Final rankings	Indicative (summary) questions (35)	Original uncertainties (117)	Evidence (reference, and weblink where available, to the most recent relevant systematic review identified by the PSP, plus a maximum of 2 other systematic reviews, including protocols for future systematic reviews, that the PSP considers relevant.)	Source of Uncertainty (if there are multiple sources, a PSP may wish to show them e.g. 1 x patient, 19 x clinician, 4 x research recommendations)
Top 10				
1	What treatments can be developed that slow or prevent progression of ADPKD and improve patients' quality of life?	* Development of disease-modifying treatments for ADPKD with the potential to maintain quality of life, delay renal decline and improve life expectancy among patients, and to reduce the economic impact on healthcare systems. * Development of new treatments to delay the progression of ADPKD. * What are the benefits of therapeutic, lifestyle and dietary interventions for people with ADPKD?	Thida M Myint Gopi K Rangan Angela C Webster (2014) Treatments to slow progression of autosomal dominant polycystic kidney disease: systematic review and meta-analysis of randomized trials. https://doi.org/10.1111/nep.12211	2 x RR and KDIGO
2	Which people with ADPKD would benefit from early treatment and how can doctors identify them?	* Development of criteria for individualisation of treatments for polycystic liver disease, in people with ADPKD, and evaluation of treatment outcomes. * In people with ADPKD which interventions are effective and safe for preventing progression of the disease, considering outcomes such as progression to ESKD, need for transplantation, mortality, hospital admissions, major morbidities and quality of life? ~ Implementation of methods to routinely assess prognosis in patients with ADPKD to inform clinical decision-making, research and innovation. ~ What is the role of modifier genes in predicting disease progression in people with ADPKD?		3 x RR and KDIGO

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3	What are the best ways to organise the care of people with ADPKD to improve their outcomes?	* What are the long-term effects of improved care, including morbidity and mortality, on people with ADPKD? * Development of criteria to develop ADPKD care-centres of excellence. * What are the benefits and harms, including cost, of care-centres of excellence for people with ADPKD? * How is telenephrology best used to improve care for people with ADPKD? * Development of a nationally coordinated, tiered approach to ADPKD care in collaboration with experts, patient organisations and other stakeholders. * Establishment of an expanded European network of ADPKD reference centres to facilitate further research and the establishment of harmonised, integrated, patient-centred care pathways. * What are the best strategies for the development of tiered care approaches to ensure that people with ADPKD have appropriate access to specialist, multidisciplinary management?		2 x RR and KDIGO
4	What effect does pregnancy have on women with ADPKD including their pregnancy health, kidney function, and liver cysts?	* What effect does pregnancy have on women with ADPKD including maternal outcomes, renal function and kidney and liver cyst burden?		Autosomal Dominant Polycystic Kidney Disease (ADPKD): Report from a Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference
5	What are the benefits and harms of drugs that can be used for the management of ADPKD including polycystic liver disease (PLD)?	* Which sub-groups of people with ADPKD, including those at higher risk of clinical outcomes such as hypertension, are more likely to benefit from early intervention for example in relation to kidney volumes, range of kidney function and tendency to rapid disease progression? * What are the benefits and harms of somatostatin analogues for the management of ADPKD?		2 x RR

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6	For people with ADPKD experiencing pain, what treatments work best to reduce this pain?	* What is the long-term impact of cyst decompression and renal denervation for kidney pain management in people with ADPKD? * How effective is catheter based renal denervation, in people with ADPKD, to reduce kidney pain? * Which interventions are most effective, including renal denervation, for the treatment of kidney pain in people with ADPKD?		Autosomal Dominant Polycystic Kidney Disease (ADPKD): Report from a Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference
7	What changes to lifestyle, exercise and/or diet (including amount of water drunk) benefit people with ADPKD and polycystic liver disease (PLD)?	* What are the benefits and harms, for people with ADPKD, of drinking water? * What lifestyle changes including dietary and water intake does a person with ADPKD need to take to improve prognosis, and what is the most effective method of monitoring improvement? * What is the impact of exercise on people with ADPKD? * What lifestyle changes, including dietary, does a person with polycystic liver disease need to take to improve prognosis?		Autosomal Dominant Polycystic Kidney Disease (ADPKD): Report from a Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference

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8	When people are newly diagnosed with ADPKD, how does this affect them psychologically and what impact does it have on their life? What information and support would help people at this time?	* Development of an appropriately sensitive ADPKD specific questionnaire for assessing how ADPKD affects quality of life (QOL) including the physical and psychological stresses of living with the disease? * What are the best strategies to inform people with ADPKD that they have the disease? * What are the most relevant and effective educational programs and tools for ADPKD to support people with the disease? * What is the psychological impact of diagnosis of ADPKD at an early age? * How can peer-to-peer support networks and youth counsellors best support children and adolescents with ADPKD? * What are the best communication tools to support children and adolescents with ADPKD? * What is the impact of psychological factors including anxiety and depressions on people with ADPKD, and what methods are best to measure and manage these factors? * Development of validated tools and / or strategies to measure the psychological impact of ADPKD.		Autosomal Dominant Polycystic Kidney Disease (ADPKD): Report from a Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference
9	What are the benefits and harms of screening for and diagnosing ADPKD in children and young people (up to 18 years) at risk of having inherited this condition?	* What are the benefits and harms of early screening for ADPKD?	Marlais M, Cuthell O, Langan D, et al Hypertension in autosomal dominant polycystic kidney disease: a meta-analysis Archives of Disease in Childhood 2016;101:1142-1147. http://dx.doi.org/10.1136/archdischild-2015-310221	Autosomal Dominant Polycystic Kidney Disease (ADPKD): Report from a Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference

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10	What causes enlarged blood vessels (aneurysms) in some people with ADPKD and what is the most effective way to screen for and treat aneurysms?	* What is the natural history, including gene mutation, of intracranial aneurysm in people with ADPKD? * Development of a decision strategy addressing cost, safety and efficacy of magnetic resonance angiography (MRA) screening, for intracranial aneurysm in people with ADPKD, and for therapeutic approaches. * Which anti-hypertensive therapy is most effective for the prevention of intracranial aneurysm (ICA) in people with ADPKD? * Is systematic screening for intracranial aneurysm effective and efficient, in people with ADPKD, undergoing pre-transplant evaluation or major surgery? * Which therapeutic interventions including endovascular coiling are most effective for intracranial aneurysm in people with ADPKD, and how do the morbidity and mortality rates compare in the ADPKD and non-ADPKD population? * In children and young people with ADPKD what is the incidence of sub-arachnoid haemorrhage and the prevalence of intracranial aneurysm? * In adults, children and young people with ADPKD with a family history of intracranial aneurysm or sub-arachnoid haemorrhage does Intracranial Magnetic Resonance (MR) imaging reduce the risk of intracranial events?	Cagnazzo, F., Gambacciani, C., Morganti, R. et al. Intracranial aneurysms in patients with autosomal dominant polycystic kidney disease: prevalence, risk of rupture, and management. A systematic review. Acta Neurochir 159, 811–821 (2017). https://doi.org/10.1007/s00701-017-3142-z ~ Zhou Z.a · Xu Y.b, c · Delcourt C.b, d · Shan J.e · Li Q.b · Xu J.a · Hackett M.L.b, c (2017) Is Regular Screening for Intracranial Aneurysm Necessary in Patients with Autosomal Dominant Polycystic Kidney Disease? A Systematic Review and Meta-analysis. Cerebrovasc Dis 44:75-82 https://doi.org/10.1159/000476073	2 x RR and KDIGO
11 - 17				

