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Cho, Y., Tong, A., Craig, J.C. et al. (28 more authors) (2021) Establishing a core outcome set for autosomal dominant polycystic kidney disease : report of the Standardized Outcomes in Nephrology–Polycystic Kidney Disease (SONG-PKD) consensus workshop. American Journal of Kidney Diseases, 77 (2). pp. 255-263. ISSN 0272-6386

https://doi.org/10.1053/j.ajkd.2020.05.024

Establishing a Core Outcome Set for Autosomal Dominant Polycystic Kidney Disease: Report of the Standardized Outcomes in Nephrology – Polycystic Kidney Disease (SONG-PKD) Consensus Workshop

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Manuscript Word Count: 3271

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Key words:

Polycystic kidney disease

Core outcome set

Patient-important outcomes

Outcomes

Trials

ABSTRACT

The omission of outcomes that are of relevance to patients, clinicians and regulators across trials in autosomal dominant polycystic kidney disease (ADPKD) limits shared decision-making. The Standardized Outcomes in Nephrology – Polycystic Kidney Disease (SONG-PKD) Initiative convened an international consensus workshop on 25th October 2018, to discuss the identification and implementation of a potential core outcome set for all ADPKD trials. This article summarizes the discussion from the workshops and the SONG-PKD core outcome set. Key stakeholders including 11 patients/caregivers and 47 health professionals (nephrologists, policymakers, industry and researchers) attended the workshop. Four themes emerged: *Relevance of trajectory and impact of kidney function* included concerns about a patient's prognosis and uncertainty of when they may need to commence kidney replacement therapy, and the lack of an early prognostic marker to inform long-term decisions; *Discerning and defining pain specific to ADPKD* highlighted the challenges in determining the origin of pain, adapting to the chronicity and repeated episodes of pain, the need to place emphasis on pain management and to have a validated measure for pain; *Highlighting ADPKD consequences* encompassed cyst-related complications and reflected patient's knowledge because of family history and the hereditary nature of ADPKD; *Risk of life-threatening but rare consequences* such as cerebral aneurysm meant considering both frequency and severity of the outcome. Kidney function, mortality, cardiovascular disease and pain were established as the core outcomes for ADPKD.

BACKGROUND

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited cause of kidney failure, and is associated with an increased risk of mortality, cardiovascular disease, and stroke from ruptured cerebral aneurysms[1,2]. Patients with ADPKD have enlarging cysts involving the kidneys and often the liver, which can increase the weight of these organs by up to 20kg, leading to debilitating pain and impaired quality of life[3,4]. It is estimated that 50% of patients with ADPKD require kidney replacement therapy by the age of 70 years[5,6]. Patients have reported anxiety in seeing the impact of ADPKD on family members and having to confront disease progression and need for kidney replacement therapy[2,7-9].

Patients with ADPKD value outcomes that enable a "normal" lifestyle, including preservation of kidney function to avoid kidney replacement therapy, ability to work, maintenance of physical function, survival and minimization of pain[7,9]. However, these patient-important outcomes are reported in less than 20% of trials in ADPKD. The need for kidney replacement therapy and mortality were reported in only 13% and 9% of trials, respectively[10-17]. Moreover, cyst-related pain, which has been shown to be the most important patient-reported outcome to patients/caregivers[9], was only reported in 22% of ADPKD trials[17].

Despite the impact that ADPKD has on patients' abilities to work, physical function, mental health, and quality of life, patient-reported outcomes (PROs) are frequently omitted from trial reports. When they are reported, the measures used vary widely. For example, cyst pain had 25 measures among 14 trials[17]. This makes it difficult to compare the effect of interventions

across trials. While there is increasing recognition and use of PROs in clinical trials, with regulators, including the U.S. Food and Drug Administration (FDA) recommending their inclusion in clinical research[18,19], the selection and reporting of PROs for trials in ADPKD remain infrequent and inconsistent.

