




CKJ REVIEW

Establishing a core outcome measure for pain in patients with autosomal dominant polycystic kidney disease: a consensus workshop report

Patrizia Natale^{1,2,3}, Ronald D. Perrone⁴, Allison Tong^{1,2}, Tess Harris⁵, Elyssa Hannan^{1,2}, Angela Ju^{1,2}, Eva Burnette⁶, Niek F. Gasteleijn⁷, Arlene Chapman⁸, Sarah Eastty⁶, Ron T. Gansevoort⁹, Marie Hogan¹⁰, Shigeo Horie^{11,12}, Bertrand Knebelmann¹³, Richard Lee¹⁴, Reem A. Mustafa¹⁵, Richard Sandford¹⁶, Amanda Baumgart^{1,2}, Jonathan C. Craig¹⁷, Gopala K. Rangan^{18,19}, Bénédicte Sautenet^{20,21}, Andrea K. Viecelli^{22,23}, Noa Amir ^{1,2}, Nicole Evangelidis^{1,2}, Chandana Guha^{1,2}, Charlotte Logeman^{1,2}, Karine Manera ^{1,2}, Andrea Matus Gonzalez^{1,2}, Martin Howell ^{1,2}, Giovanni F.M. Strippoli^{1,3} and Yeoungjee Cho^{22,23,24}

¹Sydney School of Public Health, University of Sydney, Sydney, NSW, Australia, ²Centre for Kidney Research, Children's Hospital at Westmead, Westmead, NSW, Australia, ³Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy, ⁴Medicine, Nephrology, Clinical and Translational Research Center, Tufts Medical Center and Tufts University School of Medicine, Boston, MA, USA, ⁵Polycystic Kidney Disease International, London, UK, ⁶London, UK, ⁷Department of Urology, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands, ⁸Department of Nephrology, University of Chicago, Chicago, IL, USA, ⁹Department of Nephrology, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands, ¹⁰Department of Internal Medicine, Division of Nephrology and Hypertension, Mayo Clinic, Rochester, NY, USA, ¹¹Department of Urology, Juntendo University Graduate School of Medicine, Tokyo, Japan, ¹²Department of Advanced Informatics for Genetic Diseases, Juntendo University Graduate School of Medicine, Tokyo, Japan, ¹³Service de Néphrologie, Université de Paris, APHP, Hôpital Universitaire Necker, Paris, France, ¹⁴Armidale, NSW, Sydney, Australia, ¹⁵Department of Internal Medicine, Division of Nephrology and Hypertension, University of Kansas Medical Centre, Kansas City, KS, USA, ¹⁶Academic Department of Medical Genetics, University of Cambridge, Cambridge, UK, ¹⁷College of Medicine and Public Health, Flinders University, Adelaide, SA, Australia, ¹⁸Centre for Transplant and Renal Research, Westmead Institute for Medical Research, University of Sydney, Sydney, NSW, Australia, ¹⁹Department of Renal Medicine, Westmead Hospital, Western Sydney Local Health District, Sydney, NSW, Australia, ²⁰Service de Néphrologie-Hypertension, Dialyses, Transplantation Rénale, Hôpital de Tours, Tours,

Received: 7.4.2021; Editorial decision: 14.6.2021

© The Author(s) 2021. Published by Oxford University Press on behalf of the ERA.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

France, ²¹Université de Tours, Université de Nantes, INSERM, SPHERE U1246, Tours, France, ²²Australasian Kidney Trials Network, University of Queensland, Brisbane, QLD, Australia, ²³Department of Nephrology, Princess Alexandra Hospital, Brisbane, QLD, Australia and ²⁴Translational Research Institute, Brisbane, QLD, Australia

Correspondence to: Patrizia Natale; E-mail: natale.patrizia@gmail.com

ABSTRACT

Background. Pain is the highest prioritized patient-reported outcome in people with autosomal dominant polycystic kidney disease (ADPKD) but remains infrequently and inconsistently measured in clinical trials and poorly managed in clinical settings. A recently completed systematic review of pain in ADPKD identified 26 different outcome measures. None of these measures were considered appropriate as a core outcome measure due to the lack of patient-important dimensions, inadequate content, relatively long duration of completion time and limited evidence to support psychometric robustness.

