 4	Post-progression: treatment with BSC only

5. Structure of the questionnaire

The questionnaire you are about to complete asks first about your specialism and experience.

The questionnaire then asks about hospitalisation resource use for both sorafenib and best-supportive care in each of the health states outlined above.

6. Questionnaire

The following sections represent the body of the questionnaire.

Q1 How many advanced HCC patients have you personally and directly managed in the past 12 months?

_____

Q2 In which country are you based?

England/Wales/Scotland/N Ireland

Q3 What is your profession/specialism?

Clinical oncologist / Medical oncologist / Gastroenterologist/Hepatologist /Other (please specify)

Q4 In what setting do you manage advanced HCC

Tertiary referral centre / secondary care hospital

6.1. Acute (non-elective) hospitalisations (excluding those related to adverse events)

Thinking of your patients, what acute care for advanced HCC will typically be required within an average month? We would like you to consider the need for acute (non-elective) hospitalisation related to the underlying disease itself and how this may be affected by the treatment received. We would also like you to consider Accident and Emergency attendances not resulting in hospitalisation.

Please note we are not considering hospitalisations or accident & emergency attendance associated with treatment-related adverse events. Adverse events are considered separately.

Please also consider the length of stay for the average/typical patient who is hospitalised.

Example

Please note that the following examples are for illustration purposes only.

- *If you have 100 patients in the pre-progression state and during a typical month 5 patients would be hospitalised on average i.e. two for an adverse event to treatment and three due to the advanced HCC then '3%' should be entered (3/100). The two adverse events are not considered.*
- *If on average one out of the hundred patients is hospitalised less than once per month then a fraction should be entered e.g. 0.5% represents one patient out of a hundred being hospitalised once every two months.*

In the example in the table below 5% of patients are typically hospitalised per month and on average, of those hospitalised, 80% would require one hospitalisation. Accident & Emergency attendance relates to patients who attend A&E but are not admitted – it therefore does not include the 5% of patients in the first part of the table.

Acute care for pre-progression patients – managed with sorafenib

Average percentage of patients requiring at least one hospitalisation (per month)	*5%*	
Of those hospitalised:		
- % requiring 1 hospitalisation per month	*80% (4/5)*	
- % requiring 2 hospitalisations per month	*20% (1/5)*	
Per typical/average hospitalisation	***Average proportion***	***Average length of stay (days)***
General ward admittance	*80%*	*6*
ICU admittance	*20%*	*2*
Average percentage of patients requiring at least one A&E attendance (per month) – ***not admitted (as above please exclude adverse events)***	*10%*	
Of those attending A&E		
- % requiring 1 A&E attendance per month	*95%*	
- % requiring 2 A&E attendances per month	*5%*	

PRE-PROGRESSION

In the following two tables please consider patients in the pre-progression health state who are managed with either sorafenib or best supportive care alone.

Please note we are not considering hospitalisations or accident & emergency attendance associated with treatment-related adverse events. Adverse events are considered separately.

Acute care for PRE-PROGRESSION patients –managed with SORAFENIB

Average percentage of patients requiring at least one hospitalisation (per month)		
Of those hospitalised:		
- % requiring 1 hospitalisation per month		
- % requiring 2 hospitalisations per month		
Per typical/average hospitalisation	**Average proportion**	**Average length of stay (days)**
General ward admittance		
ICU admittance		
Average percentage of patients requiring at least one A&E attendance (per month) – ***not admitted (as above please exclude adverse events)***		
Of those attending A&E		
- % requiring 1 A&E attendance per month		
- % requiring 2 A&E attendances per month		

Acute care for PRE-PROGRESSION patients – managed with BEST SUPPORTIVE CARE ONLY

Average percentage of patients requiring at least one hospitalisation (per month)		
Of those hospitalised:		
- % requiring 1 hospitalisation per month		
- % requiring 2 hospitalisations per month		
Per typical/average hospitalisation	**Average proportion**	**Average length of stay (days)**
General ward admittance		
ICU admittance		
Average percentage of patients requiring at least one A&E attendance (per month) – **not admitted *(as above please exclude adverse events)***		
Of those attending A&E		
- % requiring 1 A&E attendance per month		
- % requiring 2 A&E attendances per month		

POST-PROGRESSION

In the following two tables please consider patients in the post-progression health state who are managed with either sorafenib or best supportive care alone.