In response to these problems with outcome reporting, the Standardized Outcomes in Nephrology (SONG) Initiative was established to develop core outcome sets that are critically important to all stakeholders including patients, caregivers and health professionals, to ensure trials consistently report critically important outcomes[20-22]. The core outcomes are identified through a transparent consensus process based upon the Core Outcome Measures Effectiveness Trials (COMET) and Outcome Measures in Rheumatology (OMERACT) framework[21]. A core outcome set is defined as an agreed minimum set of standardized outcomes that must be measured and reported in all trials in a defined clinical population[23]. Researchers can add other outcomes that are relevant and important to the trial.

The SONG-PKD initiative commenced in 2017 to develop a core outcome set to be reported in all trials in people with ADPKD[9,24]. We convened a stakeholder workshop to review and discuss proposed core outcome domains identified through a multi-stage process involving a systematic review, focus groups with nominal group technique, and an international Delphi Survey[9,24,25]. This report provides a summary of the discussions and input from the workshop contributors and includes the agreed SONG-PKD core outcome set.

SONG-PKD CONSENSUS WORKSHOP

Overview and context

The SONG-PKD consensus workshop was convened to elicit stakeholder perspectives on the potential core outcome set for ADPKD. The proposed core outcomes were identified based upon interim results of an international, online, two-round Delphi survey that was completed by patients, caregivers and health professionals with experience or expertise in ADPKD[25]. From the Delphi survey of 603 patients/caregivers and 411 health professionals from 56 countries (in which the importance of each outcome was rated using a 9-point Likert Scale), we identified outcomes with mean and median scores ≥7 and those with ≥70% of the participants in both stakeholder groups (patients/caregivers and health professionals) rating the outcome to be of critical importance (7-9). The proposed core outcomes presented at the workshop were: kidney function, end-stage kidney disease (ESKD, defined as need for kidney replacement therapy), kidney cyst size/growth, cerebral aneurysm, blood pressure, death, cardiovascular disease, kidney cyst pain/bleeding/infection, life participation and chronic pain. The detailed analysis and final results of the Delphi will be published separately[25].

Participants and contributors

Patients with ADPKD, their caregivers and health professionals from a broad range of geographical practice locations, clinical and research experience, policy and industry were invited to attend the workshop. Patients/caregivers who attended the workshop received reimbursement for travel expenses.

In total, 58 participants (11 patients/caregivers and 47 health professionals) attended the workshop. Patients/caregivers were from the United States (n=11). Health professionals were from 10 countries including the United States (n=19), Australia (n=14), Republic of Korea (n=4), United Kingdom (n=3), Canada (n=2), Germany (n=1), Netherlands (n=1), New Zealand (n=1), Spain (n=1) and Taiwan (n=1). Workshop contributors (n=53 from 13 countries) were patients/caregivers and health professionals who provided feedback on the pre-workshop materials and preliminary report but were unable to attend the workshop in person. Health professionals were from diverse backgrounds and collectively represented knowledge and experience in clinical nephrology, genetics and research (basic science, clinical research, epidemiology, clinical trials, implementation research) in ADPKD. Some participants held leadership or advisory positions in national and international professional societies (e.g. International Society of Nephrology), research, policy, regulatory, funding, industry and consumer organizations, including the US Food and Drug Administration (FDA), National Institutes of Health (NIH), Kidney Disease: Improving Global Outcomes (KDIGO), National Health Service (NHS), and the PKD Foundation.

Workshop Program and Materials

The workshop was held on October 25, 2018, at a hotel function room in San Diego, California, USA. This coincided with the American Society of Nephrology's Kidney Week Annual Conference 2018 to maximize attendance. The workshop program and materials, including interim results from the Delphi survey, were distributed to all participants one week in advance. During the workshop, an overview of the SONG-PKD process, preliminary results from interim analysis of the Delphi survey and a list of potential core outcomes were

presented. Participants were allocated to one of seven breakout groups, which included at least one patient/caregiver and varying representation of health professionals (according to geographical practice location, field of expertise, industry, policy, funder) with up to ten members to foster depth and breadth in the scope of discussion. Facilitators (A.T., T.G., J.S., J.C., G.R., A.V., Y.C) attended a briefing session and were provided with a question guide (Supplementary File 1) prior to the workshop.