Methods. We convened an international Standardized Outcomes in Nephrology–Polycystic Kidney Disease consensus workshop involving 21 patients/caregivers and 40 health professionals (clinicians, nurses, researchers, policy makers and industry representatives) from 18 countries to discuss the identification or development of a core outcome measure for pain.

Results. Four themes were identified highlighting fundamental issues for the measurement of pain in ADPKD: distressing and disrupting life participation; variability and ambiguity in defining pain; stigma, frustration and adaptation to pain; and ensuring validity and feasibility of pain measures.

Conclusions. Existing measures were found to be insufficient in capturing pain as a core outcome and there was consensus on the need for a new validated measure that is simple, succinct and addresses the impact of pain on life participation. This measure will facilitate the appropriate prioritization of pain in all trials and guide clinical decision making in people with ADPKD.

Keywords: ADPKD, measure, pain, patient-reported outcomes, workshop

INTRODUCTION

Pain is a common symptom that affects >60% of adults with autosomal dominant polycystic kidney disease (ADPKD) [1–3]. Pain from progressive cyst growth and enlargement of both the kidneys and, in most cases, the liver can be severely debilitating to patients with ADPKD [4]. The pain can be chronic and caused by abdominal distension and compression of other organs [5, 6] or acute due to cyst-related complications, such as cyst rupture, bleeding or infection and urolithiasis [7, 8].

Episodes of both acute and chronic pain can adversely impact patients' quality of life and overall health [9–12]. Although pain has been identified as a critically important outcome in people with ADPKD [13–15], it is often underrecognized and therefore inadequately managed [16]. Across trials in ADPKD, pain has been inconsistently and infrequently measured, using measures (questionnaires) that often do not capture aspects of pain that are of critical importance to patients with ADPKD. In a recent review of 68 studies, only 16 (23.5%) reported pain as an outcome and with 26 different outcome measures [17]. The measures used to capture pain varied widely in terms of the dimensions, content and duration, which prevents direct comparison of effects of interventions on pain across trials [18–30, 32–35]. Moreover, these measurement tools were often not specifically developed or validated for use in people with ADPKD [35–44].

As part of the international Standardized Outcomes in Nephrology (SONG) initiative [45], SONG-PKD was launched in 2017 to establish a set of core outcomes for trials in patients with ADPKD based on consensus among patients, caregivers

and health professionals [13, 14, 46]. Among four core outcome domains in ADPKD, pain was the only patient-reported outcome [13, 14]. Establishing a validated core outcome measure for pain in ADPKD will improve and harmonize the conduct and reporting of trials for the assessment of pain as a highly prioritized outcome. Consistent measurement of pain in intervention trials will inform decision making in the identification of the best treatments to manage pain in the clinical setting, which has largely been ignored to date. To inform the selection or development of a standardized outcome measure for pain in patients with ADPKD, we held an international stakeholder workshop to discuss stakeholder perspectives on the development and implementation of the domains to include in a core outcome measure for pain to be used in all trials in ADPKD.

SONG-PKD pain consensus workshop

Context and scope. Due to the coronavirus disease 2019 pandemic, the SONG-PKD Pain Consensus Workshop was held via Zoom on 1 October 2020, to enable wider participation among the PKD community and develop a core outcome measure for pain.

