National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Ciclosporin for treating dry eye disease

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

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Allergan	[Would it be appropriate to refer this topic to NICE for appraisal?] Yes	Comment noted. No changes required.
	Royal College of Nursing	As there is a high incidence of patients reporting symptomatic Keratoconjuctival sicca (KCS) it is appropriate that NICE appraises new therapies.	Comment noted. No changes required.
	Royal College of Ophthalmologists	[Would it be appropriate to refer this topic to NICE for appraisal?] Yes as dry eye condition is very common and using such treatment is likely to be expensive and guidance will be expected to prescribers.	Comment noted. No changes required.
	Santen	Santen agrees that this is an appropriate topic for review as Dry Eye Disease (DED) / Syndrome (DES) is a priority area, particularly the severe end of the disease spectrum. However, Santen would question if an MTA is appropriate in this instance, for the following reasons: By the time of Ikervis's anticipated launch (2015) there will be no licensed alternatives for • severe patients that can be used in an MTA. Specifically, the RegeneRx thymosin beta-4 product RGN-259 has not yet begun phase III trials, so would be highly unlikely to launch before Ikervis	Comments noted. Consultees at the scoping workshop agreed that the draft scope should be rewritten to only include ciclosporin for dry eye disease, and that it should be considered as a single technology appraisal. It was noted that the regulatory timelines for thymosin beta-4 are likely to be much later than for ciclosporin, therefore combining the two technologies as an MTA would lead to untimely guidance on the use of ciclosporin. The draft remit has been updated in the scope

Section	Consultees	Comments	Action
		• The target population for thymosin beta-4 appears to be less severe than the Ikervis population: Ikervis's Phase-III trial included patients with CFS grade 4 after failure of artificial tears; the population for thymosin beta-4's trials included patients with CFS grade 2-3	to: "To appraise the clinical and cost effectiveness of ciclosporin within its marketing authorisation for treating dry eye disease".
Wording	Allergan	[Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider?] Yes	Comment noted. Following advice received during consultation, the draft remit has been amended to only include ciclosporin for dry eye disease.
	Royal College of Ophthalmologists	[Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider?] Yes	Comment noted. Following advice received during consultation, the draft remit has been amended to only include ciclosporin for dry eye disease.
	Santen	None	Comment noted. Following advice received during consultation, the draft remit has been amended to only include ciclosporin for dry eye disease.
Timing Issues	Royal College of Ophthalmologists	[What is the relative urgency of this proposed appraisal to the NHS?] Soon	Comment noted. NICE aims to produce guidance on the use of new technologies within 6 months of the approval of their marketing authorisation or launch (whichever is later). NICE can only begin to appraise a technology when it has been formally referred by the Secretary of State for Health. Following referral, NICE will schedule this topic into the work programme as soon as it is possible.
	Santen	With no currently approved products for patients with Severe DED we believe that there is urgency to allow access once there are approved products. Expected timing of approval for Ikervis is	Comment noted. NICE aims to produce guidance on the use of new technologies within 6 months of the

Section	Consultees	Comments	Action
		[redacted] with a likely UK launch in [redacted].	approval of their marketing authorisation or launch (whichever is later). NICE can only begin to appraise a technology when it has been formally referred by the Secretary of State for Health. Following referral, NICE will schedule this topic into the work programme as soon as it is possible.
Additional comments on the draft remit	Santen	None	Comment noted. No changes required.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Allergan	This section should reference the DEWS definition of dry eye. The Definition and Classification of Dry Eye Disease: Report of the management and therapy subcommittee of the international Dry Eye Workshop(2007). *The Ocular Surface* April 2007; Vol 5; No 2. www.theocularsurface.com	Comment noted. The background section of the scope is only intended to provide a brief overview of the condition and current treatment options. A more detailed description of the nature of the condition will be included in the manufacturer's evidence submission during the course of the appraisal. Following advice from consultees, the background of the scope has been amended to include a brief description of aqueous-deficient and evaporative dry eye disease, and the DEWS classification system.
	Royal College of Nursing	Adequate summary	Comment noted. No changes required.
	Royal College of	Has not included the intervention of lacrimal punctual plugging	Comment noted. Following advice from

