National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Ombitasvir/paritaprevir/ritonavir with or without dasabuvir for treating chronic hepatitis C

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Appropriateness	AbbVie	AbbVie believes that it is very important to refer this topic to NICE for appraisal. The AbbVie regimen is a combination of direct acting antivirals (DAAs) consisting of the combination of ABT-450/ritonavir (r)/ABT-267 and ABT-333. Once the AbbVie regimen receives UK marketing authorisation, it will offer an all-oral, interferon-free treatment regimen for people infected with chronic genotype 1 (G1) hepatitis C (HCV). Elimination of interferon from treatment regimens with the potential to also remove ribavirin represents a significant advance from the interferon-based approaches to therapy, which requires a combination of injection and oral administration, have been burdened with significant side-effects and limited success in patients with advanced liver fibrosis and prior null response to pegylated interferon (PegIFN) and ribavirin (RBV). To date, interferon-based regimens have thus demonstrated poor tolerability and adherence, limiting their uptake and reducing the likelihood of achieving virologic cure or sustained virologic response (SVR). As a manufacturer of an all-oral, interferon-free regimen, AbbVie fully supports a timely referral and review of its combination therapy by NICE. The timely NICE guidance would ensure that this important novel therapy reaches a broader group of chronic G1 HCV patients including those who currently have no treatment option.	Comment noted. No changes required.

Section	Consultee/ Commentator	Comments	Action
	Merck Sharp and Dohme	MSD agree it is appropriate to refer to NICE for appraisal	Comment noted. No changes required.
	Royal College of Nursing	The consultation on ABT-450/ritonavir/ABT-267 in combination with ABT-333 for patients with HCV is welcomed. It is appropriate to refer ABT-450/ritonavir/ABT-267 in combination with ABT-333 to NICE for appraisal relation to G1 treatment naïve and retreatment population patients	Comment noted. No changes required.
	BSG Liver Section	Yes	Comment noted. No changes required.
	United Kingdom Clinical Pharmacy Association – Gastroenterology /Hepatology Committee	This technology appraisal is appropriate for review by NICE	Comment noted. No changes required.
Wording	AbbVie	Commercial in confidence: [redacted]	Comment noted. [redacted]
	Merck Sharp and Dohme	Wording is appropriate	Comment noted. Attendees at the scoping workshop agreed that the wording

Section	Consultee/ Commentator	Comments	Action
			of the draft remit should be amended to reflect all genotypes.
	Royal College of Nursing	The wording provided seems to reflect the issues of clinical outcomes and cost effectiveness in QALY.	Comment noted. Attendees at the scoping workshop agreed that the wording of the draft remit should be amended to reflect all genotypes.
	BSG Liver Section	Yes	Comment noted. Attendees at the scoping workshop agreed that the wording of the draft remit should be amended to reflect all genotypes.
	United Kingdom Clinical Pharmacy Association – Gastroenterology /Hepatology Committee	No specific issues with wording as it currently stands.	Comment noted. Attendees at the scoping workshop agreed that the wording of the draft remit should be amended to reflect all genotypes.
Timing Issues	AbbVie	The current licensed therapies for chronic G1 hepatitis C virus are all interferon (IFN) containing. There is a large cohort of patients with chronic	Comment noted. NICE aims to provide

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		HCV who are IFN contraindicated, ineligible or intolerant, but urgently require antiviral therapy. Therefore eliminating interferon from HCV treatment represents a pressing medical need. As an all-oral, interferon-free combination therapy, AbbVie's investigational regimen has the potential to positively impact patient lives by allowing a significantly greater number of chronic G1 HCV patients to receive a more tolerable more efficacious and shorter treatment regimen. AbbVie therefore believes that this appraisal should carry a high priority for the NHS.	guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted.
	Merck Sharp and Dohme	No comment	Comment noted. No changes required.
	Royal College of Nursing	This is welcomed as it offers the option of an evidence base all oral regimen which seems to be well tolerated by most patients with minimal co-morbidities with good adherence and Sustained Virologic Response (SVR) rates in the G1 populations. Given the potential to improve the quality of life and SVR rates of patients it seems appropriate that this technology should be reviewed and fast tracked	Comment noted. NICE aims to provide guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted.
	Terrence Higgins Trust	Current treatments are effective 60% of the time. The improved efficacy of this treatment, in addition to the innovation in administration of the treatment, mean that it should be a priority to ensure the most effective treatment is available on the NHS and that NHS resources are used effectively.	Comment noted. NICE aims to provide guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted.