Attendees and contributors

We convened an international SONG-PKD consensus workshop involving 20 (32%) patients with ADPKD, 1 (2%) caregiver and 40 (66%) health professionals (clinicians, nurses, researchers, policy makers and industry representatives) from 18 countries to discuss how to best identify or develop a core outcome measure for pain. In total, 61 participants attended the workshop. We

sent targeted invitations to health professionals with clinical experience in ADPKD or an interest in research in terms of commitment, goal or value relating to pain and patient-reported outcome measures and those who held leadership or advisory roles in professional societies (American Society of Nephrology, Asian Pacific Society of Nephrology, Australian and New Zealand Society of Nephrology and European Renal Association–European Dialysis and Transplant Association), funding organizations (National Institutes of Health) and regulatory agencies (US Centers for Medicare and Medicaid Services and US Food and Drug Administration). Using an opt-in snowballing sampling frame, we invited patients and caregivers through participating hospitals, patient/consumer organizations and social media. Adult patients and caregivers worldwide with any experience of pain in ADPKD were invited by SONG-PKD pain investigators. In order to capture the experience of the wider ADPKD community, we invited patients and/or their caregivers globally and the workshop was attended by patients/caregivers from Australia, Hong Kong, South Africa, Switzerland, the UK and the USA. Caregivers included family members/friends involved in the care of a patient with ADPKD. Those who were unable to attend provided feedback before and after the workshop to add additional perspectives to this report. The full list of SONG-PKD pain workshop attendees and contributors is provided in [Supplementary data, Item S1](#).

Workshop programme and breakout discussions

Background materials and preliminary results of the systematic review on measures used to assess pain in ADPKD [31] were sent to all attendees 1 week before the workshop ([Supplementary data, Item S2](#)). The workshop commenced with a brief presentation of the SONG-PKD initiative, an overview of preliminary results from the systematic review and existing measures including their feasibility (e.g. number of response items, completion time and cost) as a core outcome measure, aims and focused questions for the breakout discussions. All participants were allocated to one of six facilitated discussion groups with approximately 10 participants in each and at least 2 patients and/or caregivers. Each group used a question guide developed by the SONG-PKD pain investigators, available in [Supplementary data, Item S2](#), related to which aspects of pain were important, how the impact of pain on life participation could be measured and the suggested recall period. In brief, participants were asked to discuss their views on important aspects of pain to report in trials in ADPKD, the way to measure the impact of pain on life participation and potential recall periods to inform the choice of a core measure for pain in ADPKD. Afterwards, a member from each group provided a brief summary to the wider group of the key points raised during the discussion. The final plenary session was moderated by the workshop chair (R.D.P.), who summarized the perspectives, recommendations and implications addressed during the workshop. All breakout discussions were audiotaped and transcribed verbatim. Transcripts were coded and analysed using HyperRESEARCH software (Researchware, Randolph, MA, USA). Thematic analysis was used to summarize the qualitative data. One investigator (P.N.) conducted line-by-line coding of the transcripts to inductively identify themes and subthemes related to establishing a core outcome measure for pain in ADPKD. The coding was independently checked by another investigator (A.T.) to ensure that the themes covered the full range and depth of the discussion. All attendees and contributors were contacted to provide feedback on a draft report over a

2-week time frame. Further comments were integrated into the final report.

Summary of workshop discussion

We reached the consensus from the preliminary data of our systematic review that the existing measures validated in ADPKD were not able to report pain in this setting due to the lack of patient-important dimensions, inadequate content, duration of completion time and unavailability of psychometric properties. Four main themes that reflected the range of perspectives on establishing a core outcome measure for pain were identified. Three themes referred to the content that patients and health professionals believed was important to capture in the core outcome measure for pain in ADPKD: distressing and disrupting life participation; variability and ambiguity in defining pain; and stigma, frustration and adaptation to pain. The fourth theme pertained to the required characteristics of the measure, i.e. ensuring validity and feasibility. Both patients and health professionals contributed to the themes unless otherwise indicated. Selected quotations to support each theme are provided in [Table 1](#). Recommendations from the consensus workshop are listed in [Table 2](#).

Distressing and disrupting life participation

Severe limitations on daily and social activities. For some patients, pain severely restricted their ability to perform ‘normal’ activities of daily living, including housework. They described having a ‘time limit that we can spend doing one particular type of thing’ because physical activities exacerbated pain. Patients could be ‘bedridden for a week or two’, resulting in the need to take leave from work or study, and they felt lost and hopeless without the ‘capacity to do what [they] wanted to’. Some patients, particularly those of younger age, mentioned that the extreme intensity and frequency of pain meant it impaired their sexual function and they had to cease their social activities—‘I’ve missed theater experiences and going out [with friends] when I’ve got tickets to things because of pain’.

