National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Tolvaptan for treating autosomal dominant polycystic kidney 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	British Society of Genomic Medicine	Yes	Comment noted. No action required
	MHRA	Yes given that there is no cure for this disease a treatment to slow progression will be of interest to patients	Comment noted. No action required
	Otzuka Pharmaceuticals	Yes	Comment noted. No action required.
	PKD Charity	Yes	Comment noted. No action required.
	Renal Association	Yes	Comment noted. No action required.
	Royal College of Pathologists	Very appropriate, most common inherited renal disease with currently no treatment options. Many patients progress to chronic renal failure requiring either dialysis or transplantation with significant impact of quality of live and life expectancy and cost to the health service.	Comment noted. No action required.
Wording	British Society of Genomic Medicine	Yes	Comment noted. No action required.
	Otzuka Pharmaceuticals	Yes	Comment noted. No action required.

Appendix D - NICE's response to consultee and commentator comments on the draft scope and provisional matrix

Section	Consultees	Comments	Action
	PKD Charity	We cannot comment on the clinical and cost effectiveness of Tolvaptan within its licensed indication, as it does not currently have EMA marketing authorisation.	Comment noted. No action required.
	Renal Association	Yes	Comment noted. No action required.
	Royal College of Pathologists	Yes	Comment noted. No action required.
Timing Issues	British Society of Genomic Medicine	It is urgent as there are no other disease specific therapies , interventions or technologies for treating ADPKD.Treatment here is meant to indicate slowly the rate of decline of renal function to end-stage renal failure rather than disease cure. Data from the UK Renal Registry reveals that 1 in 8 people with a renal transplant has ADPKD. The average age of renal failure in ADPKD is 55 years, a figure which has not changed for over a decade suggesting that standard care for CKD does not alter outcomes in ADPKD.	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.
	Otzuka Pharmaceuticals	Given the lack of any other treatment for this condition and the high unmet need that it represents, we believe that this appraisal should proceed at the earliest possible opportunity.	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.

Section	Consultees	Comments	Action
	PKD Charity	This appraisal is urgent as there are no other recognised technologies for treating ADPKD - the most common genetic cause of established renal failure (ERF)/end stage renal disease (ESRD) with a significant clinical, psychological and financial impact on the estimated 60,000 people affected in the UK, their families and carers. UK Renal Registry (UKRR) data from 2011 shows that 1 in10 of all dialysis patients under 65 has ADPKD, and 1 in 8 of people with a kidney transplant has ADPKD - representing a substantial cost to the NHS alone. Kidney patients with ADPKD are amongst the youngest to reach ERF/ESRD. Of the 3,111 individuals with ADPKD on the UKRR, who commenced Renal Replacement Therapy (RRT) between 1/1/2000 and 2/10/2010, the median age of starting RRT was 55 years (IQR 47-63) - compared to 62 years (IQR 50-71) for those with diabetes and 65 (IQR 49-75) years for those with all other causes of PRD. This median age of starting RRT has not changed over the past 10 years - despite the improvements in CKD management since the introduction of the Renal NSF and NICE Guidelines. The main impact of CKD prevention therapy is in those with proteinuria; RAAS based therapy has limited renal progression benefit in ADPKD patients. ADPKD patients generally have fewer comorbidities. Reaching ERF/ESRD early can result in them dropping from the workforce and many will need to claim disability benefits. The economic benefits of preventing progression are likely to be greater compared with other conditions.	Comments noted. No changes to the scope required.
	Renal Association	Moderate	Comment noted. No changes to the scope required.