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	BSG Liver Section	Yes	Comment noted. No changes required.
	United Kingdom Clinical Pharmacy Association – Gastroenterology /Hepatology Committee	Due to the rapidly evolving HCV treatment climate there is an urgency to get this appraisal completed and finalised by end of year.	Comment noted. NICE aims to provide guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted.
Additional comments on the draft remit		No response received	Response noted.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	AbbVie	The following sentence in the draft scope merits further clarity: "The trials compared the 12-week regimen with a 24-week regimen or with placebo (given for 12 weeks, then ABT-450/ritonavir/ABT-267 in combination with ABT-333 treatment given for another 12 weeks)." AbbVie proposes the following description to be added to the paragraph "The technology" to ensure clarity: AbbVie's investigational regimen was evaluated in five Phase III multicentre, randomised, double-blind, placebo-controlled trials assessing the safety and	Comment noted. The specific details of the clinical trials are not usually included in the scope. These should instead be presented in the submission. However, the sentence

Section	Consultee/ Commentator	Comments	Action
		efficacy of co-formulated ABT-450/r/ABT-267 with ABT-333 plus/minus ribavirin administered for 12 weeks to treatment naïve or treatment experienced chronic G1 HCV patients. In addition, a global, multicentre, randomised, open-label, Phase III trial was conducted to evaluate the safety and efficacy of co-formulated ABT-450/r/ABT-267 with ABT-333 and ribavirin administered for either 12 or 24 weeks in treatment naïve or treatment experienced chronic G1 HCV patients with compensated cirrhosis.	was amended slightly to; "The trials compared the 12-week regimen with a 24-week regimen or the 12-week regimen compared with placebo, followed by ombitasvir/paritaprevir /ritonavir in combination with dasabuvir for another 12 weeks in the placebo arm."
	Merck Sharp and Dohme	No comment	Comment noted. No changes required.
	Royal College of Nursing	Seems appropriate	Comment noted. No changes required.
	BSG Liver Section	Yes	Comment noted. No changes required.
	United Kingdom Clinical Pharmacy Association – Gastroenterology /Hepatology	Standard background information –no issues with current content.	Comment noted. No changes required.

Section	Consultee/ Commentator	Comments	Action
	Committee		
The technology/ intervention	AbbVie	The name of the technology should read as co-formulated ABT-450/r/ABT-267 in combination with ABT-333 with or without ribavirin	Comment noted. The name of the technology has been updated.
	Merck Sharp and Dohme	No comment	Comment noted. No changes required.
	Royal College of Nursing	Seems appropriate	Comment noted. No changes required.
	BSG Liver Section	Yes	Comment noted. No changes required.
	United Kingdom Clinical Pharmacy Association – Gastroenterology /Hepatology Committee	Yes the technology content is accurate	Comment noted. No changes required.
Population	AbbVie	Commercial in confidence: [redacted]	Comment noted. [redacted].
	Merck Sharp and Dohme	If the phase III trials demonstrate that ABT-450/ritonavir/ABT-267 in combination with ABT-333 achieved different SVR rates for genotype 1a and 1b, it would be appropriate to sub-group the genotype 1 chronic hepatitis C	Comment noted. Following the scoping workshop consultees

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		patients by type G1a and G1b	were in agreement that the scope should be updated to note that if evidence allows the following subgroups will be considered: • Genotype • Co-infection with HIV • People with and without cirrhosis • People who have received treatment pre- and post-liver transplantation • Response to previous treatment (non-response, partial response, relapsed) • People who are intolerant to or ineligible for interferon treatment
	Royal College of Nursing	Seems appropriate	Comment noted. No changes required.
	BSG Liver	Should consider rapid viral responders separately as respond well to PEG-	Comment noted.