Exacerbating sleep problems. Sleep disturbance was attributed to pain as patients found that ‘staying comfortable in bed is difficult, and therefore [pain] interrupts sleep’ because ‘I have to change positions many, many times’. Poor sleep quality led to fatigue and low mood ‘because [if I] haven’t slept, I don’t have a good day the next day’.

Inflicting psychological consequences. Participants emphasized the emotional and psychological burden of pain on everyday life. For example, caregivers reported that ‘if they’re not going to want to get up and go to work because of pain, their mental health is affected’. Depression and anxiety from recurrent episodes of pain were blamed for loss of appetite, motivation and capacity for self-management. Pain constantly reminded patients about their disease, which in turn exacerbated worry and uncertainty of ‘what the future may hold’.

Disintegration of role and identity. Pain limited patients’ abilities to ‘take care of family’ or ‘interact and play with children’. Inability to meet expectations for work and family lives triggered some patients to question their self-worth and value in society: ‘If you can’t work you start to question, what’s your purpose in life?’

Table 1. Quotations to support each theme

Theme	Quotations
Distressing and disrupting life participation Severe limitations on daily and social activities	<p>‘The most important aspects of the pain is, “Can I get out of bed today? Can I go to work today?”, and will it actually impact me, majority of the time for me personally, it doesn’t, it’s just there always, but sometimes I can’t go for a run that day, but other days I can. So for me, the impact is what can I do on that day, the day I wake up, and I guess if you have more days where you can’t do the things you want to do in life, than the days you can do things in your life, then that’s really quite impactful and fairly easy to measure actually’. (Patients)</p> <p>‘Then to the amount of time you can spend doing something before the pain becomes overwhelming, look like something like gardening or vacuuming, doing basic things around the house is sort of, for me, there’s a time limit to how long I can spend doing one particular type of thing. Yeah. I can do a lot of things, but I can’t do them for long’. (Patients)</p> <p>‘I think it is important, even if you just say the ability to enjoy food, because it is a social activity. It limits, potentially, your life participation if you don’t want to go out for dinner with your friends any longer, because you can eat only amounts like a bird’. (Patients)</p>
Exacerbating sleep problems	<p>‘In terms of pain and how it would impact similarly on your quality of life, so for me, it’s a matter of sleeping, discomfort in being able to sleep and because you haven’t slept, you don’t have a good day the next day’. (Patients)</p> <p>‘I think sleep would be a very important one to capture and then that as sleep affects so many other aspects as well. And when you’re in pain, it’s hard to sleep’. (Patients)</p> <p>‘I do believe the sleep one is very important because staying comfortable in bed is difficult, and therefore it interrupts your sleep because you have to change positions many, many times...’ (Patients)</p>
Inflicting psychological consequences	<p>‘I really look at more of the psychological impact that prior to transplant, it just reminded me of my condition and it just framed the uncertainty of what the future may hold, so for me, it was really more of a psychological impact’. (Patients)</p> <p>‘This is not on here, but I would say mental health. So if you have sort of very tough pain situation it eventually drags in your mental health and you end up being depressed or you lack interaction with other people and you don’t get that kind of energy from being out and being a part of society’. (Patients)</p> <p>‘Having chronic pain and acute pain, really can get you down’. (Patients)</p>
Disintegration of role and identity	<p>‘I also do think about how it affects my ability to sort of take care of my family and my children’. (Patients)</p> <p>‘I remember when we had our children that were young, sometimes you’d get sort of kicked in the stomach when you’re mucking around...’ (Patients)</p> <p>‘If that is effective, that that affects that person’s being and the ability to be useful and part of society. And if you can’t work, then you know, you start to question, well, what’s your purpose in life?’ (Patients)</p>
Restricting function and activities to minimize pain	<p>‘And also as soon as we’ve been given instructions, as soon as we have the diagnosis, we’re told to not involve ourselves in certain activities, so you can’t take part in contact sports and things like that, which would put you at risk of experiencing more pain’. (Patients)</p> <p>‘And from there, of course, you’re in pain, so you start giving up certain activities because it bothers you. And that is, then, the negative impact on the quality of life’. (Patients)</p> <p>‘I tend to avoid contact sports. I gave up football and I took up golfing’. (Patients)</p>
Variability and ambiguity in defining pain Unable to distinguish location and cause	<p>‘I’m not sure location is so relevant. My pain is in different areas overnight to during day’. (Patients)</p> <p>‘Type is a really difficult thing to nail, because there’s so many adjectives people use to describe the type of pain they have. Sharp, it’s nagging, it’s dull, it’s crippling. I don’t think we need type, actually’. (Health professional)</p> <p>‘And I don’t know what it’s related to, what it’s caused by. I try and shift around and move my body a little bit to try and move the cyst. Maybe the cyst is bumping up against something. I don’t know’. (Patients)</p>
Potential symptom of other condition or complications	<p>‘And then the converse of that is, pain that is associated with another serious acute problem that may require hospitalization such as system infection or a cyst burst or significant hematuria that’s accompanied by pain. So, pain becomes the symptom of another issue, rather than something that affects daily life’. (Health professional)</p> <p>‘If the patient notices something else that’s associated with the pain, just to understand the pain itself more, but I would add’. (Health professional)</p>
Fluctuation and variability of severity	<p>‘I always have pain, and it’s almost like if I don’t have pain, something’s a bit strange. There are some days I don’t have any pain, so I guess I can probably pick out the ones where I’m in severe pain when it really hurts, perhaps I’ve taken an extra bunch of codeine that day or something, but yeah, for me, it’s always, but sometimes I can probably point out when it’s more so, and it would be quite easy for me’. (Patient)</p>