Section	Consultees	Comments	Action
	Royal College of Pathologists	Quite urgent, common with no current treatment and trials look very promising.	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	British Society of Genomic Medicine	None.	No action required.
	Otzuka Pharmaceuticals	None.	No action required.
	PKD Charity	None.	No action required.
	Renal Association	None.	No action required.
	Royal College of Pathologists	None.	No action required.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	British Society of Genomic Medicine	This is a very brief background description and does not fully describe the current knowledge base about ADPKD. In particular it does not provide information on disease biomarkers, family screening and the role of genetic testing for prognostic purposes. Ideally it should be rewrtitten to more fully inform the draft scope.	Comment noted. The background section of the scope is meant to a brief overview of the condition. No changes to the scope required.
	MHRA	No comment.	No action required.
	Otzuka Pharmaceuticals	The draft scope states a prevalence of 1-2:1,000. This figure is often quoted but not verified by epidemiological studies. We suggest adding the following text: *"A review of existing epidemiology literature suggests that the prevalence of this disease is approximately 4.3/10,000 in the UK, which includes an uplift accounting for a 90% diagnosis rate based on figures from a German study (Neumann et al NDT 2013). A similar prevalence rate of 4.1/10,000 is reported in a Welsh study (Davies et al QJM 1991). The actual prevalence of both diagnosed and undiagnosed population remains unclear.* *ADPKD is characterised by a progressive increase in the number and size of bilateral renal cysts, resulting in enlargement of the kidneys to 3 or 4 times their normal size, renal impairment and, ultimately complete loss of kidney function (referred to as kidney failure or end-stage renal disease (ESRD)). Approximately 50% of individuals with ADPKD progress to ESRD by age 60 years (Harris & Torres, 2002, updated 2011).* *Renal function decline caused by ADPKD is usually classified by the standardised 5 stages of chronic kidney disease which are defined by kidney function.*" It is worth noting, too, that there are no treatments currently available for this disease.	Comments noted. The background section of the scope is meant to a brief overview of the condition. However, the background section has been updated to include the following sentence, "*the actual prevalence of both diagnosed and undiagnosed population remains unclear*".

Section	Consultees	Comments	Action
	PKD Charity	The wording in this section does not reflect the current state of knowledge about ADPKD. We have drafted alternative wording - see attached.	Comments noted. The background section of the scope is meant to a brief overview of the condition. However, the scope has been amended to include more information on the associated complications that need to be managed for people with ADPKD (for example, pain, cyst infections, urinary tract infections and high blood pressure).
	Renal Association	There is no comment on genotype or total kidney volumes and their known effects on renal prognosis	Comments noted. The background section of the scope is meant to a brief overview of the condition.
	Royal College of Pathologists	Is it worth mentioning screening - pick up children of known families? early treatment could prevent or delay the onset of chronic renal impairment and failure? The current assumption is that you wait until they present with renal impairment.	Comment noted. The background section of the scope is meant to a brief overview of the condition. However, NICE clinical guideline No.182 includes recommendations on identifying people with suspected hereditary kidney disease.
The technology/ intervention	British Society of Genomic Medicine	Yes	Comment noted. No changes to the scope required.

Appendix D - NICE's response to consultee and commentator comments on the draft scope and provisional matrix

Section	Consultees	Comments	Action
	MHRA	No comment.	Comment noted. No action required.
	Otzuka Pharmaceuticals	The technology's brand name will be submitted as "Jinarc" (Otsuka Pharmaceuticals).	Comment noted. The scope has been amended accordingly.
	PKD Charity	Yes	Comment noted. No action required.
	Renal Association	Yes	Comment noted. No action required.
	Royal College of Pathologists	The effect on "Epithelial cell growth" is unclear - is "reducing cyst fluid accumulation and increase in cyst size" what is meant. I can see nothing in the literature about effects on epithelium - although I guess there will be an increase in epithelial cells required to line a bigger cyst.	Comment noted. Pre-clinical studies suggested that tolvaptan may reduce epithelial cell growth (Irazabal et al 2011. Kidney International 80; p295-301). No changes to the scope required.
Population	British Society of Genomic Medicine	Yes. Children should also be included as rarely they may also develop renal failure.	Comment noted. NICE can only appraise a technology within its marketing authorisation. No changes to the scope required.
	MHRA	No comment	No action required.
	Otzuka Pharmaceuticals	The suggested population of "People with autosomal dominant polycystic kidney disease" is appropriate.	Comment noted. No action required.