Section	Consultee/ Commentator	Comments	Action
	Section	IFN/RIB	Attendees at the workshop agreed that rapid virological response is not a relevant outcome for interferon free regimens.
	United Kingdom Clinical Pharmacy Association – Gastroenterology /Hepatology Committee	Population appropriate but as outlined in other considerations a broader subgroup should ideally be considered	Comment noted. The population has been amended in the scope.
Comparators	AbbVie	In light of the of recent marketing authorisations for interferon-containing DAAs and the subsequent marketing authorisation for new IFN-free treatment regimens, AbbVie firmly believes that pegIFN and RBV will no longer constitute standard of care for patients infected with chronic G1 HCV owing to its comparably limited efficacy and poor tolerability. AbbVie therefore proposes that PegINF and RBV be removed from the list of comparators. Furthermore, of the two first generation protease inhibitors (PIs) telaprevir and boceprevir, telaprevir (TVR) is considered more established in clinical practice and the preferred regimen by the treating community. Therefore, AbbVie suggests that TVR should be regarded as the main comparator for its combination regimen for chronic G1 HCV patients. [redacted]	Comment noted. Attendees at the scoping workshop agreed that peginterferon alfa plus ribavirin is a recommended treatment option and should remain a comparator.

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		[redacted]	
	Merck Sharp and Dohme	The three comparators in the draft scope are appropriate for this appraisal. We would like to bring to NICE's attention the timing of this scope consultation and scoping workshop with the first appraisal meeting for sofosbuvir. The scoping workshop for ABT-450/ritonavir/ABT-267 in combination with ABT-333 is May 6th, with the first appraisal meeting for sofosbuvir on May 15th. If at the first appraisal meeting the FAD is developed, then there will be published NICE guidance on sofosbuvir approximately 10 weeks post the first appraisal meeting. As sofosbuvir has a marketing authorisation for the UK, and likely NICE guidance prior to referral of ABT-450/ritonavir/ABT-267 in combination with ABT-333 from the DoH, sofosbuvir could be considered a comparator for ABT-450/ritonavir/ABT-267 in combination with ABT-333 in genotype 1 patients. MSD believe this should be discussed at the scoping workshop with NICE, clinical experts, consultees and commentators.	Comment noted. Attendees at the scoping workshop agreed that sofosbuvir in combination with other medicinal products should be considered a comparator subject to NICE appraisal.
	Royal College of Nursing	Yes	Comment noted. No changes required.
	BSG Liver Section	Yes BUT all new DAAs need to be considered together Also need to compare in easier to treat patient i.e. rapid viral responders with PEG-IFN and ribavirin alone.	Comment noted. Attendees at the scoping workshop agreed that because of different timings of regulatory approval and need for timely guidance to the NHS it is appropriate to appraise the new

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			directly acting antivirals through STAs.
	United Kingdom Clinical Pharmacy Association – Gastroenterology /Hepatology Committee	Comparators are appropriate for now but if Sofosbuvir and the Sofosbuvir/Ledipasvir combination should be added based on the likely arrival of NICE Guidance on these agents by 2014/15.	Comment noted. Attendees at the scoping workshop agreed that sofosbuvir in combination with other medicinal products should be considered a comparator subject to NICE appraisal. Attendees also agreed that it would not be appropriate to include the treatments which do not have marketing authorisation as comparators for this appraisal.
Outcomes	AbbVie	AbbVie accepts the majority of the outcomes listed for consideration, but disagrees with the following: 1. RVR Rapid Viral Response (RVR) is typically associated with interferon-based therapies and is defined as undetectable HCV RNA at week 4 into treatment. It is seen as one of the strongest predictors of SVR in patients on PegINF+ RBV based therapies. Given that the co-formulated ABT-450/r/ABT-267 in	Comment noted. 1. Attendees at the scoping workshop agreed that rapid virological response is not a relevant outcome for interferon free