During the breakout discussion, facilitators asked participants to reflect and comment on the potential core outcomes identified in the SONG-PKD Delphi survey. Three to five core outcome domains were recommended as a core outcome set to ensure feasibility, and had to include at least one patient-reported outcome domain[20]. Therefore, we included questions about combining clinical outcomes (kidney function, ESKD, cerebral aneurysm, cardiovascular disease, cyst bleeding/infection/growth) and selection of PROs (cyst-related pain or chronic pain). At the conclusion of the breakout discussion, the Chair (G.R.) asked the nominated speaker from each group to provide a summary of their discussion.

All breakout and plenary discussions were audiotaped and transcribed verbatim. Transcripts were entered into HyperRESEARCH (ResearchWare Inc, version 3.0) to enable coding and analysis of the data. Y.C. identified and coded concepts into themes, and the preliminary findings were discussed among the investigative team (A.T., B.S., C.L.) to ensure they reflected the range of perspectives on the core outcome domains for ADPKD.

SUMMARY OF WORKSHOP DISCUSSION

Overview

Based on discussion from the workshop, four themes relating to the identification of the core outcome and consideration for implementation in ADPKD were identified. Selected quotations supporting each theme are provided in Box 1. Figure 1 shows the SONG-PKD core outcome domains. Box 2 provides a summary of recommendations based on the workshop discussions.

Relevance of trajectory and impact of kidney function

Deliberating between the journey and destination: Workshop participants confirmed that kidney function was of top priority because it was seen as a signal of disease progression and projected onset of kidney failure, requiring kidney replacement therapy. Patients mentioned that the need for kidney replacement therapy (in particular dialysis) was ultimately the worst outcome that they feared. They wanted to "put off [dialysis] as long as possible because… that would be a big change of life" and "represented loss of hope." Moreover, participants agreed that "decline in kidney function," expressed as a downward slope of trajectory, was much more powerful in informing anticipated onset of dialysis, rather than a snapshot of kidney function.

Lacking a practical early marker for progression: Some health professionals were concerned about delayed manifestation of clinically evident decline in kidney function and emphasized the importance of "kidney volume change" as early "evidence that the disease is changing."

They noted that this was particularly relevant because of the increasing availability of disease modifying medications. Regional variation in practice with regards to monitoring kidney size using imaging was evident, ranging from a lack of monitoring in Australia and New Zealand, to a broad range of routine radiology investigations in the USA. However, participants agreed that the relevance of kidney size or volume "depended on the stage of kidney disease" and expressed uncertainty about the feasibility of implementing measurement of kidney size/volume in all trials in ADPKD globally (considering practicality, cost, time burden) as clinicians "wouldn't want to have a patient be assessed with imaging for every study."

Discerning and defining pain specific to ADPKD

Indistinguishable and unpredictable: Participants reflected on the high priority given to pain-related outcomes in the results of the Delphi survey[25], including chronic pain and cyst pain related to cyst growth, bleeding and infection. Participants agreed it was "impossible to distinguish between different sources of pain," and often patients and healthcare providers "don't understand why there is pain," particularly for chronic pain. One patient explained that they suffered from "back pain… that might be kidney related, but it's actually back pain." Because the source of pain is often poorly understood (particularly for chronic pain), participants proposed that "pain" should be a core outcome domain as it was difficult to ascertain if pain originated from the "cysts."

Adaptation to new threshold: The chronicity and repeated episodes of pain meant that some patients "get used to it and say oh, it's just discomfort, it's not really pain." They acknowledged the profound and broader consequences of pain on the patients' functioning and daily activities, "the pain ends up having so many downstream effects on active, daily

living like ability to work, ability to do so many things," and therefore "captures a lot more than just pain."

Bringing pain to prominence: Health professionals acknowledged that pain was often under-recognized and inadequately managed because "there aren't very good treatments for pain, and so they [patients] kind of give up mentioning it because it's futile." They remarked that the limited time available for consultation was focussed on other clinical priorities, such as blood pressure, even though pain has significant impact on functional capacity. Although patients wanted to enjoy life free of pain, they were often reluctant to discuss pain because they thought they were "going to be treated differently" among their social or professional network.