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	PKD Charity	The population is described accurately. Regarding sub-groups: children should be considered separately as ADPKD is an inherited condition; cysts and associated CKD symptoms develop in childhood.	Comment noted. NICE can only appraise a technology within its marketing authorisation. No changes to the scope required.
	Renal Association	The trial data has addressed adult patients (18-50 years) with Stage 2 CKD with more rapidly progressive disease as reflected by larger kidney volumes (>750ml). This group would be the obvious population to benefit from treatment. The benefit for patients with milder or more advanced disease and children/teenagers is still to be determined.	Comment noted. NICE can only appraise a technology within its marketing authorisation. No changes to the scope required.
	Royal College of Pathologists	This could be clearer. As it is inheritied, screening - either genetic or by ultrasound during childhood could pick up affected individuals prior to the development of cysts and/or renal impairment. This study is designed for those with established renal impairment of the various CKD stages. It should state "people with ADPKD with CKD stage 1 or more" etc	Comment noted. NICE clinical guideline No.182 includes recommendations on identifying people with suspected hereditary kidney disease (such as ADPKD). NICE can only appraise technologies within the marketing authorisation and so attendees at the scoping workshop agreed that the population specified in the scope was appropriate and should remain unchanged.
Comparators	British Society of Genomic Medicine	Yes, standard CKD care is the only treatment available for ADPKD. Tolvaptan will not replace this standard of care but will potentially be added to it.	Comment noted. No changes to the scope required.

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Section	Consultees	Comments	Action
	MHRA	There are no comparators in drug therapy so it is important to define 'standard care' and at what stage treatment is introduced as outlined in the questions.	At the workshop, attendees agreed that standard care will vary depending on each patient noted that it not possible to define the standard of care treatment for this condition. No changes to the scope required.
	Otzuka Pharmaceuticals	The comparator is correctly identified as "standard of care without tolvaptan". Since there are currently no available pharmacological treatments for ADPKD, current "standard of care" does not actually treat ADPKD. Therefore we propose that "standard of care without tolvaptan" should be defined as no treatment such that the economic analysis would compare tolvaptan with no treatment/placebo. Any significant changes to underlying "standard of care" resulting from the introduction of tolvaptan would be explored within the analysis itself.	At the workshop, attendees agreed that standard care will vary depending on each patient noted that it not possible to define the standard of care treatment for this condition. No changes to the scope required.
	PKD Charity	Standard care without Tolvaptan is the only comparator. There is no dedicated NICE Guidance or NHS Pathway for people with ADPKD. Patients are managed according to the prevailing CKD and related Guidance. Tolvaptan is not considered as an alternative to standard care.	Comment noted. No changes to the scope required.
	Renal Association	Standard treatment is not defined but includes monitoring of renal function, blood pressure control and treatment of complications (pain, UTI)	Comment noted. The background section of the scope has been amended to reflect this.
	Royal College of Pathologists	This is the only comparator group available as there is no other treatment available.	Comment noted. No changes to the scope required.

Appendix D - NICE's response to consultee and commentator comments on the draft scope and provisional matrix

Section	Consultees	Comments	Action
Outcomes	British Society of Genomic Medicine	No. It would be better to use alternative outcomes including rate of decline in renal function using GFR or an appropriate biomarker such as total renal volume. THis would capture early stage disease.	Consultees and workshop attendees agreed that 'time to established renal failure' should be replaced with 'rate of decline of renal function'. The scope has been amended accordingly.
	MHRA	Do the outcome measures correspond to primary and seconday outcomes at clinical trial?	Consultees considered the outcomes in the scope to be largely appropriate. However, consultees and workshop attendees agreed that 'time to established renal failure' should be replaced with 'rate of decline of renal function'. The scope has been amended accordingly. This is more in line with the outcomes captured in the relevant clinical trial.

Section	Consultees	Comments	Action
	Otzuka Pharmaceuticals	We consider that the outcome measures defined in the scope are appropriate and would propose additional outcomes that consider the relative rate of disease progression (prior to ESRD), namely "total kidney volume" and "rate of renal function decline". We agree that mortality is an appropriate outcome to consider as part of the appraisal. However we would note that any potential effect of tolvaptan on mortality would be demonstrated as an indirect effect through economic modelling since the clinical evidence for tolvaptan does not support a direct effect on mortality within the timeframe of the pivotal trial. Nevertheless, the potential knock-on effect of variable rates of renal function decline on mortality in the longer term will be explored in the economic analysis.	Consultees considered the outcomes in the scope to be largely appropriate. However, consultees and workshop attendees agreed that 'time to established renal failure' should be replaced with 'rate of decline of renal function'. The scope has been amended accordingly. This is more in line with the outcomes captured in the relevant clinical trial.
	PKD Charity	Regarding the listed Outcomes, we recommend the following changes: (1) replace 'time to established renal failure' with 'rate of decline of renal function or suitable surrogate marker such as rate of increase in total kidney volume (TKV)' (2) insert the word 'all' before 'symptoms' (3) replace 'health related quality of life' with 'reported quality of life and patient experience measures'	Consultees considered the outcomes in the scope to be largely appropriate. However, consultees and workshop attendees agreed that 'time to established renal failure' should be replaced with 'rate of decline of renal function'. The scope has been amended accordingly. Health-related quality of life is a standard outcome included in all NICE scopes.
	Renal Association	Yes	Comment noted. No action required.