Please note we are not considering hospitalisations or accident and emergency attendance associated with treatment-related adverse events. Adverse events are considered separately.

Acute care for POST-PROGRESSION patients – managed with SORAFENIB

Average percentage of patients requiring at least one hospitalisation (per month)		
Of those hospitalised:		
- % requiring 1 hospitalisation per month		
- % requiring 2 hospitalisations per month		
Per typical/average hospitalisation	**Average proportion**	**Average length of stay (days)**
General ward admittance		
ICU admittance		
Average percentage of patients requiring at least one A&E attendance (per month) – **not admitted** ***(as above please exclude adverse events)***		
Of those attending A&E		
- % requiring 1 A&E attendance per month		
- % requiring 2 A&E attendances per month		

Acute care for POST-PROGRESSION patients – managed with BEST SUPPORTIVE CARE ALONE

Average percentage of patients requiring at least one hospitalisation (per month)		
Of those hospitalised:		
- % requiring 1 hospitalisation per month		
- % requiring 2 hospitalisations per month		
Per typical/average hospitalisation	**Average proportion**	**Average length of stay (days)**
General ward admittance		
ICU admittance		
Average percentage of patients requiring at least one A&E attendance (per month) – ***not admitted (as above please exclude adverse events)***		
Of those attending A&E		
- % requiring 1 A&E attendance per month		
- % requiring 2 A&E attendances per month		

6.2. Clinical management of post-progression patients

This section considers patients who have progressed whilst being treated with sorafenib and their ongoing management.

Do you continue to treat these patients with sorafenib post-progression

Yes [ ] No [ ]

If yes, what percentage of patients would you continue to treat on average [%]

For those patients who continue to receive sorafenib after progression please provide an indication of how long, on average, treatment would be continued

_____ weeks

Thank you for your time.

Appendix 2 – Resource use survey results

Please see excel file (provided separately) for the results, a summary of which is provided in table 5 below.

Twenty-eight physicians were contacted to determine interest in completing the survey. Nine physicians participated. To meet eligibility criteria for the survey, clinicians must have treated at least 10 patients with advanced HCC in the previous 12 months, and had must have had experience prescribing, or have been involved in managing patients treated with sorafenib.

Table 5. Updated survey results 2017

	Sorafenib		**BSC**	
	Pre-progression	***Post-progression***	***Pre-progression***	***Post-progression***
Hospitalised (%)	7.56%	18.89%	12.67%	25.33%
General Ward	7.47%	18.89%	12.51%	25.02%
ICU	0.08%	0.00%	0.16%	0.32%
Of those hospitalised				
1 visit	89%	82%	86%	84%
2 visits	11%	18%	14%	16%
Average number of visits	1.11	1.18	1.14	1.16
Length of stay				
General Ward	4.4	6.0	5.5	5.8
ICU	2.0	0.0	4.0	3.0
AE attendance (%)	7.78%	18.89%	15.33%	25.89%
1 visit	93%	85%	88%	84%
2 visits	8%	15%	13%	16%
Average number of visits	1.08	1.15	1.13	1.16

Appendix 3 – Wastage statements

University Hospitals Birmingham NHS
NHS Foundation Trust

Queen Elizabeth Hospital
Edgbaston
Birmingham
B15 2TH

Tel: 0121 472 1311

3rd November 2017

Dear [redacted]

Re: Oral chemotherapy and wastage with regorafenib (Stivarga)

As per our previous statement in September 2016, and due to the continued specialist nature of the Queen Elizabeth Hospital Birmingham, the usage of high cost medication is a routine and regular occurrence and continues to be managed in compliance with UK best practice guidance for oral anticancer medicines (e.g. BOPA 2004; NPSA 2008).[1,2] Please find below a summary of our approach to managing medicines wastage with oral anti-cancer medicines. This statement was originally produced to support the supply of sorefenib (Nexavar) and would also apply for the supply of regorafenib for the treatment of hepatocellular carcinoma (HCC) in patients who have been previously treated with sorafenib.