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		combination with ABT-333 is an all-oral, interferon free combination regimen, RVR is not a required marker for treatment success/failure. Furthermore, RVR has not been requested as an outcome in the NICE scoping documents of simeprevir or sofosbuvir treatments despite both therapies being interferon containing. Therefore, given that for interferon free therapies clinical utility of RVR has not been established, AbbVie suggests that this outcome measure should be removed. 2. Development of resistance to ABT-450/r/ABT-267 combination therapy AbbVie suggests that this outcome measure should be removed given that this outcome has not been considered in the scope of simeprevir or sofosbuvir.	regimens 2. Development of resistance was considered an important outcome because of high risk of emergence of drug resistant hepatitis C virus. The scope has been updated accordingly
	Royal College of Nursing	Seems appropriate	Comment noted. No changes required.
	BSG Liver Section	Yes	Comment noted. No changes required.
	United Kingdom Clinical Pharmacy Association – Gastroenterology /Hepatology Committee	Standard outcomes no objections to those outlines.	Comment noted. No changes required.
Economic	AbbVie	AbbVie believes that the life-time horizon is the appropriate time horizon for this analysis. Life-time analysis will allow for the natural history of chronic	Comment noted. NICE recommends using a

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analysis		HCV to be fully captured, including its long term consequences such as cirrhosis, hepatocellular carcinoma (liver cancer), end stage liver disease (ESLD), and death. It will also allow for the differences in costs and health outcomes between the technologies being compared to be fully appreciated. Life-time analysis is consistent with the scope of previous NICE appraisals for HCV treatment regimens. Increased background mortality in HCV patients is found to negatively impact the incremental cost-effectiveness ratio. Therefore as LYG are a major driver of cost-effectiveness for SVR increasing regimens, AbbVie considers it important that the impact of age on the ICER be excluded from consideration if subgroups are examined separately.	lifetime time horizon when the technology leads to differences in survival or benefits that persist for the remainder of a person's life. Please see Guide to the methods of technology appraisal (2013) for further details.
	Terrence Higgins Trust	Current treatments are effective 60% of the time. The improved efficacy of this treatment, in addition to the innovation in administration of the treatment, mean that it should be a priority to ensure the most effective treatment is available on the NHS and that NHS resources are used effectively.	Comment noted. No changes required
	BSG Liver Section	Yes	Comment noted. No changes required.
	United Kingdom Clinical Pharmacy Association – Gastroenterology /Hepatology Committee	Agree that the time horizon for estimating clinical and cost effectiveness should be sufficiently long enough to accurately reflect differences in cost between other comparators	Comment noted. No changes required.

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Equality and Diversity	AbbVie	Increased background mortality in HCV patients is found to negatively impact the incremental cost-effectiveness ratio. Therefore as LYG are a major driver of cost-effectiveness for SVR increasing regimens, AbbVie considers it important that the impact of age on the ICER be excluded from consideration if subgroups are examined separately.	Comment noted. The issues related to health economic evaluation will be considered by the Appraisal Committee. Attendees at the scoping workshop agreed that it not an equality issue.
	Royal College of Nursing	Not aware of any at this stage.	Comment noted. No changes required.
	BSG Liver Section	I don't see any problems	Comment noted. No changes required.
	United Kingdom Clinical Pharmacy Association – Gastroenterology /Hepatology Committee	No comments- satisfied with content	Comment noted. No changes required.
Innovation	AbbVie	AbbVie considers co-formulated ABT-450/r/ABT-267 in combination with ABT-333 to be innovative, offering a step-change in the way chronic HCV patients are treated for the following reasons: 1. Once licensed, ABT-450/r/ABT-267 in combination with ABT-333 will offer chronic G1 Hep C patients an all oral, interferon-free treatment option.	Comment noted. The innovative nature of the technology will be considered by the Committee during the