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Section	Consultees	Comments	Action
	Royal College of Pathologists	It will be important to compare the different CKD stages at commencing the trial with each other rather than all together. It is possible that the earlier in the renal disease progression (earlier CKD stage) the easier it will be to see the differences as other mechanisms of disease progression may come into play in latter stages of CKD. Could look at rate of change of renal deterioration rather than wait till established renal failure.	Comment noted. Consultees and workshop attendees agreed that 'time to established renal failure' should be replaced with 'rate of decline of renal function'. The scope has been amended accordingly.
Economic analysis	British Society of Genomic Medicine	Do not have the expertise to comment on this section. We would ask the scope to also consider the impact of tolvaptan on family screening. If a proven treatment exists it is likely that many more at risk individuals will consier screening at a younger age. The impact of this needs to be assessed.	Comment noted. If introduction of the technology requires additional infrastructure to be put in place, consideration should be given to including such costs (and benefits) in the analysis.
	Otzuka Pharmaceuticals	In line with the reference case, the appropriate time horizon for estimating clinical and cost-effectiveness in this appraisal is lifetime. ADPKD is a chronic disease with life-long potential implications for patients, particularly with respect to ESRD.	Comment noted. No changes to the scope required.

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	PKD Charity	The wording of this section is not transparent to a lay audience. We do not understand what the 'reference case' is, nor what is the 'time horizon' for clinical and cost effectiveness in ADPKD. ADPKD is a long-term, lifelong, progressive disease often requiring continual and sometimes intensive care, increasing in cost over time. We do not understand what a 'Personal Social Services perspective' means.	When estimating clinical and cost effectiveness, the reference case specifies the methods considered by NICE to be the most appropriate for the Appraisal Committee's purpose and consistent with an NHS objective of maximising health gain from limited resources. This is explained in more detail in the *Guide to Methods of Technology Appraisal 2013.*
	Renal Association	Since there are significant cost implications for the drug and this is likely to be a life-long treatment, there should be a requirement to identify eligible patients as well as measure and monitor efficacy. Kidney MRI at baseline and 12 months would be a potential intermediate outcome measure.	Comments noted. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Attendees agreed that the scope should be updated so that, where evidence allows, subgroups would be stratified by the rate of decline of renal function and by baseline kidney volume.

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Section	Consultees	Comments	Action
	Royal College of Pathologists	Rate of change of renal deterioration over a stipulated time period eg 3 years or 5 years for each CKD stage may provide a shorter time period to assess, than time to established renal failure. If assessing a screened pre-CKD group - time to cyst development or rate of size increase in kidney as well as time to/or age at CKD1 could be assessed.	Consultees and workshop attendees agreed that 'time to established renal failure' should be replaced with 'rate of decline of renal function'. The scope has been amended accordingly.
Equality and Diversity	British Society of Genomic Medicine	Consideration about prescribing for children and ethnic minority groups would need to be assessed. Children and not routinely screened for this condition and formal guidelines do not exist. Ethnic minorities aften present late with CKD and specific advice about a new technology would need to be produced as ADPKD affects all ethnic groups.	Comments noted. The issue regarding prescribing for children will depend on the wording in the marketing authorisation of tolvaptan. NICE clinical guideline 182 provides recommendations on the identification and management of people with suspected hereditary kidney disease. Consultees and scoping workshop attendees agreed that the issue of ethnic minorities presenting late with CKD was not a specific equalities issue associated to access of treatment with tolvaptan. No changes to the scope required.
	Otzuka Pharmaceuticals	We have no comment here.	No action required.