- Only one month of oral anti-cancer therapy is prescribed at any given time; treatment is initiated by a cancer specialist and patients are fully informed about appropriate use of their oral anticancer therapy (both verbally and written)
    - In cases where patients are determined to be high risk, a decision may be taken to issue only **one week's supply** and a re-assessment is made after one week of therapy

- Prescribing of regorafenib will occur at the patient's monthly follow-up appointment, where a clinical decision is made regarding the patient's suitability for treatment in the following month. Based on a standard evaluation of the patient, including blood tests where appropriate, a following month's supply of regorafenib will be prescribed

- The clinician, pharmacist and patient discuss and determine what medicines were used in the month (patients are asked to bring their medicines pack and any unused tablets to the appointment with them). Where the patient has not used some tablets, only the remainder of another month's supply will be issued. The supply is actively managed by splitting packs where appropriate to ensure only the outstanding amount is issued

- Whilst this process cannot eliminate wastage entirely, we find this approach minimises the risk. As such, wastage of oral anticancer medicines is generally uncommon and is not considered to be a major issue within the Trust

Kind regards

[redacted]

1. British Oncology Pharmacists Association (BOPA) (2004). Position statement on the care of patients receiving oral chemotherapy. Pharmaceutical Journal; 272:422–423.
2. National Patient Safety Agency (NPSA) Rapid Response Report. 'Risks of Incorrect Dosing of Oral Anticancer Medicines.' 22nd January 2008. Available at http://www.npsa.nhs.uk/patientsafety/alerts-and-directives/rapidrr/risks-of-incorrect-dosing-of-oral-anti-cancer-medicines/ (Accessed November 2017).

healthcare at home
it's where you want to be

Dear [redacted]

Healthcare at Home policy for avoidance of wastage with oral chemotherapy
The approach and procedure for dispensing and avoiding wastage with oral chemotherapy agents, such as sorafenib (Nexavar) at Healthcare at Home for NHS patients is set out as below:

- Healthcare at Home will receive a prescription following the patient's routine follow-up appointment at the hospital, and once the clinical decision has been made to continue treatment for the following month
- The prescription is logged onto the Healthcare at Home system and the patient is contacted to assess how much medication they have left from the previous month
- Where the patient has not used the full supply from the previous month, the next delivery will only be made when they have one week's worth of tablets left. This only ever leaves the patients with one week of additional medication

This process has been employed by Healthcare at Home to keep wastage of oral chemotherapy agents to a minimum.

Kind regards,

[redacted]

Healthcare at Home Ltd
Ext: 7353 | T: 01283501483 | M: 07553372716 | F: 00
hah.co.uk

healthcare at home
it's where you want to be

INVESTORS IN PEOPLE | Silver

Appendix 4 – Duration of treatment analyses (methodology)

Applying an AUC methodology to the log-logistic time-to-discontinuation curve (the ERGs preferred curve) the total mean number of treatment cycles for the population was estimated as [redacted] (see Pat_cohort tab). Using the same methodology (applied to the PFS curve and conservatively assuming no discontinuations) the average number of pre-progression cycles was estimated to be [redacted]. The difference between the total cycles and pre-progression cycles provides an approximation of the average number of cycles post-progression i.e. [redacted] cycles.

This mean number of post-progression treatment cycles was then adjusted to account for 20% of patients receiving post-progression treatment (not [redacted]% as in the RESORCE trial). The adjustment results in the post-progression treatment cycles reducing by nearly [redacted] cycles to approximately [redacted] cycle (i.e. 20/[redacted] cycles).