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11	What symptoms are associated with cyst infection in people with ADPKD, and how are cyst infections best managed (investigated and treated)?	* Development of an evidence-based algorithm to guide evaluation and treatment of renal cyst infection. * What is the value of fluorodeoxyglucose positron emission tomography (FDG-PET) and biomarkers, for people with ADPKD, to support the diagnosis and management of renal cyst infection? * What is the most effective route of administration and optimal duration of antibiotics for the treatment of renal cyst infection in people with ADPKD? * What are the indications for and value of cyst drainage for the treatment of renal cyst infection in people with ADPKD? * Development of diagnostic criteria for polycystic liver disease cyst infection in people with ADPKD. * What are the risk factors, in people with ADPKD, of polycystic liver disease cyst infection? * What is the optimal duration of antibiotic treatment for polycystic kidney disease cyst infection, in people with ADPKD, and what is the risk of relapse/recurrence of cyst infection? * How effective is penetration of the newer antibiotics into cyst fluid for the treatment of polycystic liver disease cyst infection in people with ADPKD?	Marten A. Lantinga, Niek F. Casteleijn, Alix Geudens, Ruud G.L. de Sévaux, Sander van Assen, Anna M. Leliveld, Ron T. Gansevoort, Joost P.H. Drenth, on behalf of the DIPAK Consortium, Management of renal cyst infection in patients with autosomal dominant	Autosomal Dominant Polycystic Kidney Disease (ADPKD): Report from a Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference
12	What causes severe (acute) and long-term (chronic) kidney pain in people with ADPKD?	* What is the pathogenesis of chronic kidney pain in people with ADPKD?		Autosomal Dominant Polycystic Kidney Disease (ADPKD): Report from a Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference
13	What are the most effective treatments for high blood pressure (hypertension) for people (children and adults) with ADPKD?	* Which antihypertensive agents are most effective for hypertension in people with ADPKD? * Development of strategies to define second-line treatment agents for the management of hypertension in people with ADPKD. * What is the efficacy of aldosterone antagonists for the management of hypertension in people with ADPKD? * What is the impact, in people with ADPKD, of blood pressure control on kidney function?		Autosomal Dominant Polycystic Kidney Disease (ADPKD): Report from a Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference

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14	In which circumstances should removal of a kidney (known as nephrectomy) be considered in people with ADPKD, and are there alternative treatments?	* What are the indications and best timing for nephrectomy and transplantation; pre-transplant compared with simultaneous compared with post, for people with ADPKD? * What alternative strategies are there to nephrectomy, for volume space restriction in people with ADPKD, including embolization and laparoscopy? * C18 What is the impact of unilateral nephrectomy on residual kidney function in people with ADPKD?	Taking organ transplantation to 2020: A UK Strategy	Autosomal Dominant Polycystic Kidney Disease (ADPKD): Report from a Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference
15	Does early treatment of high blood pressure improve the long-term health of people with ADPKD and/or reduce the risk of thickened heart walls (left ventricular hypertrophy)?	* How effective are Angiotensin converting enzyme inhibitors (ACEi) compared to Angiotensin Receptor Blockers (ARB), in people with ADPKD, for first-line treatment of blood pressure control? * What is the benefit of low blood pressure targets in people with early stage ADPKD or with left ventricular hypertrophy? * What are the benefits and harms of formal screening for hypertension in children with ADPKD; when benefits outweigh harms; at what age should screening be started in and what is the recommended frequency of screening? * What are the benefits and harms of detecting and treating prehypertension (BP 90-95th or even 75-95th percentile) in children with ADPKD?		Autosomal Dominant Polycystic Kidney Disease (ADPKD): Report from a Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference
16	When a person is found to have kidney cysts but they do not have a family history of ADPKD, what tests should be performed to confirm their diagnosis and check for ADPKD?	* Development of a diagnostic algorithm for ADPKD, in newborns, children and adults without a family history of the disease.		Autosomal Dominant Polycystic Kidney Disease (ADPKD): Report from a Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference
17	Why do the symptoms and severity of polycystic liver disease (PLD) vary between people?	* How does liver size, in people with ADPKD, correlate with the symptoms of Polycystic liver disease and quality of life? * What are the effects of hormonal therapies including low-dose oral contraceptives, topical estrogens and hormonal replacement therapy on liver cyst growth in people with ADPKD?		Autosomal Dominant Polycystic Kidney Disease (ADPKD): Report from a Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference
18-35 (additional indicative (summary) questions not ranked)				