Section	Consultees	Comments	Action
	PKD Charity	Tolvaptan has been studied in adults. The patient population in the scope states 'people'. We seek clarity on whether this includes children. If Tolvaptan is licensed, NICE needs to ensure that ethnic groups have equality of access - these patients are known to be referred late in CKD and also access services later, especially transplant. Clarification is also sought on the stage of CKD that Tolvaptan will be licensed for.	Comment noted. NICE can only appraise a technology within its marketing authorisation. No changes to the scope required. Consultees and scoping workshop attendees agreed that the issue of ethnic minorities presenting late with CKD was not a specific equalities issue associated to access of treatment with tolvaptan. No changes to the scope required. Tolvaptan was studied in people with ADPKD with chronic kidney disease stages 1-3. However, the proposed licensed wording will depend on the final marketing authorisation issued by the European Medicines Agency.
	Renal Association	No	Comment noted. No action required.
	Royal College of Pathologists	Possibly individuals with ADPKD with predominantly liver symptoms. They may be prejudiced against in not meeting criteria eg CKD1 or CKD2 - can't find any information on liver cysts to see if they may also have a slowing in growth. Liver cysts occur more commonly in women.	Comment noted. The eligible population will be determined by the wording in the marketing authorisation for tolvaptan.
Innovation	British Society of	This is a novel treatment and the first of its kind in ADPKD. It has the potential	Comment noted. Consultees

Section	Consultees	Comments	Action
	Genomic Medicine	to improve both clinical and social outcomes. ADPKD affects people of working and reproductive age. Therefore the effects of treatment are potentially diverse.	at the scoping workshop were in agreement that the introduction of tolvaptan, which is the first treatment aimed to modify disease progression in ADPKD, would be a 'step-change' in the management of ADPKD. They also noted that some of the health related benefits of tolvaptan may not be included in the incremental QALYs (such as the benefit of oral management of the condition compared with nephrectomy) and that this technology was innovative.
	Otzuka Pharmaceuticals	**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)?** Yes, we believe tolvaptan represents a breakthrough in the treatment of ADPKD, being the first technology which delays the disease progression towards ESRD. . The potential positive impact for patients and their families, and clinicians, is substantial. ADPKD is a genetic disease for which there is no cure or currently available treatment. To be diagnosed with ADPKD therefore sets the patient on an uncertain life-long journey where the clinician is unable to offer any effective	Comment noted. Consultees at the scoping workshop were in agreement that the introduction of tolvaptan, which is the first treatment aimed to modify disease progression in ADPKD, would be a 'step-change' in the management of ADPKD. They also noted that some of the health related benefits of tolvaptan may not be included in the incremental QALYs (such as the benefit of oral management of the

Section	Consultees	Comments	Action
		treatment. The damage to the kidneys caused by ADPKD can be life-threatening and have a substantial short and long-term impact on quality of life, mental wellbeing and social participation. Early manifestations such as urine concentration defects, hypertension, renal pain, renal infection and haematuria can be debilitating. As the condition progresses towards ESRD, patients face increasing impact on their lives.[Harris & Torres (2002, updated 2011); Perrone et al. (2001)]. The requirement for renal replacement therapy, particularly dialysis, is life-changing for patients. Both in terms of the physical effects of renal failure (e.g. chronic fatigue) but also in terms of the impact the dialysis procedure and regimen has on patients' quality of life. Provision of dialysis services also represents a significant burden to the NHS. The introduction of tolvaptan will for the first time present clinicians with an effective treatment option for ADPKD, and also give patients the psychological benefit that something can be done to treat their disease. **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, the benefits of tolvaptan are highly likely to extend beyond the domains considered within the QALY calculation. A diagnosis of ADPKD may affect the patient's ability to obtain health or life insurance. Being a genetic disorder, patients with ADPKD are often faced with the risks associated with the decision to start a family, or indeed whether their own children should be screened for the disease. ADPKD can lead to ESRD, often resulting in the need for dialysis which has a wide impact on both patients and their families/carers beyond the effect on patient health-related quality of life. If the patient is of working age, it may affect their ability to gain and/or stay in employment. The patient's ability to	condition compared with nephrectomy) and that this technology was innovative.

Section	Consultees	Comments	Action
		travel is also likely to be restricted. The factors associated with dialysis are likely to have significant knock-on consequences for the families and/or carers of patients, particularly in how the burden and restrictions of the dialysis regimen affect their own quality of life. **Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** We understand that consideration of the wider impact on societal costs and benefits associated with the use of tolvaptan in ADPKD is currently outside the scope of the NICE Reference Case for inclusion in the economic analysis. However we propose to review the literature on these factors associated with ADPKD and ESRD and include them in a narrative/qualitative fashion within our submission, for further consideration by the Appraisal Committee. If appropriate under the revised scope of value based pricing, we would look to include these additional impacts as part of our economic analyses.	