In order to calculate drug costs for inclusion in the model the total number of cycles was multiplied by the per cycle drug cost. This analysis was not able to utilise the per-cycle average dose information available in the KM discontinuation tab (column D) and therefore a simplifying assumption of a constant average per cycle dose was used in any calculations.

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[redacted]

Ms Stephanie Yates
Project Lead
Guidance ID991
NICE
tacommc@nice.org.uk

24 November 2017

Dear Stephanie

Re: Regorafenib for previously treated unresectable hepatocellular carcinoma

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 34,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to make the following comments.

There are currently no funded systemic therapy options for patients with advanced HCC who have failed sorafenib therapy, and the RESORCE trial demonstrated that regorafenib provides a significant and clinically-meaningful improvement in survival compared to placebo in patients who previously tolerated sorafenib1. Hence, as acknowledged in the appraisal consultation document, regorafenib meets an important unmet need.

Whilst there is disappointment that the appraisal committee has not recommended the use of regorafenib in patients with previously-treated advanced HCC, it is noted that the application was based on the marketing authorisation for regorafenib in this indication, and hence includes patients that would not have been eligible for recruitment to the RESORCE trial1. In the interest of patients with HCC, we would encourage the committee to recommend that Bayer consider a revised application based on the eligibility criteria applied within the RESORCE trial. This would restrict the use of regorafenib to those that have shown benefit from treatment, and improve outcomes for patients with HCC in the UK.

Yours sincerely

[redacted]

1. Bruix J. et al. Lancet 2017: 389; 56-66.

ERG question 30 November 2017

Question

Thank you for submitting your response to the ACD for regorafenib for previously treated unresectable hepatocellular carcinoma. The ERG have asked for clarity on some of the issues below:

- *In the additional evidence submitted on page 2 (Table 1), it is stated that using the new hospitalisation estimates the ICER becomes £69,137. The ERG note that changing the drop down box entitled 'Include 2017 hospitalisations' to Yes rather than No changes the ICER to £66,525. The ERG also considered changing 'include ERG hospitalisations', from a Yes to a No, but this results in an ICER of £66,887. Note: this relates to the model supplied with the additional evidence with the default being the £74,459 ICER that is described as NICE's base case model and various drop-down boxes to select parameter values.*

Can you please provide a step-by step guide detailing how to get the values reported in the submitted additional evidence?

- *The ERG also note that some of the drop down boxes in the supplied model, for wastage etc, appear to have no impact at all. Kindly check these drop-downs and verify if this is correct.*

- *Can you also provide the excel file for the clinician results in relation to the survey (as mentioned in Appendix 2 of your ACD response)?*

Response

Please find as a separate document a revised version of the ACD response (Regorafenib_ID991_ACD_response_ACIC_Instructions_30Nov17_Final). This includes instructions regarding the model settings required to replicate the results.

The ERG is correct in respect of the ICER in table 1 which should be £66,887 and not £69,137 – please accept our apologies for this error.

With respect to the 'Wastage' drop-down option this functions only when either 'Original KM discontinuation' or 'Discontinuation with 20% post-progression treatment' are also selected. The drop-down boxes added to the ERG model for the ACD response are functional. However we note that some earlier drop-down boxes appear to have been overwritten in the model that the ERG sent to us.

The excel file relating to the survey is attached (Regorafenib_ID991_ResourceUseSurvey_Hospitalisation_2017_Final).

ERG question: 4th December 2017

Question

The ERG have identified a possible error in the model uploaded as part of the ACD response. The ERG note that there could potentially be an error in the cell K69 of the cost sheet of the model. The cell currently says 6% which the ERG note should be 6. Correcting this increases the ICER to £68,705 from the £66,887 reported in your response. Can you please check this and verify that this is an error?

Response

We can confirm that the input should be 6 and not 6%. Furthermore, cell G69 should be 4.40 and not 3.93 to align with the updated resource survey inputs. We can only apologise for these two errors which should both have been picked up during model checking.

The first correction can be implemented in the model by removing '%' from the formula for this cell. The correction in cell G69 should be implemented by removing '=2' from the last argument.