Need for a consistent and validated measure: Although pain was regarded as a critically important outcome, participants felt it would be challenging to "capture it" in a way to accurately identify source and severity. They noted the lack of a validated tool with "good metrics about how to categorize and specify pain," and suggested the need for a validated measure for pain in patients with ADPKD.

Highlighting ADPKD consequences

Complications of cyst growth: Participants considered whether kidney cyst infection, bleeding and cyst growth should be 'core outcome domains.' Some patients with "huge cysts" did not consider "growth" to be "important" as it did not affect their "daily life" whereas other cyst-related complications, such as "infection," were critical because "it almost killed me [patient]." Other participants considered "cyst infection and cyst bleeding…[to

be] ..not necessarily important every time." Some health professionals focused on complications such as bleeding and infection as they were "all linked to cyst size and growth."

Heightened realization because of family history and hereditary nature: Health professionals commented that the priorities of patients with ADPKD from the Delphi survey appeared different compared to those of patients with chronic kidney disease from other causes. They remarked that patients with ADPKD seemed to be "incredibly well-informed…," possibly influenced by the familial nature of ADPKD where "a lot of it has gone on for generations." For example, "most people with polycystic kidneys have had experience with dialysis from a family member, whereas people who have other forms of kidney disease don't actually know what's going to happen to them, so they're not quite so aware of all the issues and limitations that dialysis brings." Patients supported including cardiovascular disease and mortality in the core outcome set because they were worried that their children would be at risk of premature death from cardiovascular disease and kidney failure.

<u>Risk of life-threatening but rare consequences</u>

Trying to make connections between outcomes: Participants discussed whether cerebral aneurysm should be captured within the outcome domain of cardiovascular disease. Health professionals strongly opposed combining cerebral aneurysm and cardiovascular disease as they were regarded as "a separate entity" driven by "different biologies." Moreover, "the typical cardiovascular protection doesn't come with the aneurysm protection" whereas they could easily accept that "cardiovascular disease [I can see] is linked to hypertension." Cardiovascular disease was considered by participants as relevant to "kidney disease of any

sort, whether it's ADPKD or diabetic kidney disease" and closely related to "progression of [kidney] disease."

Uncommon occurrence of cerebral aneurysm: Cerebral aneurysm was an outcome "patients care a lot about" and feared because "when it happens it's devastating." Some patients from the workshop were surprised at the high prioritization in the Delphi survey because it reflected "existential fear" that they have not experienced personally or through "family history." Health professionals, particularly researchers were hesitant about including cerebral aneurysm as a core outcome because it was a "very, very, very rare event," and therefore not of critical importance to all ADPKD patients.

POST-WORKSHOP CONSULTATION

All workshop participants, including non-attending contributors, were provided with the draft workshop report for comment and approval. The SONG-PKD core outcome set (Figure 1) was reviewed by all participants, and was uploaded on the SONG website for feedback and comment (https://songiniative.org/projects/song-pkd/). We incorporated the feedback received into the final report.

DISCUSSION

Patients with ADPKD, their caregivers and health professionals who contributed to this workshop report agreed that a core outcome set for ADPKD should include kidney function, mortality, pain and cardiovascular disease, based on their importance to decision-making. Kidney function was the foremost priority for all stakeholders, because it indicated the

potential need for kidney replacement therapy, the most feared consequence among patients with ADPKD. As such, patients with ADPKD preferred kidney function to be described as a change in function over time to estimate when they may need to commence dialysis. Mortality and cardiovascular disease were deemed acceptable as core outcome domains by participants due to their frequency, devastating consequence and direct relevance to all patients with ADPKD.

In the Delphi survey[25], outcomes related to pain, including cyst pain from growth, bleeding, infection and chronic pain, were highly prioritized due to their impact on life participation (e.g. ability to work, activities of daily living). The under-recognition of the chronicity of pain from ADPKD and a lack of effective treatment options in clinical settings were emphasized. All stakeholder groups agreed that pain was of central importance but were uncertain about identifying the source of pain. Hence, the participants recommended to change 'cyst pain' to 'pain' to be included as a core outcome domain. A recent study with patients and clinicians in the United States, Europe and Japan found that ADPKD-related pain was the most important outcome impacting physical functioning, with complex and distinctive presentations ranging from feeling full/discomfort to acute sharp pain. The Autosomal Dominant Polycystic Kidney Disease Impact Scale (ADPKD-IS), is a measure that was developed to assess the impact of ADPKD on health-related quality of life, and examines the overall symptom burden[26]. Although the ADPKD-IS includes questions specific to ADPKD-related pain, the investigators recommended further evaluation due to the complexity of pain. The workshop contributors also indicated the need for valid and relevant measure to assess pain in ADPKD.