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		Given the well-documented and harmful side effects of interferon, its elimination from the treatment regimen represents a significant advance and step-change from the current interferon-based regimens. Interferon-based regimens have demonstrated poor tolerability and adherence, limiting their uptake and reducing the likelihood of achieving SVR. AbbVie's all-oral, interferon-free anti-viral combination thus has the potential to significantly improve patients' HRQoL by allowing greater numbers of patients, including those who are not eligible for or intolerant to the current regimens, to receive shorter, more efficacious and more tolerable therapy. This represents a significant, incremental innovation. 2. ABT-450/r/ABT-267 in combination with ABT-333 demonstrated significant improvements in clinical efficacy even in cirrhotic patients. Therefore by offering high probability of SVR even to the hardest to treat patients, AbbVie's regimen meets the Government's objectives of reducing numbers of people living with preventable ill health and people dying prematurely due to liver disease – a well-recognised downstream consequence of chronic HCV. (NHS and Public Health Outcomes Framework 2013-2016) AbbVie considers that the use of its technology can also result in significant and substantial health-related benefits that are unlikely to be included in the QALY calculation. These benefits include: • Improved work productivity – by offering an all-oral, interferon free regimen of a shortened treatment duration and improved treatment side effect profile, the regimen has the potential to improve all measures of patients' work productivity or usual daily activities for those not working. • Reduction in onward transmission of the virus through improved SVR rates and the ability to treat a greater patient population particularly those who have been ineligible for or intolerant of interferon-based regimens.	appraisal.

Section	Consultee/ Commentator	Comments	Action
	Royal College of Nursing	Yes without interferon, this may allow the treatment of more diverse populations as side effects become more tolerable and is not a factor in resistance to accessing treatment. This has the potential to allow access for those with significant co-morbid conditions and more difficult to cure with current available therapies.	Comment noted. The innovative nature of the technology will be considered by the Committee during the appraisal.
	Terrence Higgins Trust	This is a highly innovative treatment which is administered orally unlike current treatments which are all injections. Additionally, current treatments have severe side effects including depression, weakness, flu like symptoms, aches, coughs and itching. Reduced side effects in addition to the psychological benefits from an oral treatment will be of great importance to individuals. Ease of application and reduced effects on daily life with less need of support from others will be a significant improvement for people taking the treatment. The course of treatment down to 12 weeks from 24-48 weeks is a notable advancement and is likely to result in improved treatment fidelity and completion rates.	Comment noted. The innovative nature of the technology will be considered by the Committee during the appraisal.
	BSG Liver Section	DAAs all innovative with potential for high cure rates of HCV and improved quality of life for many HCV patients.	Comment noted. The innovative nature of the technology will be considered by the Committee during the appraisal.
	United Kingdom Clinical	This product is innovative in that it can be used in the absence of interferon and possibly ribavirin which will undoubtedly result in greater patient	Comment noted. The innovative nature of the

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	Pharmacy Association – Gastroenterology /Hepatology Committee	tolerability and possibly less intensive specialist follow up. The duration of treatment will also likely to be less that current standard of care for Genotype 1 HCV again resulting in greater patient satisfaction and reduced follow up.	technology will be considered by the Committee during the appraisal.
Questions for consultation	AbbVie	Response to previous treatment (non-response, partial response, relapsed) AbbVie will have data to allow for this subgroup analysis. If evidence allow, sustained virological response at 12 and 24 weeks will be considered. It is unclear why SVR 24 should be given a consideration in this scope when it has not been considered in the scopes of simeprevir and sofosbuvir. SVR12 and SVR 24 measurements were found concordant in a large population of subjects with HCV infection who participated in clinical trials with various treatment regimens and durations. In addition SVR 12 is deemed suitable and accepted primary end point for regulatory approval. AbbVie therefore does not see a merit for its consideration within this appraisal only. In light of all the reasons outlined in the above paragraphs, AbbVie strongly supports a single technology assessment for its regimen to insure timely guidance is issued to the NHS in England and Wales for this important therapy.	Comment noted. Attendees at the scoping workshop agreed that SVR24 should not be considered as a separate outcome if concordance between SVR12 and SVR24 is demonstrated.
	Merck Sharp and Dohme	If evidence allows then the subgroup of cirrhotic patients should be considered.	Comment noted. Attendees at the scoping workshop agreed that 'patients with cirrhosis' is a