Section	Consultees	Comments	Action
	Ophthalmologists		consultees at the scoping workshop, the background of the scope has been amended to describe current treatment options for people with severe dry eye disease, including ocular preparations of ciclosporin (which are not currently licensed for dry eye disease) or punctual plugging (in people with aqueous-deficient dry eye disease).
	Santen	Santen considers the Background section to be accurate and appropriate. There are a few additional points to consider for completeness: • It may be important to more fully emphasise the chronic nature of the condition and highlight that the QoL impact can be considerable; (QoL has been likened to that for dialysis patients or those with severe angina) and that DED is often associated with depression • As well as the symptomatic burden of DED and the impact on QoL, which the draft scope captures, Santen feels it is also important to emphasise that DED can cause inflammation in the ocular surface, damage to the ocular surface, infections, ulcers with irreversible loss of visual acuity and corneal perforation. Preventing this damage to the cornea becomes particularly important in severe DED patients.	Comment noted. The background section of the scope is only intended to provide a brief overview of the condition and current treatment options. A more detailed description of the nature of the condition and the impact of the condition on a patient's quality of life will be included in the manufacturer's evidence submission during the course of the appraisal. The background has been amended to state that dry eye disease is a chronic condition, and to note that in severe cases, it can cause damage to the surface of the eye, irreversible loss of visual acuity and corneal perforation.
The technology/ intervention	Royal College of Nursing	[Is the description of the technology or technologies accurate?] Yes	Comment noted. No changes required.
	Royal College of Ophthalmologists	[Is the description of the technology or technologies accurate?] Yes	Comment noted. No changes required.
	Santen	The brand name for the cationic emulsion of Ciclosporin (CsA) described in the scope is Ikervis® and has been developed by Santen SAS, formerly known as Novagali Pharma.	Comment noted. The brand name Ikervis has been added to the scope. The technology section of the scope is

Section	Consultees	Comments	Action
		The product is formulated as a 1mg/ml solution of CsA in a cationic emulsion. Topical instillation results in a long-lasting lipid film over the entire surface of the eye and the ocular bioavailability of Ikervis® is therefore improved. Ikervis® has been studied versus a vehicle* (not placebo) in both moderate and severe forms of DED, but is intended for severe forms of immune-mediated ocular diseases such as DED and vernal keratoconjunctivitis. Its proposed indication is the treatment of dry eye disease in adult patients with severe keratitis that does not improve despite treatment with tear substitutes. *It is important to note that the Ikervis® vehicle is similar to Cationorm® ocular lubricant, which itself demonstrates significant effect on signs and symptoms versus Vismed®. NOSIKA Study Protocol NVG11F120 a Phase III Study: a randomized, single masked parallel group, reference controlled, study to compare the efficacy of Cationorm® with Vismed® in patients with moderate to severe dry eye disease with keratitis or keratoconjunctivitis. Santen would question whether following the MTA process and comparing with Thymosin beta-4 is the most appropriate approach. Publicly available data suggest that Thymosin beta-4 may be further from approval than Ikervis® as it is currently in Phase II and may be targeting a different patient population.	only intended to provide a brief description of the technology and the clinical trials supporting the indication. A detailed description of the clinical trials, the specific mechanism of action of the technology and the dosing will be included in the manufacturer's evidence submission. The description of the clinical trials in the scope has been amended to state that ciclosporin was compared with a vehicle (similar to an ocular lubricant) and not placebo as originally stated. It was agreed at the scoping workshop that this topic should only consider ciclosporin. The scope has been amended to remove thymosin beta-4 from the technology section.
Population	Allergan	The population should be based on the DEWS classification system. The Definition and Classification of Dry Eye Disease: Report of the management and therapy subcommittee of the international Dry Eye Workshop(2007). *The Ocular Surface* April 2007; Vol 5; No 2. www.theocularsurface.com	Comment noted. Consultees at the scoping workshop agreed that the population in the scope should be amended to 'People with severe dry eye disease (DEW 3 or 4) whose disease has not adequately responded to tear substitutes' in line with the clinical trial population and the population most likely to be treated with ciclosporin in clinical practice.