Kidney cyst size/volume was debated because of differences in practice patterns across regions whereby monitoring of kidney size was routine in the United States, and in other countries it was either not routinely done or not available. This was challenging because total kidney volume (TKV) is a prognostic biomarker for use in clinical trials for ADPKD recently qualified by the FDA[27] and the European Medicines Agency (EMA), and use of tolvaptan was approved based on changes in TKV by the FDA, Health Canada and the Pharmaceuticals and Medical Devices Agency of Japan[28]. However, because its main applicability being limited to stages of ADPKD prior to decline in kidney function and recognition that it would not be necessary to mandate its measurement in all ADPKD trials, it was not included as part of the core outcome set, and instead was positioned in the middle tier of the core outcome set (Figure 1). Similarly, rupture of cerebral aneurysm was considered important but not universally relevant due to infrequent occurrence and therefore was not included as part of the core outcome set.

The discussions from this workshop were used to establish the core outcome domains to be reported in trials in patients with ADPKD (Figure 1). Although the workshop involved 111 collaborators from 17 countries, only US patients/caregivers participated in the in-person workshop, which may limit generalizability of findings. The next step will be to develop the core outcome measures for each of these outcome domains informed by the recommendations from this workshop (Box 2). For the patient-reported outcome of pain, we will follow the Consensus-based Standards for the selection of Health Measurement Instruments-Core Outcome Measures in Effectiveness Trials (COSMIN-COMET) process[29,30]. This will involve systematic reviews and consensus workshops with patients with ADPKD, their caregivers and health professionals to ensure content validity of the measure. Pilot and validations studies will follow to ensure that the measure is appropriate,

psychometrically robust and feasible to be implemented in patients with ADPKD. Implementation of core outcomes in addition to outcomes of interest to study investigators in ADPKD trials is expected to enhance shared decision making for patients and health professionals, and ultimately improve outcomes that are critically important to patients with ADPKD and those involved in their care.

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Support YC is supported by a National Health and Medical Research Council (NHMRC) Early Career Fellowship (APP1126256). AT is supported by a NHMRC Fellowship

(APP11067716). KEM is supported by a NHMRC Postgraduate Scholarship (APP1151343). DWJ is supported by a NHMRC Practitioner Fellowship (APP1117534). The study was financially supported by a grant from Polycystic Kidney Disease Foundation of Australia. The funders or affiliated institutions played no role in study design; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication.

Financial Disclosure BC is an employee of Fresenius medical Care; DOb and MT are employees of Ostsuka. FT and MK are employees of Davita. FC is an employee of Goldfinch Bio. The other authors declare that they have no relevant financial interests.

Acknowledgements We acknowledge, with permission, all the attendees listed below who attended the consensus workshop. Aliza Thompson, Allison Tong, Andrea Viecelli, Andrew Mallet, Angela Ju, Ankit Sharma, Annie-Claire Nadeau-Fredette, Arlene Chapman, Carmel Hawley, Carol Pollock, Charlotte Logeman, Chia-Ter Chao, Curie Ahn, Eric Au, David Baron, David Clark, David Johnson, Donal O'Donoghue, Dorien Peters, Dorothee Oberdhan, Dwight Odland, Elizabeth King, Francis Vickers, Frank Czerwiec, Frederic Rhabari Oskoui, Gopi Rangan, Gregory Germino, Hyunjin Ryu, Hayne Park, Jean Odland, Jenny Shen, Jonathan C Craig, Kai-Uwe Eckardt, Lisa Guay-Woodford, Lynore Lee, Marie Hogan, Marvin Vickers, Mary Johnston-Clark, Michal Mrug, Michel Chonchol, Michelle Ta, Peter Harris, Pranav Garimella, Ragada El-Damanawi, Reem Mustafa, Robin Dorsey, Ron Perrone, Roser Torra, Samaya Anumudu, Suetonia Palmer, Susan Mendley, Talia Gutman, Terry Watnick, Thomas Hiemstra, Thomas Weimbs, Yeoungjee Cho, Yun kyu Oh, Zachary Baron

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Box 1. Selected quotations from the workshop discussions to illustrate each theme.