(continued)

Table 1. (continued)

Theme	Quotations
Internal conflicts and adaptation to pain Fear of marginalization from the community	<p>'Some days I take nothing [medications], and other days I take something every four to six hours'. (Patient)</p> <p>'In terms of this acute on chronic pain status, ADPKD patients might have the chronic episodes that are predictable and maybe could adjust to that. It's the acute episodes that sporadic, completely on random interfering in such a way that it's just so difficult to manage and there might be surrogates for that'. (Health professional)</p>
Deprioritized by health professionals Normalizing and tolerating pain	<p>'The example was the fact that I like doing horseback riding, and I was planning to go with friends, but I said, "You know what? I cannot really join you because I have this pain that really prevents me from doing that activity." And then, the question is how can, obviously, the people who don't understand what the disease is about or who don't feel the pain, how they could react to you as a person, to your, somehow, problem. And you never know what reaction you're going to get'. (Patient)</p> <p>'So I consider this kind of an invisible disability is how they labelled it. And people can't see that we're in pain. And so I think that's another psychological side of it too. That if you're in pain, nobody knows'. (Patient)</p> <p>'And I think I've said that several times, but there's a big gap between what you do, US, and what we do here, because in Europe the rate of patients who receive morphine or such type of drugs is variable and the, okay, we need to record that of course, but consider the different approaches depending on the country'. (Health professional)</p> <p>'I've suffered with pain for seven years now. Never once have I been asked to complete a scale on pain assessment. So it's largely overlooked'. (Patient)</p> <p>'Because most of us, I mean, we have this our whole lives, and you start to become accustomed to certain types of things, that you acknowledge that as normal, you don't actually see it as any different to somebody else, who's normal, normal, if that makes any sense'. (Patient)</p> <p>'So I think that there's a certain amount of adaptation that you do if you want to live your life, right, so my pain hasn't been that bad'. (Patient)</p> <p>'Just because I think people have different thresholds of pain. I think people can experience large amounts of pain and not really be in pain. And then virtually the opposite people could be perceived as not having much . . . having a lot of . . . not much pain, but then saying that they're in a lot of pain'. (Caregiver)</p>
Accepting the inevitability of pain	<p>'And just something to think about too, is that, but based upon the family history of what you saw a parent go through, I just chose to keep my head down, because the message was, there's nothing you could do, so it was like you push it out and ignore it'. (Patient)</p> <p>'Burden of pills taken, and types of medications, the pain is just simply not controlled at all. And I think efficacy of the pain med regimen would be important to assess, and the iterations of treatments and combinations of meds that were needed to get to a point of some relief'. (Caregiver)</p>
Ignoring pain to avoid diagnosis of ADPKD	<p>'But the chronic pain was the one where in discussions with my nephrologist and other medical professionals, that nobody really had a great idea for that'. (Patient)</p> <p>'When I was in my twenties, and I would notice that I did certain things like, just admittedly if I drank like more beer or different things, I would feel really bad pain, and I kind of knew it was there, but I just chose to ignore it'. (Patient)</p> <p>'I think that the part that, I guess I kind of think of now, with the landscape chasing or changing, right, is that if patients become more aware early-on, right, there's now more of a chance to change the course of that outcome, as opposed to living in fear and denial of what you saw your parents go through'. (Caregiver)</p> <p>'I remember my mom standing up and she used to take pain medications, but I remember her standing with pain, and so when I started having them, I just wanted to deny it because I want to deny that I had PKD, and why did I want to deny PKD? Because there was no hope at that time'. (Patient)</p>
Ensuring validity and feasibility of pain measures Minimizing burden of administration	<p>'I have found that the easiest is in a right now, because it's so immediate, there is no recall bias. There is no judgment on anything, but only for very simple questions. If you've got to judge recall, then of course the availability of the previous rating to the rating that you, to the knowledge of that and the record that can be quite important as well. It really does depend on, and it's really difficult to know in terms of its sensitivity to change as well when it comes to recall. But if you've got a questionnaire, I think I can't do it every day, it's just too onerous'. (Health professional)</p> <p>'I think one of the challenges that we have to think about when we're thinking about how to identify, quantify, and measure these things is, in a clinical study and in clinical trials, what's</p>