Section	Consultees	Comments	Action
	Royal College of Nursing	It would be helpful if the population defines if this technology is aimed at mild moderate or severe symptomatic patients.	Comment noted. The population has been amended to specify that patients have severe dry eye disease (DEWS 3 or 4) in line with the clinical trial population and the population most likely to be treated with ciclosporin in clinical practice.
	Royal College of Ophthalmologists	May wish to distinguish between evaporative dry eye and aqueous deficient dry eye conditions.	Comment noted. Consultees acknowledged that the clinical trials for ciclosporin did not differentiate between evaporative or aqueous-efficient dry eye disease, and therefore data would be lacking to inform individual recommendations for each group. Therefore the population in the scope should not be divided into evaporative and aqueous deficient dry eye conditions.
	Santen	The population defined in the scope is broad and should include definition of the different levels of severity as we believe these have different needs, treatment options and outcomes. A potential additional sub-group could also include Sjögren's syndrome. Ikervis® is likely be indicated for a subset of the keratoconjunctivitis sicca population; namely adults with severe keratitis that do not improve despite treatment with lachrymal substitutes. Approximately one third of the severe keratitis patients in Ikervis®'s trial had Sjögren's syndrome.	Comment noted. Consultees at the scoping workshop agreed that the population in the scope should be amended to 'People with severe dry eye disease (DEW 3 or 4) whose disease has not adequately responded to tear substitutes' in line with the clinical trial population and the population most likely to be treated with ciclosporin in clinical practice. The clinical specialist at the scoping workshop confirmed that patients with Sjogren's syndrome are often easier to diagnose and treat; therefore if evidence on the effectiveness of ciclosporin in patients with Sjogren's syndrome is available, it will be considered as a

Section	Consultees	Comments	Action
			subgroup analysis.
Comparators	Allergan	Comparators should be approved therapeutics that treat the underlying condition, therefore artificial tears or ointments should not be considered as comparators. Topical steroids should not be considered as comparators, because of the chronic nature of dry eye disease patients are likely to be on long term treatment and can develop steroid-related complications and adverse effects, such as ocular hypertension, cataracts, and opportunistic infections. Stevenson W, Chauhan SK, Dana MR. Dry Eye Disease: An immune-mediated ocular surface disorder. *Arch Ophthalmol* 2012;130:90-100. Marsh P and Pflugfelder SC. Topical nonpreserved methylprednisolone therapy for keratoconjunctivitis sicca in Sjogren Syndrome. *Ophthalmology* 1999;106:811-816. Shafiee A, Bucolo C, Budzynski E, Ward KW, Lopez FJ. In vivo ocular efficacy profile of mapracorat, a novel selective glucocorticoid receptor agonist, in rabbit models of ocular disease. *Invest Ophthalmol Vis Sci.* 2011;52:1422-1430.	Comments noted. Consultees noted that moderate to severe dry eye disease is predominantly treated in a secondary care setting, and treatment may include the use of anti-inflammatory agents, specialised eyewear (e.g. goggles to reduce moisture loss), eye ointments and artificial tears. It was noted that topical corticosteroids are only given for short periods of time due to the risk of potential adverse effects, including glaucoma and cataracts following long-term use. On the advice of consultees, the comparator in the scope has been amended to: "Standard treatment for dry eye disease without ciclosporin (such as artificial tears, eye ointments and acute use of topical corticosteroids)."
	Royal College of Nursing	[Is this (are these) the standard treatment(s) currently used in the NHS with which the technology should be compared? Can this (one of these) be described as 'best alternative care'?] Yes-punctum occlusion is widely used for tear insufficiency.	Comment noted. It was acknowledged during the scoping workshop that punctual plugging could be undertaken in addition to ciclosporin use,