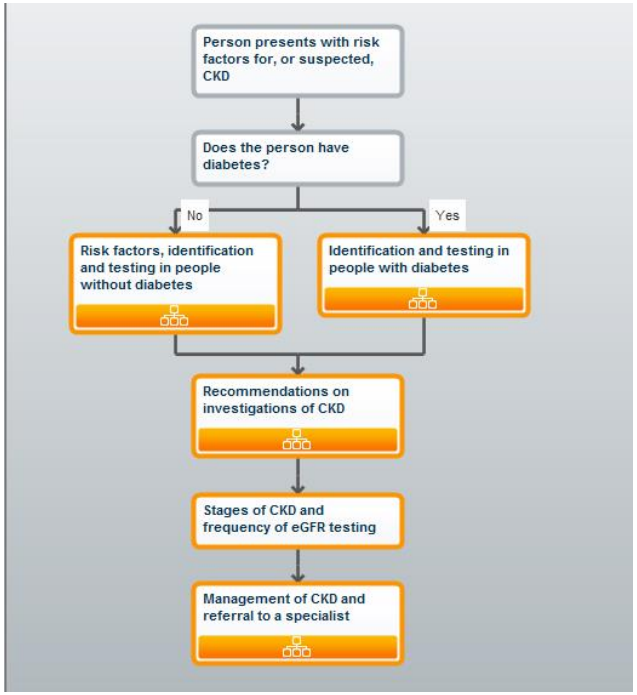
Section	Consultees	Comments	Action
	PKD Charity	Yes. Tolvaptan is a 'step-change' from current management. We will be concerned if there are other outcomes measures not covered by the QALY, eg employability (ability to gain and stay in employment), financial impact on patients, families and carers (eg life/travel insurance, reduced working hours). UKRR data shows that ADPKD patients reach ERF/ESRD during working age. HES data can be analysed to demonstrate degree/cost of hospitalisation owing to cyst infections, especially in the years just preceding RRT. All these have a consequential impact on employability, family life, socio-economic status and overall quality of life.	Comment noted. Consultees at the scoping workshop were in agreement that the introduction of tolvaptan, which is the first treatment aimed to modify disease progression in ADPKD, would be a 'step-change' in the management of ADPKD. They also noted that some of the health related benefits of tolvaptan may not be included in the incremental QALYs (such as the benefit of oral management of the condition compared with nephrectomy) and that this technology was innovative.

Section	Consultees	Comments	Action
	Renal Association	Yes this represents a step change in management. There are currently no other disease modifying drugs for this disease.	Comment noted. Consultees at the scoping workshop were in agreement that the introduction of tolvaptan, which is the first treatment aimed to modify disease progression in ADPKD, would be a 'step-change' in the management of ADPKD. They also noted that some of the health related benefits of tolvaptan may not be included in the incremental QALYs (such as the benefit of oral management of the condition compared with nephrectomy) and that this technology was innovative.

Section	Consultees	Comments	Action
	Royal College of Pathologists	There is no current alternative treatment so this is innovative and could produce major health-related benefits QALY should detect any benefits	Comment noted. Consultees at the scoping workshop were in agreement that the introduction of tolvaptan, which is the first treatment aimed to modify disease progression in ADPKD, would be a 'step-change' in the management of ADPKD. They also noted that some of the health related benefits of tolvaptan may not be included in the incremental QALYs (such as the benefit of oral management of the condition compared with nephrectomy) and that this technology was innovative.
Other considerations	British Society of Genetic Medicine	Startification should be added to the scope as not every person with ADPKD will need treatment. Identification of those at high risk of progression will be essential.	Attendees agreed that the scope should be updated so that where evidence allows subgroups would be stratified by the rate of decline of renal function and by baseline kidney volume. In addition, attendees agreed that if evidence allows, the use of different stopping rules based on treatment response should also be considered.