(continued)

Table 1. (continued)

Theme	Quotations
Applicable across diverse population	<p>the goal of capturing this information? It's really to be able to identify something that we can hopefully reverse or delay its progression or prevent with whatever interventions that we're describing'. (Health professional)</p> <p>'I suppose I'd sit there and think, well, is this question about chronic pain or is this question about acute pain? And I suppose perhaps we ought to delineate between the two because yeah. You know, I'm going to answer that question. Yes. I've been in pain over the last month. It's always there. What's your question about? But if you want to know has the experimental treatment affected any of the acute pains? They're different questions'. (Patient)</p> <p>'My view of this, is we are always going to be looking towards a composite measure, there is going to be no one parameter or measurable thing that is going to be a surrogate for everything. So drug burden, days off work, sleep disturbance, it's going to be a composite which I guess is going to be taking us forward into how much of that is reproducible, validated, and consistent and so on. So that's my view of thinking about what do we need to measure, it's no one aspect'. (Health professional)</p> <p>'Sort of do the scales relate to the right age group? Because if we are... We're talking about, yeah, can you get yourself dressed? I have seen scales that actually have those kind of questions and you think, well, yeah. Okay. I can do that. Is that actually going to assess... Do I feel restricted at work or university or whatever is I'm doing? I don't know if they do relate because we're assessing pain in perhaps later age groups. If your patients have got severe arthritis or something and they can't move. I mean, I don't know about anyone else, but I don't usually have a problem dressing myself. So you asking me that question is irrelevant'. (Health professional)</p> <p>'Where people are in their stage of life. And I remember we talked to patients that were... The Young college students, we talked to teenagers and we talked to people up in their seventies and eighties. And how do you get a common theme that you can then compare'? (Health professional)</p> <p>'These are things that are typically are much less relevant to elderly populations where most of these scales have been sort of... I'm not a big expert on this case, but I'm just thinking, and you don't ask those questions about having a sports life, being able to go jogging or the sexual life. So clearly there seems to be an issue by what I'm hearing from you, that there is the age specific factor in related to using these scales'. (Health professional)</p>