Section	Consultees	Comments	Action
			and therefore consultees agreed that it should not be included as a comparator as it was unlikely to be displaced if ciclosporin was recommended. On the advice of consultees, the comparator in the scope has been amended to: "Standard treatment for dry eye disease without ciclosporin (such as artificial tears, eye ointments and acute use of topical corticosteroids)."
	Royal College of Ophthalmologists	Could include treatment of punctual plugging or measures to improve meibomian gland dysfunction	Comment noted. It was acknowledged during the scoping workshop that punctual plugging could be undertaken in addition to ciclosporin use, and therefore consultees agreed that it should not be included as a comparator as it was unlikely to be displaced if ciclosporin was recommended. On the advice of consultees, the comparator in the scope has been amended to: "Standard treatment for dry eye disease without ciclosporin (such as artificial tears, eye ointments and acute use of topical corticosteroids)."
	Santen	The comparators noted in the scope are appropriate for mild and moderate patients. However artificial tear formulations and eye ointments provide only symptomatic short-term relief, leading to the necessity of frequent dosing throughout the day. Neither product is able to control inflammation of the ocular surface and thus as Ikervis is indicated for patients where artificial tears are not appropriate as sole therapy, these do not provide appropriate comparators.	Comments noted. Consultees noted that moderate to severe dry eye disease is predominantly treated in a secondary care setting, and treatment may include the use of anti-inflammatory agents, specialised eyewear (e.g. goggles to reduce moisture loss), eye ointments and

Section	Consultees	Comments	Action
		Topical steroids are not labelled for treatment of DED, but have shown some promise for improving the signs and the symptoms of DED. However, their potential benefit in this chronic disease is limited by their known iatrogenic ocular side effects, e.g. intraocular hypertension and cataract upon long-term use. For the more severe end of the disease spectrum, other considerations may be important such as autologous serum tears and surgery. In the absence of any approved pharmaceutical product for the severe patients, pharmacy-compounded Ciclosporin formulations are used in some centres but these are of different strengths and may vary in quality. Given this lack of currently licenced products with an anti-inflammatory mechanism, we suggest there is no, one, formal comparator for this assessment.	artificial tears. It was noted that topical corticosteroids are only given for short periods of time due to the risk of potential adverse effects, including glaucoma and cataracts following long-term use. Consultees acknowledged that for patients with very severe dry eye disease, autologous serum tears could be used; however it was acknowledged that only about 10 patients currently receive this type of treatment in England, due to the high risk of infection. Consultees noted that this procedure would only be considered after ciclosporin use, and therefore it would not be a suitable comparator to ciclosporin. On the advice of consultees, the comparator in the scope has been amended to: "Standard treatment for dry eye disease without ciclosporin (such as artificial tears, eye ointments and acute use of topical corticosteroids)."
Outcomes	Allergan	Clinical signs on staining / schirmer score should be included as stated in the DEWS classification system showing that both signs and symptoms are used to classify and treat patients. The Definition and Classification of Dry Eye Disease: Report of the management and therapy subcommittee of the international Dry Eye Workshop(2007). *The Ocular Surface* April 2007; Vol 5; No 2. www.theocularsurface.com	Consultees agreed that the suggested outcomes in the scope were appropriate. They also considered that the most important outcome was 'symptoms of dry eye disease', which could include photosensitivity, ability to open eyes, visual acuity and ability to concentrate. The following additional outcome has been included in the scope: "Symptoms of dry eye disease (including photosensitivity, ability to open eyes,