The above corrections impact the results in several tables from the ACD response which utilise the updated survey results. Please find attached an updated ACD response incorporating the corrections. Once again we apologise for these errors.

Regorafenib for previously treated unresectable hepatocellular carcinoma: A Single Technology Appraisal

ERG commentary on the company response to the Appraisal Consultation Document

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8th December 2017

Introduction

This document has been prepared following the company's response to the appraisal consultation document (ACD) issued by NICE in relation to ID991 – Regorafenib for previously treated unresectable hepatocellular carcinoma. The company's ACD response includes additional evidence relating to hospitalisation use and regorafenib wastage and summarises the results of additional economic analyses relating to a broader set of issues undertaken using the ERG's base case model.

The company's ACD response states that the incremental cost effectiveness ratio (ICER) preferred by the NICE Appraisal Committee was £74,559 per QALY gained. The ERG notes that this does not appear to be the case in the ACD, whereby the ICER of £74,559 per QALY gained appeared to represent an upper limit.

The company have altered four aspects of the model:

(1) The proportion of patients who are hospitalised and how often they are hospitalised
(2) The ability of the NHS to manage wastage of oral medications
(3) The average duration of treatment
(4) The choice of extrapolation curve for overall survival.

Fuller details are provided in the company's ACD responses. There were many iterations of documents and subsequent revisions following identification of errors, but only the last version (received by the ERG on the 7th of December) is discussed. A summary of each point, together with an ERG comment on the robustness and plausibility of each model amendment is provided below.

(1) The proportion of patients who are hospitalised and how often they are hospitalised

In order to address perceived limitations with the resource use surveys undertaken by the company in 2007 and 2015, the company conducted a further resource use survey in 2017. Twenty-eight clinicians were approached, and if they met the eligibility criteria were invited to complete the survey. The eligibility criteria were that '*clinicians must have treated at least 10 patients with advanced HCC in the previous 12 months, and had must have had experience prescribing, or have been involved in managing patients treated with sorafenib.*' Nine clinicians responded. Whilst there is a possibility for selection bias to be present as those that responded were self-selected, the ERG believes that this is unlikely to impact the results. The updated survey results are reproduced in Table 1.

Table 1: Results of the 2017 hospitalisation resource use survey

	Sorafenib		BSC	
	Pre-progression	***Post-progression***	***Pre-progression***	***Post-progression***
Hospitalised (%)	7.56%	18.89%	12.67%	25.33%
General Ward	7.47%	18.89%	12.51%	25.02%
ICU	0.08%	0.00%	0.16%	0.32%
Of those hospitalised				
1 visit	89%	82%	86%	84%
2 visits	11%	18%	14%	16%
Average number of visits	1.11	1.18	1.14	1.16
Length of stay				
General Ward	4.4	6.0	5.5	5.8
ICU	2.0	0.0	4.0	3.0
AE attendance (%)	7.78%	18.89%	15.33%	25.89%
1 visit	93%	85%	88%	84%
2 visits	8%	15%	13%	16%
Average number of visits	1.08	1.15	1.13	1.16

ERG comment

The ERG is generally satisfied with the results of the company's 2017 resource use survey. However, the ERG notes that the resources associated with patients who progress but remain treated with sorafenib are unlikely to be generalisable to the group who had sorafenib treatment discontinued on progression. The ERG notes that the company's corrected version of the model appears to include a programming error which sets all A&E costs equal to zero unless the new 2017 survey data are selected.

(2) The ability of the NHS to manage wastage of oral medications

The company have adapted the model in an attempt to take the cost of any drug wastage into account. This has been undertaken using '*an assumption that every patient wastes an additional* [redacted] *of medicine at the maximum daily dose (*[redacted]*) over the course of their treatment. The wastage is applied as a one-off cost to every patient.*'

ERG comment

The ERG comments that there are two ways in which there may be drug wastage. One is that a patient may die in possession of regorafenib tablets which cannot be re-prescribed to other patients. The second is that patients may miss doses during a cycle and, for example only use 19 out of 21 tablets. In this instance, clinical advice to the ERG is that a full pack of 21 tablets is likely to be prescribed in the next cycle and that the two unused tablets are wasted. In this circumstance the patient would, assuming a dose of 160mg per day, have received an average dose of 145mg per day (19/21*160mg). The model submitted by the company would in this instance assume that the costs associated with a dose of 145mg per day was appropriate.