Section	Consultee/ Commentator	Comments	Action
			relevant subgroup for this appraisal. The scope has been updated to include 'patients with and without cirrhosis'.
	United Kingdom Clinical Pharmacy Association – Gastroenterology /Hepatology Committee	As outlined in draft scope would advocate inclusion of HIV co-infected population and treatment failures	Comment noted. No changes required.
	BSG Liver Section	Ease of using new drugs (lack of side effects) potential to treat in community.	Comment noted. No changes required.
	Royal College of Pathologists	Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? It is important to ensure that the long-term adverse effects arising from the use of interferon-based therapy are taken into account in the cost-effectiveness analyses – clearly the technology is designed to replace the use of interferon-based therapy, and therefore one of its potential advantages is that it will avoid generating those long-term side effects, which do incur costs.	Comment noted. The long-term adverse effects of interferon based therapy including its impact on health related quality of life as well as implications on NHS resource would be considered by the Appraisal Committee.
Additional	AbbVie	No further comments.	Comment noted. No

Section	Consultee/ Commentator	Comments	Action
comments on the draft scope			changes required.
	Merck Sharp and Dohme	In the related NICE recommendations and NICE pathways section Technology appraisal no. 300 is missing. Additionally, we would like to make NICE aware of a clinical guideline on liver disease and quality standard on prisons: physical conditions and diseases that are currently under development.	Comment noted. Technology appraisal 300 is for treating chronic hepatitis C in children and young people and ABT-450 combination therapy is not expected to be approved for paediatric population at this moment. The draft scope of clinical guideline in preparation 'Liver disease: management of liver disease (non-alcoholic) states that people with secondary cause of fatty liver (for example hepatitis C infection) will not be covered. No changes required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health

Healthcare Improvement Scotland

NATIONAL INSTITUTE FOR HEALTH CARE EXCELLENCE

Single Technology Appraisal (STA)

Ombitasvir/paritaprevir/ritonavir with or without dasabuvir for treating chronic hepatitis C

Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1.	Remove Action on Hepatitis C	NICE Secretariat		Removed	This organisation has disbanded.
2.	Add HIV i-Base	NICE Secretariat		Added	This organisation has an area of interest directly related to this appraisal and meets the selection criteria to participate in this appraisal. HIV i-Base has been added to the matrix of consultees and commentators under 'patient' groups.

3.	Add Association of Surgeons of Great Britain and Ireland	NICE Secretariat		Added	This organisation has an area of interest directly related to this appraisal and meets the selection criteria to participate in this appraisal. Association of Surgeons of Great Britain and Ireland has been added to the matrix of consultees and commentators under 'professional' groups.
4.	Remove British Association for the Study of the Liver Nurses Forum	NICE Secretariat		Removed	This organisation is a sub-group of British Association for the Study of the Liver who are already listed on the matrix of consultees and commentators under 'professional groups'
5.	Remove Transplant Support Network	NICE Secretariat		Removed	This organisation has disbanded.
6.	Remove Commissioning Support Appraisals Service	NICE Secretariat		Removed	This organisation has disbanded.

7.	Add Gilead Sciences	NICE Secretariat		Added	This organisation has an area of interest directly related to this appraisal and meets the selection criteria to participate in this appraisal. Gilead Sciences has been added to the matrix of consultees and commentators under 'comparator manufacturers.'
8.	Remove Research Institute for the Care of Older People	NICE Secretariat		Removed	This organisation's interests are not closely related to the appraisal topic and as per our inclusion criteria. Research Institute for the Care of Older People has not been included in the matrix of consultees and commentators.