Section	Consultees	Comments	Action
			visual acuity and ability to concentrate)".
	Royal College of Nursing	It may be good to include objective measurements such as osmolarity values	Consultees agreed that the suggested outcomes in the scope were appropriate. They also considered that the most important outcome was 'symptoms of dry eye disease', which could include photosensitivity, ability to open eyes, visual acuity and ability to concentrate. The following additional outcome has been included in the scope: "Symptoms of dry eye disease (including photosensitivity, ability to open eyes, visual acuity and ability to concentrate)".
	Royal College of Ophthalmologists	[Will these outcome measures capture the most important health related benefits (and harms) of the technology?] Yes but could also include improvement in best corrected visual acuity	Consultees agreed that the suggested outcomes in the scope were appropriate. They also considered that the most important outcome was 'symptoms of dry eye disease', which could include photosensitivity, ability to open eyes, visual acuity and ability to concentrate. The following additional outcome has been included in the scope: "Symptoms of dry eye disease (including photosensitivity, ability to open eyes, visual acuity and ability to concentrate)".
	Santen	The proposed outcomes described in the scope are appropriate, but Santen would also recommend inclusion of measures of inflammation and signs of the physical damage to the cornea. Measures such as Corneal Fluorescein Staining (CFS) to detect corneal damage and HLA-DR as a marker for inflammation could be considered.	Consultees agreed that the suggested outcomes in the scope were appropriate. It was noted that the EQ-5D is not particularly sensitive to eye conditions, and therefore an additional measurement of health-related quality of life, such as

Section	Consultees	Comments	Action
		Specific measures of the suggested outcomes in the draft scope would include: • Ocular Surface Disease Index (OSDI) questionnaire • Eye Pain by Visual Analogue Scale (VAS) • In addition to the EuroQol 5D questionnaire (EQ-5D), the National Eye Institute visual function questionnaire (NEI-VFQ-25) should be included • Regarding the disutility's the adverse events, which should be followed, are: impairment of visual acuity, an increase in intraocular pressure (IOP), and an increase in corneal sensitivity	NEI-VFQ-25, should also be considered. They also considered that the most important outcome was 'symptoms of dry eye disease', which could include photosensitivity, ability to open eyes, visual acuity and ability to concentrate. The following additional outcome has been included in the scope: "Symptoms of dry eye disease (including photosensitivity, ability to open eyes, visual acuity and ability to concentrate)". Consultees were advised by the NICE technical team at the scoping workshop that the outcomes in the scope are not prescriptive and the manufacturer is welcome to include evidence for additional outcomes in their submission.
Economic analysis	Royal College of Ophthalmologists	Will need to look over a long period of time possibly 5 year cycle	Comment noted. No changes required.
	Santen	No comments	Comment noted. No changes required.
Equality and Diversity	Royal College of Ophthalmologists	No issues	Comment noted. No changes required.
	Santen	No comments	Comment noted. No changes required.
Innovation	Allergan	Any product indicated to treat the underlying cause of dry eye verses temporarily relieve symptoms should be considered innovative.	Comment noted. No changes required.
	Royal College of Ophthalmologists	[Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?	Comment noted. The Committee will consider the innovative nature of ciclosporin for dry eye disease during the course of the appraisal. No changes

Section	Consultees	Comments	Action
		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?] Yes, measurement that will help are improvement in comfort levels, improved visual acuity, increased hours for reading or computer work. This would suggest a change in economic activity	required.
	Santen	Ikervis® will be the first licensed product for the treatment of Dry Eye Disease in adult patients with severe keratitis that does not improve despite treatment with tear substitutes.	Comment noted. The Committee will consider the innovative nature of ciclosporin for dry eye disease during the course of the appraisal. No changes required.
Other considerations	Royal College of Ophthalmologists	Should consider different groups of dry eye syndromes, namely evaporative dry eye and aqueous dry eye conditions.	Comment noted. Consultees acknowledged that the clinical trials for ciclosporin did not differentiate between evaporative or aqueous-efficient dry eye disease, and therefore data would be lacking to inform individual recommendations for each group. Therefore the population in the scope has not been divided into evaporative and aqueous deficient dry eye conditions.
	Santen	As noted above we believe evaluating DED by subgroups would be important, particularly because for more severe patients it has been observed that damage to the cornea can lead to decreased sensitivity of corneal nerves and lower ability to detect symptoms. Thus the relative importance of symptoms versus signs may be different depending on the severity of the patient.	Comment noted. Consultees acknowledged that ciclosporin is likely to only be licensed for (and used in) patients with severe dry eye disease; therefore, a subgroup analysis in patients with mild or moderate disease was not required. It was acknowledged that approximately 1/3 of patients in the ciclosporin trials had Sjogren's syndrome. The clinical specialist confirmed that this group of patients is often easier to diagnose and