The ERG believes that the amendment made by the company attempts to address the second issue, as the cost of the last packet prior to death or discontinuation is incorporated. However, it is not known how accurate the amendment is: it is unclear whether the observed reduced dosage in the study reflects patients randomly missing tablets, or whether there had been a planned reduction in dose, in which case the reduction in regorafenib costs would be appropriate. The company have provided no further data on individual patients' dosages within the response to the ACD which would reduce this uncertainty. As such, the assumption of [redacted] days of drug wastage is arbitrary, and the ERG has instead presented a pessimistic analysis of regorafenib, whereby all patients are scheduled to be on 160mg per day, and an optimistic analysis of regorafenib whereby the drug costs are assumed to be 160mg multiplied by relative dose intensity (RDI).

Notwithstanding the concerns noted above, the ERG also highlights two further issues with respect to the implementation of the drug costs within the company's new model. Firstly, the time to treatment discontinuation curve for regorafenib is not constrained by the overall survival curve. The projected log logistic time to treatment discontinuation curve and the Weibull overall survival curve cross at around 4 years; this is logically inconsistent as it indicates that patients are still incurring drug costs after they have died. This logical consistency constraint was included in the ERG's exploratory analyses in the ERG report, but this functionality was bypassed in the company's new analyses regarding drug wastage. Secondly, the RDI for regorafenib assumed in the company's model follows an unusual pattern over time: [redacted] (Figure 1). The rationale

for this assumed pattern of drug usage is unclear. This issue was not present in the company's earlier models as they erroneously truncated the time to treatment discontinuation curve at 29 cycles.

Figure 1: Modelled regorafenib relative dose intensity over time

(3) The average duration of treatment

In the RESORCE study, [redacted] of patients were provided with regorafenib treatment post-progression. The company's ACD response states that this does not represent the anticipated use of regorafenib in England: a clinical expert at the NICE appraisal committee suggested that '*this did not represent clinical practice in England because 80% of patients would stop treatment at progression*', further, eight out of nine (89%) respondents to the company's survey stated that treatment with sorafenib is discontinued at progression. In order to reflect current practice, the company estimated the average of the number of cycles of treatment provided post-progression ([redacted]) and multiplied this by 20% /[redacted] to estimate that in current practice only [redacted] would be prescribed post-progression. The company assumed that treatment beyond progression would be at a dose of 160mg per day.

ERG comment

Whilst the ERG acknowledges that current practice in England may differ from that observed in the RESORCE study, it does not alter the fact that the survival estimates observed in RESORCE are likely to have been influenced by the post-progression treatment provided to the patients. The ERG considers it unreasonable to include health benefits associated with post-progression treatment, but to exclude a proportion of the costs associated with generating those health gains. As such, the ERG does not consider the uncoupling of treatment costs and benefits in the manner undertaken by the company to be appropriate.

(4) The choice of extrapolation curve for overall survival

The company comment that '*it is our understanding, from the ERG report, that the preference for the Weibull curve was not absolute as the Gompertz and Exponential curves were also considered to be clinically plausible by the clinical advisors*'. As such, the company have in additional to the Weibull made the previous amendments to the Gompertz and the exponential curves.