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	How does ADPKD affect children and young people (up to 18 yrs), including those who might not have symptoms (e.g. those diagnosed based on an ultrasound of their kidneys or genetic test)?	* What is the natural progression of ADPKD in children including sub-groups identified by for example mutation screening and / or total kidney volume?		Autosomal Dominant Polycystic Kidney Disease (ADPKD): Report from a Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference
	What are the benefits and harms of treating high cholesterol and/or high uric acid (known as hyperuricemia) in people with ADPKD?	* What are the benefits and harms of treating hyperlipidaemia and / or hyperuricemia in people with ADPKD?		Autosomal Dominant Polycystic Kidney Disease (ADPKD): Report from a Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference
	How common is it for people with ADPKD to have blood in their urine and how should this be assessed and treated according to severity and complications?	* Development of a classification system to support categorisation of cyst haemorrhage in people with ADPKD. * Development of a classification system to support categorisation of gross haematuria in people with ADPKD. * What is the prevalence, significance and evaluation of microscopic haematuria in people with ADPKD? * What is the role of tranexamic acid to treat haemorrhagic complications in people with ADPKD?		Autosomal Dominant Polycystic Kidney Disease (ADPKD): Report from a Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference
	In people with ADPKD, do kidney stones increase the risk of kidney function decline?	* Does nephrolithiasis, in people with ADPKD, increase the risk of renal function decline?		Autosomal Dominant Polycystic Kidney Disease (ADPKD): Report from a Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference
	If a woman with ADPKD is pregnant, what effect does her condition have on her child before birth?	* What effect does pregnancy have on fetal outcomes in women with ADPKD including the intrauterine environment on disease severity?		Autosomal Dominant Polycystic Kidney Disease (ADPKD): Report from a Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference

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	What information resources are required to support family planning for people with ADPKD?	* What are the attitudes and awareness, of people with ADPKD and physicians, on Preimplantation Genetic Diagnosis (PGD)? * What are the barriers to accessing Preimplantation Genetic Diagnosis (PGD) within the ADPKD community? * What are the best strategies to ensure people with ADPKD are educated to recognise the extrarenal manifestations of ADPKD? * Development of an evidence-based family planning guide, for people with ADPKD, including Information relating to genetics and preimplantation genetic diagnosis (PGD) / in vitro fertilization (IVF).		Autosomal Dominant Polycystic Kidney Disease (ADPKD): Report from a Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference
	For women with polycystic liver disease (PLD), does using oral contraceptives to prevent pregnancy or hormone replacement therapy (HRT) to treat the menopause affect their PLD?	* What is the impact of hormones including oral contraceptives, hormone replacement therapy and non-estrogen based contraceptives on people with polycystic liver disease?		Autosomal Dominant Polycystic Kidney Disease (ADPKD): Report from a Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference
	How does social inequality affect long term outcomes in people with ADPKD?	* How does social inequality effect individuals with ADPKD?		Autosomal Dominant Polycystic Kidney Disease (ADPKD): Report from a Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference
	When researching ADPKD, including new treatments, what measurements such as kidney size, kidney function, quality of life and other side effects reported by patients themselves be used?	* Development of globally accepted patient-reported outcome measures for ADPKD. * Identification and validation of new endpoints for ADPKD research such as thresholds for clinically meaningful changes in kidney function or the assessment of patient-reported outcomes. * Development of early disease biomarkers to facilitate clinical trials in ADPKD.		2 x RR and KDIGO
	How can healthcare practitioners recognise the need for and provide a holistic approach to the care of people with ADPKD and family members?	* What are the best strategies to ensure physicians are trained to recognise and manage the extrarenal manifestations of ADPKD? * How can healthcare practitioners be supported to recognise and manage the psychological, functional and economic effects of ADPKD on patients and their relatives and ensure that procedures are in place to assess these effects routinely during consultations?		1 x RR and KDIGO

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	Are people with ADPKD and kidney failure who are receiving peritoneal dialysis more likely to suffer complications or failure of this treatment than people without ADPKD?	* What are the risk factors for peritoneal dialysis (PD) complications and failure in people with ADPKD based on history and total kidney volume / total liver volume, size and abdominal cavity volume?		Autosomal Dominant Polycystic Kidney Disease (ADPKD): Report from a Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference
	What are the risks of complications of kidney transplantation in people with ADPKD (during transplantation and in the long term) compared to patients without ADPKD?	* What are the complications of kidney transplant and the impact of these complications on long-term outcomes in people with ADPKD, and how does this compare to non-ADPKD?	Taking organ transplantation to 2020: A UK Strategy	Autosomal Dominant Polycystic Kidney Disease (ADPKD): Report from a Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference
	What proportion of people with ADPKD and kidney failure develop kidney cancer, and what tests and care should patients with signs of kidney cancer receive?	* What is the incidence of renal cell carcinoma in dialysis and transplant patients with ADPKD? * What is the optimal management of suspicious renal cell carcinoma lesions in people with ADPKD?		Autosomal Dominant Polycystic Kidney Disease (ADPKD): Report from a Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference
	For people receiving medicines to reduce the risk of a blood clot during dialysis or transplantation, what is the risk of having blood in the urine and what problems can this cause?	* What is the incidence and severity of kidney related bleeding complications in people with ADPKD receiving systemic anticoagulation on dialysis and transplantation?		Autosomal Dominant Polycystic Kidney Disease (ADPKD): Report from a Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference

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	How can other measures of kidney structure and function be used alongside commonly used measures such as kidney length or total kidney volume to monitor disease progression in people without symptoms or with early stage ADPKD?	* How do specific volumes (cyst, parenchyma, intermediate) and cyst patterns (number, distribution, complexity, etc.) add to the value of total kidney volume (TKV) for monitoring progression of ADPKD? * Under what conditions is total kidney volume (TKV) a relevant study endpoint for early stage ADPKD? * How does the assessment of available total kidney volume (TKV) rendering from clinically obtained renal images by Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and Ultrasonography (US) support monitoring of ADPKD progression? * Which methods are best to measure functional nephron mass or renal reserve capacity to assess renal outcomes especially in early stage ADPKD? * What is the association, in people with ADPKD, between kidney-volume growth and renal function? * What is the correlation between the estimated-glomerular filtration rate (eGFR) and total kidney volume (TKV) in people with subclinical ADPKD (ie, eGFR >90 mL/min/1.73 m²)? * TKV has been the primary endpoint in recent clinical trials but its value as a surrogate variable for renal function has been debated. The decline in eGFR in adults with ADPKD (as seen in control groups in some studies averaged 2.3–3.7 mL/min/1.73 m² per year, whereas the maximum statistically significant gain in renal function was 1.0 mL/min/1.73 m² per year. * Apparently small benefits can translate into a meaningful	Marcos Wolf, Anneloes de Boer, Kanishka Sharma, Peter Boor, Tim Leiner, Gere Sunder-Plassmann, Ewald Moser, Anna Caroli, Neil Peter Jerome, Magnetic resonance imaging T1- and T2-mapping to assess renal structure and function: a systematic review and state	Autosomal Dominant Polycystic Kidney Disease (ADPKD): Report from a Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference
	Can assessment of the way the blood is flowing through the kidney be used to see how much a person's ADPKD has progressed (i.e. how much damage it has caused to the kidney)?	* How reliable is renal blood flow (RBF) measured by magnetic resonance imaging (MRI) to monitor disease progression in people with ADPKD? * Would the standardization of renal blood flow (RBF) measurements support better monitoring of disease progression in people with ADPKD?		Autosomal Dominant Polycystic Kidney Disease (ADPKD): Report from a Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference

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	How useful is assessment of glomerular filtration rate (GFR is a way to measure kidney function) in the early stages of ADPKD?	* What is natural history of Glomerular filtration rate (GFR) during the course of ADPKD; is there a phase of hyperfiltration and when does GFR start declining? * Under which conditions is measured Glomerular filtration rate (mGFR) versus estimated Glomerular filtration rate (eGFR) superior in clinical trials of people with ADPKD * Is there an added value of eGFR equations using cystatin C measurement?		Autosomal Dominant Polycystic Kidney Disease (ADPKD): Report from a Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference
	Is measuring levels of protein in a person's urine helpful for assessing how far their ADPKD has progressed?	* What is the source and pathogenesis of proteinuria and albuminuria in people with ADPKD? * What is the value of monitoring proteinuria and / or albuminuria, in people with ADPKD, as a response to therapeutic interventions, and are these measurements useful as secondary outcomes in clinical trials? * What is the diagnostic and prognostic value of proteomic and metabolomics signatures in people with ADPKD? * In children and young people with ADPKD does regular, for example yearly or every 2 years, urine albumin:creatinine monitoring and treatment improve outcome?		1x RR and KDIGO