Theme	Quotations
Relevance of trajectory and impact of kidney function	
Deliberating between the journey and destination	"I think that kidney function overall would be more important, because that's what we're trying to prolong in the long fight against the disease, prolong our kidney function as long as possible." [G1, Patient] "End-stage kidney disease is, yeah, it's something I would like to put off as long as possible because I know that that would be a big change of life for me, from being active and working full time and doing the things that I do. Also all the things that can come with end-stage kidney disease, it's a scary thought when you watch somebody go through that and they lose their thought processes and their cognitive skills. You're like, I don't want to be that. It's scary." [G2, Patient]. "What that represents to me and what I hear patients tell me about is it represents loss of hope." [G2, Health Professional] "I think the point is not kidney function or ESKD, I think it's progression of decline." [G2, Health Professional]. "They don't want end-stage kidney disease but you can't get there unless you have decline in kidney function, so I think that the objective is to prevent the decline in kidney function which as a consequence will defer end-stage kidney disease." [G7, Health Professional].
Lacking a practical early marker for progression	"I think it's unique evidence that we have in this kidney disease, how kidney volume changes and size changes. We don't have this ability to do in any of the kidney diseases, this is primary evidence that the disease is changing, that we have a modifying disease drug." [G1, Health Professional]. "I think it also depends on the stage of kidney disease, because I think the kidney size is more important in younger patients where renal function isn't really indicative of progression, whereas in the late stage you might get away with just using renal function." [G1, Health Professional]. "we wouldn't want to have a patient be assessed with imaging for every study. It was decided that perhaps it should be an important outcome but kept to the second level of the outcomes." [G2, Health Professional].
Discerning and defining pain specific to ADPKD	
Indistinguishable and unpredictable	"..often the pain occurs really early on so when patients are still teenagers, when the kidneys are quite small relatively speaking still. We don't understand why there is pain." [G2, Health Professional] "…there's really several different types of pain and pain – not even kidney pain, because it's the other organs that are getting smushed." [G2, Health Professional]. "..I think a lot of people cannot specify if it's from the cyst or if it's from the lower back." [G4, Health Professional]. "Back pain because of changes in body center of gravity. That might be kidney related, but it's actually back pain." [G7, Health Professional].
Adaptation to new threshold	"I may have pain, but it's something I live with everyday so it's not something that I can't handle. Whereas someone that just had it, it would probably be something life-changing for them that they wouldn't be able to deal with." [G2, Patient]. "Pain is a problem, and it's not just the pain. The pain ends up having so many downstream effects on active, daily living like ability to work, ability to do so many things. I think that captures a lot more than just pain." [G5, Health Professional] "Become used to it. You become used to it, so you don't think of it as pain." [G7, Patient]. "The early stages you may recognize something as painful and then get used to it and say oh, it's just discomfort, it's not really pain." [G7, Health Professional]
Bringing pain to prominence	"If someone finds that they have the disease process, they feel like they're going to be treated differently, that they have a deficit of some kind, like oh, they can't do that. They don't want people to know it." [G2, Health Professional] "They complain, and if they get dismissed then they learn how to manage what's going to get them the attention that they need, so pain will drop off the scale." [G2, Health Professional]