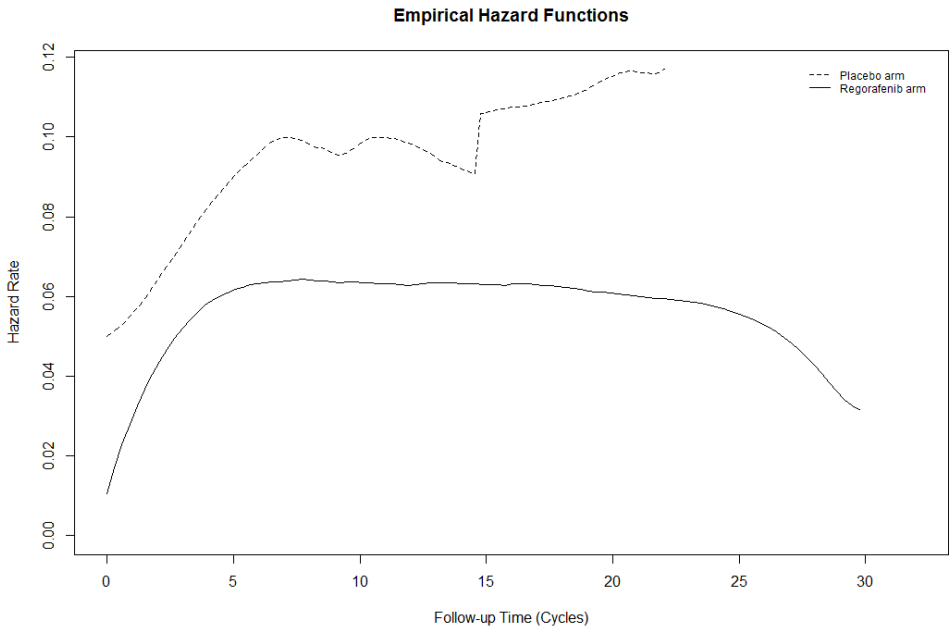
ERG comment

The ERG's selection of the Weibull distribution for inclusion in the preferred analyses was based on the clinical opinion on the plausibility of the extrapolated curves, the goodness-of-fit to the observed data (reproduced in Table 2) and also the empirical hazards provided by the company within the clarification period (reproduced in Figure 2). No further information has been provided and therefore the opinion of the ERG has not changed.

Table 2: Goodness of fit to the overall survival curves

Distribution	Best Supportive Care		Regorafenib	
	AIC	BIC	AIC	BIC
Log logistic	1885.867	1892.403	3314.643	3322.518
Log normal	1885.879	1892.415	3312.354	3320.229
Generalised gamma	1886.313	1896.117	3314.032	3325.845
Weibull	1891.882	1898.417	3328.78	3336.655
Gompertz	1900.373	1906.908	3339.502	3347.377
Exponential	1901.015	1904.283	3338.979	3342.917

Figure 2: Empirical hazards for overall survival from RESORCE



Company's results presented in the ACD response

The results presented by the company are provided in Table 3 and Table 4, based on the company's last revised model submitted in response to the ACD.

Table 3: Company's new results (using a Weibull distribution for overall survival)

Scenario	Incremental costs	Incremental QALYs	ICER
NICE's base case	*£23,768*	*0.319*	*£74,559*
1) Pooled survey with new hospitalisation estimates	£22,054	0.319	£69,182
2) Assuming [redacted] tablets wasted per person	£21,896	0.319	£68,685
3) Assuming only 20% of patients receive treatment beyond progression at 160mg per day	£20,120	0.319	£63,115
Combining 1) and 2)	£20,427	0.319	£64,077
Combining 1), 2) and 3)	£16,085	0.319	£50,456

Table 4: Company's new results (using a Gompertz distribution or an exponential distribution for overall survival)

Scenario	Incremental costs	Incremental QALYs	ICER
NICE's base case	*£23,768*	*0.319*	*£74,559*
Changing to a Gompertz distribution			
Combining 1) and 2)	£19,091	0.343	£55,589
Combining 1), 2) and 3)	£14,748	0.343	£42,944
Changing to an Exponential distribution			
Combining 1) and 2)	£19,240	0.348	£55,260
Combining 1), 2) and 3)	£14,897	0.348	£42,788

All values are taken from the company's ACD response

ERG comment

As noted above, the ERG has concerns regarding the company's analyses. The subsequent section presents additional analyses undertaken by the ERG which correct these errors and provide an exploration of uncertainty around the impact of drug wastage and the use of alternative survivor functions.