Section	Consultees	Comments	Action
	Otzuka Pharmaceuticals	None	No action required.
	PKD Charity	We would like the STA to cover stratification of the treatment population by risk of progression, ie fast or slow. Stratification methods could include genetic analysis, assessment of renal volume and other validated bio-markers.	Attendees agreed that the scope should be updated so that where evidence allows subgroups would be stratified by the rate of decline of renal function and by baseline kidney volume. In addition, attendees agreed that if evidence allows, the use of different stopping rules based on treatment response should also be considered. Stratification by genotype was not considered since consultees at the workshop acknowledged that genotyping the PKD mutation is not routinely carried out in current UK clinical practice.
	Renal Association	Due to the liver signal in a few patients, careful and regular monitoring of LFTs will be needed. Prescribing and monitoring should ideally take place through specialist clinics in secondary care.	Comment noted. The clinical experts in attendance at the meeting will advise the Committee on relevant issues related to management of PKD and the use of tolvaptan in clinical practice in England.

Section	Consultees	Comments	Action
	Royal College of Pathologists	Could also look at influence on cyst development and size in other organs eg liver and pancreas	Comment noted. The clinical experts in attendance at the meeting will advise the Committee on relevant issues related to management of PKD and the use of tolvaptan in clinical practice in England.
NICE Pathways	Otzuka Pharmaceuticals	**Where do you consider tolvaptan will fit into the existing NICE pathway; Chronic kidney disease (http://pathways.nice.org.uk/)?** The existing CKD Pathway [Recommendations on Investigations of CKD>Indications for renal ultrasound] recommends that renal ultrasound should be offered to all people with CKD who have a family history of PKD. In line with CG182, patients would be referred to a renal specialist at this point and following a diagnosis of ADPKD would be considered for treatment with tolvaptan.	Comment noted. No changes to the scope required.
	PKD Charity	None	No action required.
	Renal Association	None	No action required.
	Royal College of Pathologists	None	No action required.
Questions for consultation	Otzuka Pharmaceuticals	A number of answers to the questions for consultation are not covered elsewhere, so they are set out below. **What stage of chronic kidney disease would treatment with tolvaptan be started?** The CKD stage at which tolvaptan may be started will depend on the final marketing authorisation. The pivotal phase 3 clinical trial of tolvaptan included patients with CKD stages 1-3.	Comments noted. The eligible population will be determined by the wording in the marketing authorisation for tolvaptan.

Section	Consultees	Comments	Action
		Are there any subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately? Otsuka are currently working with clinical advisors to define the patient subgroups which will benefit most from tolvaptan, specifically those who are otherwise likely to reach ESRD and/or experience rapidly progressing disease. These subgroups will be investigated as part of our submission. It should be noted, however, that all the defined subgroups within the pivotal study showed an effect size of similar magnitude.  We consider STA to be the most appropriate process for appraisal of tolvaptan	Comments noted. Attendees agreed that the scope should be updated so that where evidence allows subgroups would be stratified by the rate of decline of renal function and by baseline kidney volume. In addition, attendees agreed that if evidence allows, the use of different stopping rules based on treatment response should also be considered.

Section	Consultees	Comments	Action
	PKD Charity	Standard care without Tolvaptan is defined by CKD stage. Tolvaptan was only studied on adults at CKD Stage 1-2 (>eGFR of 60), so it is not known at what CKD stage Tolvaptan treatment should start. We can potentially identify individuals at high risk and low risk and this should be considered. As said above, there is no dedicated ADPKD Guidance or NHS care pathway. We would like NICE to recommend an ADPKD Guidance and Pathway as part of the STA process.	Comments noted. The eligible population will be determined by the wording in the marketing authorisation for tolvaptan. Wider guidance on ADPKD would be outside the remit of a single technology appraisal, however, NICE clinical guideline no.182, 'Chronic kidney disease' has recently been published (an update of clinical guideline no.73). The NICE guideline includes recommendations on identifying people with suspected hereditary kidney disease (such as ADPKD).
	Renal Association	No comments	No action required.
	Royal College of Pathologists	Malignancy does occur in kidneys with ADPKD, it is unclear if they are at increased risk, compared to the normal population.	Comment noted. No changes to the scope required.
Additional comments on the draft scope.	Otzuka Pharmaceuticals	None	No action required.
	PKD Charity	Please ensure that the BAPN is included as consultee.	Comment noted. The British Association of Paediatric Nephrology (BAPN) will be included as a consultee.