	"There aren't very good treatments for pain, and so they kind of give up mentioning it because it's futile and it takes up time in a consultation and the end result is always the same." [G2, Health Professional]
Need for a consistent and validated measure	"Pain is a really good outcome, a very important outcome. The challenge is how to capture it." [G2, Health Professional] "..pain was a very important domain, that it should be included in the core outcomes, but perhaps not only cyst pain or acute pain or chronic pain, but just pain as a global domain and then there should be a good measurement and toolkit to have good metrics about how to categorize and specify pain in studies." [G2, Health Professional]. "Pain is not a single entity but it's a constellation and has to be better addressed." [G5, Health Professional]
Highlighting ADPKD consequences	
Complications of cyst growth	"Just knowing what I've learnt over the years is that we don't see a lot of pain episodes in small kidneys, we don't see a lot of bleeding or infection, infection sometimes but… and they're all linked to cyst size and growth." [G1, Health Professional] "My personal opinion is that the cyst infection and cyst bleeding, that these are not necessarily important every time." [G4, Health Professional] "Speaking from a patient who has huge cysts and no symptoms, growth is not important to me. I know that it impacts function, but in my daily life? Doesn't matter. Infection definitely does because it almost killed me once already. Bleeding I've never had. I'm lucky." [G6, Patient]
Heightened realization because of family history and hereditary nature	"Because a lot of it has gone on for generations." [G1, Health Professional] "This list looks like a group of incredibly well-informed patients. They've been well-educated by their doctors to tell them that blood pressure is important, that cardiovascular disease is important, and dialysis is important, kidney function is important. It doesn't sound like 'how do I feel differently every day'. It's such a different patient group than other chronic kidney disease patients." [G1, Health Professional] ".. it's a scary thought when you watch somebody go through that and they lose their thought processes and their cognitive skills. I don't want to be that. It's scary." [G2, Patient] "..My sister is on dialysis." [G5, Patient] "..most people with polycystic kidneys have had experience with dialysis from a family member, whereas people who have other forms of kidney disease don't actually know what's going to happen to them, so they're not quite so aware of all the issues and limitations that dialysis brings. But a lot of patients that I see also worry about their children's future." [G7, Health Professional]
Risk of life-threatening but rare consequences	
Trying to make connection between outcomes	"..they're two quite different diseases and quite different biologies. Cardiovascular disease and cerebral aneurysm. I don't think that they should be collapsed together because collapsing them together, they have different interventions, different processes," [G3, Health Professional] "Cardiovascular disease in kidney disease of any sort, whether it's PKD or diabetic kidney disease, is usually a progression of disease and all your risk factors. You could have cerebral aneurysm without having significant kidney function decline." [G5, Health Professional]. "The typical cardiovascular protection doesn't come with the aneurysms protection." [G6, Health Professional] "…cardiovascular disease I can see is linked to hypertension." [G7, Health Professional]
Uncommon occurrence of cerebral aneurysm	"It's what every patient worries about, right? Because when it happens it's devastating, so people know about it a lot. It's not something that anyone in a trial would be focusing on, because it's not very common. It also requires fairly extensive imaging." [G1, Health Professional] "I was surprised that cerebral aneurysm, even though it's not top four, is up there. Because that seems sort of an existential fear that I certainly never had, maybe it's because our family history doesn't include it, but even for those families that do, they're, what, 6% maybe?" [G3, Patient] "aneurysm rupture is actually quite rare." [G3, Health Professional] "It's a very, very, very rare event. We don't screen for it." [G4, Health Professional]

Box 2. Key workshop recommendations for establishing and implementing core outcome domains for autosomal dominant polycystic kidney disease (ADPKD).

Core outcome domains for ADPKD should:
• Support ability to determine prognosis, particularly in terms of the need to commence kidney replacement therapy • Include clinical outcomes, such as cardiovascular disease, that have long-term implications to facilitate long-term planning • Be applicable for patients across all stages of kidney disease • Include outcomes that enable participation in daily activities and achievement of life goals, such as those related to study, work and family • Include pain in general terms (rather than ADPKD-pain) as it may not always be feasible to accurately identify the cause or source of pain
Implementation of core outcomes requires:
• Development of clinical measures that consider priorities of patients to support decision-making, particularly about kidney replacement therapy • Measures that can be feasibly implemented in health care and research settings internationally • Development of a standardized and validated patient-reported outcome measure to capture pain

Figure Legends

Figure 1. SONG-PKD core outcome domain shown as three circles representing the core outcomes (1), middle tier (2) and outer tier (3)