Additional analyses undertaken by the ERG

The ERG undertook four additional analyses using the company's new model:

- Analysis 1 includes the company's 2017 hospitalisation resource use survey results, including correction of the transcription errors detailed above. This analysis assumes the full 160mg dose of regorafenib for all patients and excludes any potential cost savings due to dose reductions. This represents the least favourable ERG analysis.
- Analysis 2 is the same as Analysis 1, but uses the company's approach to modelling treatment costs by assuming that the full drug cost is multiplied by the RDI, rather than assuming 160mg per day.
- Analysis 3 is the same as Analysis 2, with the inclusion of a logical consistency constraint to ensure that the proportion of patients on treatment is not greater than the proportion of patients alive.
- Analysis 4 is the same as Analysis 3, with a change to the estimated RDI. The last observed RDI value (cycle 29) is extrapolated forward assuming a last observation carried forward imputation rule.

All ERG analyses also include the correction of an additional error introduced in the company's re-analyses of the later RESORCE data-cut whereby additional PFS data points had erroneously been excluded from the model calculations. This programming error has not been corrected in the ICERs presented by the company: the impact on the ICER is minor. The ERG analyses also include the correction of the error introduced in the company's revised post-ACD model whereby non-zero A&E visits accrue a zero cost.

The results of the ERG's exploratory analyses are provided in Table 5 when assuming a Weibull function for overall survival. In
Table ***6***, the least favourable and most favourable of the ERG's exploratory analyses are reported for the Weibull, Gompertz and exponential distributions.

Table 5: The ERG's exploratory analyses assuming a Weibull function for overall survival

Scenario	**Regorafenib versus BSC**		
	Inc. QALYs	**Inc. Costs**	**ICER**
'NICE base case' (full 160mg dosing)*	£23,768	0.319	£74,559
Analysis 1: 'NICE base case' using the 2017 survey values (full 160mg dosing)	£21,791	0.320	£68,137
Analysis 2: Analysis 1 but using company's modelled RDI rather than 160mg per day	£19,570	0.320	£61,193
Analysis 3: Analysis 2 but incorporating a logical consistency constraint	£18,095	0.320	£56,582

Analysis 4: Analysis 3 but using last observation carried forward RDI extrapolation	£17,854	0.320	£55,829

** Excludes PFS programming error correction*

Table 6: The ERG's exploratory analyses assuming alternative parametric functions for overall survival

Scenario	Analysis 1 (least favourable wastage scenario)	Analysis 4 (most favourable wastage scenario)
Weibull	£68,137	£55,829
Gompertz	£60,295	£48,510
Exponential	£60,910	£48,873

** Includes PFS lookup error correction*

The ERG estimation of the ICER

The ERG believes that the ICER is likely to lie between £55,829 and £68,137 per QALY gained. The uncertainty in this value is caused by the unknown level of drug wastage that occurs during a patient's treatment. This uncertainty could be reduced by the company analysing the dosing regimens of individual patients in RESORCE to ascertain whether reductions in dose were planned (and therefore the drug acquisition costs could be reduced) or not. For reductions in dose that were not planned, for instance by patients not taking a pill, analyses would need to be undertaken to determine whether there were any changes to the frequency of prescriptions to account for th30 unused pills.

The clinical study report provides some insight into reasons for the reduced RDI stating that "*Dose reduction was recorded for 189 (50.5%) subjects in the regorafenib group and 21 (10.9%) subjects in the placebo group. The most common reason for dose reductions in both treatment groups was TEAEs [Treatment Emergent Adverse Events] with 93.0% (280 events) in the regorafenib group and 76.0% (19 events) in the placebo group (Table 14.3.1/22). Other reasons for dose reductions included subject error and 'Other'*." It is unclear whether patients stayed at the lower dose in a planned fashion after an adverse event, although it is noted that 47 patients (12.6%) receiving regorafenib re-escalated their dose at some point in the study.