Section	Consultees	Comments	Action
	Renal Association	None	No action required.
	Royal College of Pathologists	None	No action required.

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

Genetic Alliance UK
Royal College of Nursing

NATIONAL INSTITUTE FOR HEALTH CARE EXCELLENCE

Single Technology Appraisal (STA)

Tolvaptan for the treatment of autosomnal dominant polycystic kidney 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 British Lung Foundation	Otsuka Pharmaceuticals and PKD Charity		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria. British Lung Foundation has not been included in the matrix of consultees and commentators.

2.	Add Clinical Reference Group (Renal Disease)	Otsuka Pharmaceuticals		Not added	This organisation is a sub-group of NHS England who are already listed on the matrix of consultees and commentators under 'consultee –others.'
3.	Remove Cystic Fibrosis Trust	Otsuka Pharmaceuticals and PKD Charity		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria. Cystic Fibrosis Trust has not been included in the matrix of consultees and commentators.
4.	Remove Independent Age	NICE Secretariat		Removed	Independent Age have been removed from the matrix at their own request.
5.	PKD Consortium	Otsuka Pharmaceuticals		Not added	Organisations that are invited to participate in a technology appraisal are national organisations based in the UK/Wales. This organisation does not meet our inclusion criteria and therefore PKD Consortium has not been included in the matrix of consultees and commentators.

6.	Add RCN Nephrology Nursing Forum	Otsuka Pharmaceuticals		Not added	This organisation is a sub-group of Royal College of Nursing who are already listed on the matrix of consultees and commentators under 'consultee –professional groups.'
7.	Add Rare Disease UK	Otsuka Pharmaceuticals		Added	This organisation has an area of interest directly related to this appraisal and meets the selection criteria to participate in this appraisal. Rare Disease UK has been added to the matrix of consultees and commentators under 'patient' groups.
8.	Remove Association of Respiratory Nurse Specialists	Otsuka Pharmaceuticals and PKD Charity		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria. Association of Respiratory Nurse Specialists has not been included in the matrix of consultees and commentators.

9.	Add UK Renal registry	PKD Charity		Not added	This organisation is part of Renal Association who are already listed on the matrix of consultees and commentators under 'consultee – professional groups.'
10.	Add British Association of Paediatric Nephrology	PKD Charity		Not added	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria. British Association of Paediatric Nephrology has not been included in the matrix of consultees and commentators.
11.	Remove British Association for Services to the Elderly	NICE Secretariat		Removed	This organisation has disbanded.

12.	Remove British Thoracic Society	PKD Charity		Remove	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria. British Thoracic Society has not been included in the matrix of consultees and commentators.
13.	Add British Transplantation Society	PKD Charity		Added	This organisation has an area of interest directly related to this appraisal and meets the selection criteria to participate in this appraisal. British Transplantation Society has been added to the matrix of consultees and commentators under 'professional' groups.

14.	Add ESPRIT	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. ESPRIT has been added to the matrix of consultees and commentators under 'professional' groups.
15.	Remove Primary Care Respiratory Society	Otsuka Pharmaceuticals and PKD Charity		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria. Primary Care Respiratory Society has not been included in the matrix of consultees and commentators.

16.	PKD Charity suggested that a number of individuals with an interest in this appraisal should be added to the matrix	PKD Charity		Not added	Individual persons do not meet the selection criteria to be included on the matrix of consultees and commentators. Individuals who wish to participate in an appraisal can do so by feeding their comments through one of the national organisations already listed on the matrix. Alternatively, consultees and commentators will be invited, at the beginning of an appraisal, to nominate experts. This is another opportunity for individuals to be involved.
17.	Remove Commissioning Support Appraisals Service	NICE Secretariat		Removed	This organisation has disbanded.
18.	Re-classify Public Health England	NICE Secretariat		Re-classified	This organisation has been re-classified as an 'associated public health group - commentator'.
19.	Re-classify Public Health Wales NHS Trust	NICE Secretariat		Re-classified	This organisation has been re-classified as an 'associated public health group - commentator'.

20.	Remove Health Research Authority	NICE Secretariat		Removed	Health Research Authority has been removed from the matrix at their own request.
21.	Remove Research Institute for the Care of Older People	NICE Secretariat		Removed	This organisation's interests are not directly 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.