Section	Consultees	Comments	Action
			treat, and therefore if evidence on the effectiveness of ciclosporin in patients with Sjogren's syndrome is available, it should be considered as a separate subgroup. The manufacturer is welcome to include other subgroup analyses if specific groups have been pre-specified in the clinical trials and there is sufficient evidence available.
Questions for consultation	Royal College of Nursing	Current NHS practice depends on underlying pathology and the patient's level of symptoms. If the KCS is associated with rheumatological disorders causing tear deficiency, the treatment will vary from that of a tear evaporative problem. There is evidence that higher tear film osmolarity demonstrates KCS pathology. This tool is not widely used in the NHS so most clinicians make a judgement on the severity of the disease from the patient's perceived severity of symptoms and microscope examination of the cornea which does not correlate so it is difficult to comment on the question ...should the treatment be considered for moderate or severe, unless we have a quantifiable diagnostic measurement.	Comment noted. Consultees was noted that tear film osmolarity is being used as a diagnostic tool in the US; however, it is not widely used in the UK beyond a clinical trial setting and the machines required to perform this test are not readily available. Therefore, consultees considered that it was not appropriate to define the population in the scope according to this diagnostic criterion.
	Royal College of Ophthalmologists	Frequency of drop instillation, drug stability at room temperature (ie able to take eye drop anywhere), preservative and preservative free formulations	Comment noted. A detailed description of the technology and the dosing will be included in the manufacturer's evidence submission. No change to the scope required.
	Santen	[Have all relevant comparators for ciclosporin been included in the scope? Which treatments are considered to be established clinical practice in the NHS dry eye syndrome? Should these treatments are considered for moderate or severe dry eye syndrome? Should	Comments noted. Please see previous responses above. Consultees were advised by the NICE

Section	Consultees	Comments	Action
		autologous serum tears be included as comparators? Are there other comparators that should be included?] Addressed in comparator section comments [Should damage to the eye that may lead to visual impairment or, for example, the need for a corneal transplant, be included as an outcome?] Santen strongly believe that assessment of the impact of damage to the eye and the downstream consequences of this need to be included, as well as consideration of improvement in signs as a marker of the damage to the eye. [Where are thymosin beta-4 and Ikervis likely to be used in the current treatment pathway for dry eye syndrome?] Ikervis will be used only in severe keratitis patients where use of artificial tears to manage symptoms is no longer sufficient [Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom these technologies are expected to be more clinically effective and cost effective or other groups that should be examined separately?] Addressed in population section comments	technical team at the scoping workshop that the outcomes in the scope are not prescriptive and the manufacturer is welcome to include evidence for additional outcomes in their submission.
Additional comments on the draft scope	Cochrane Eyes and Vision Group	We currently have a systematic review for ciclosporin A for dry eye underway. We anticipate the review will be completed within the next six months. The protocol for the review if published in the Cochrane Library as Topical cyclosporine A therapy for dry eye syndrome.	Comment noted. All clinical evidence on dry eye disease available at the time of appraisal should be included in the manufacturer's evidence submission and for consideration by the Appraisal Committee. No changes required.
	Santen	None	Comment noted. No changes required.

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

Alcon Eye Care UK
Department of Health

Single Technology Appraisal (STA)

Ciclosporin for treating dry eye disease

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 RegeneRx Biopharmaceuticals	NICE Secretariat		Removed	As this appraisal is now a STA for Ciclosporin for treating dry eye disease only, RegeneRx Pharmaceuticals have not been included in the matrix.

2.	Add The Keratoconus Self Help and Support Association	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. The Keratoconus Self Help and Support Association has been added to the matrix of consultees and commentators under 'patient/carer groups'.
3.	Remove Commissioning Support Appraisals Service	NICE Secretariat		Removed	This organisation's interests are not closely related to the appraisal topic and as per our inclusion criteria Commissioning Support Appraisals Service has not been included in the matrix of consultees and commentators.

4.	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.