Table 2. Summary of workshop recommendations for establishing a core outcome measure for pain

- The core outcome measure for pain should be meaningful and relevant to patients, caregivers and health professionals, and should capture intensity, frequency and impact on life participation (ability to do usual or meaningful activities of life) to inform decision-making in clinical practice
- Consideration should be given to psychological aspects (e.g. depression and anxiety) and impaired sexual function
- Abdominal fullness or discomfort should be captured as a different symptom from pain
- Ensure that the measure is applicable across the ADPKD populations (i.e. age) and geographical settings
- Identify an appropriate recall period able to minimize recall bias and capture patients' experiences of pain in an accurate and detailed way without being burdensome
- The core outcome measure for pain should be feasible to be used in all trials in ADPKD, i.e. have small number of items, be easily accessible and free to use, easy to administer and interpret and psychometrically robust

Restricting function and activities to minimize pain. Some patients learned to adapt to living with pain by avoiding activities that would potentially trigger episodes of pain: 'I tend to avoid contact sports. I gave up football and I took up golfing'. In addition, health professionals advised patients to refrain

from strenuous physical activities that would increase their 'risk of experiencing more pain'.

Variability and ambiguity in defining pain

Unable to distinguish location and cause. Participants mentioned that 'often patients find it difficult to say which organ [pain] is related to'. Although knowing the exact location could be helpful in determining 'specific treatments for pain in ADPKD', patients were uncertain and puzzled if their pain was related to PKD because they experienced 'pain in different parts of their body'. Patients explained that they could not always identify the type and source of pain. One participant remarked: '[the cause of pain] is hard to determine, is it your kidney that hurts or is it because that big old kidney is pushing on something else that's making something else hurt?'

Potential symptom of other condition or complication. Pain could also be a symptom of cyst-related complications that lead to hospitalization, including 'infection, cyst rupture or significant haematuria'. Some medications provided relief from pain, but their adverse effects led to other complications.

Fluctuation and variability of severity. The frequency and severity of pain were often unpredictable, which made it challenging

to decide on how to take medications to help relieve pain, 'because some days I take nothing, and other days I take something every 4–6 h'.

Stigma, frustration and adaptation to pain

Fear of marginalization from the community. Participants felt they often 'needed to justify or to provide a reason why [they] cannot do certain things' because 'people who don't feel pain' cannot understand and sympathize with them. Patients felt frustrated because they were suffering from 'an invisible disability [because] people can't see that we're in pain'. Community acceptance of taking opioids or analgesics varied across countries. For example, participants noted that the use of such agents was more common and widely accepted in Europe and the USA, whereas in Asia, patients 'declined to have acetaminophen or morphine', possibly because of the stigma attached to dependence on chronic analgesic medications.

Deprioritized by health professionals. Pain was perceived by some to be overlooked and deprioritized by health professionals. One patient stated, 'never once have I been asked to complete a scale on pain assessment'. Patients felt that some doctors were unfamiliar with and not able to evaluate and manage their ADPKD-related pain and believed that there were no treatments available for effective pain management.

Normalizing and tolerating pain. Some patients 'became accustomed to certain types of [pain], that [they] acknowledge as a normal' symptom of the disease. Pain was regarded as difficult to assess because it was 'very different [things] for everyone'. People had 'different thresholds' of tolerance, where younger people reported pain more frequently compared with elderly who 'accept the situation and try to live with it'.

Accepting the inevitability of pain. Patients felt hopeless because medications did not alleviate pain, which 'was always there'. One patient accepted the burden of pain, reporting: 'I chose to keep my head down, because there's nothing you could do'.

Ignoring pain to avoid diagnosis of ADPKD. Some patients ignored pain because they 'wanted to deny that [they] had PKD'. Other participants reported delay in seeking a diagnosis, leading to exacerbation of symptoms, including pain, because they 'saw a parent go through [and having troubles when in pain] and [people] push it out and ignore it'.

Ensuring validity and feasibility of pain measures

Minimizing burden of administration. Participants suggested that the core outcome measure for pain should be an 'easy tool' with 'very simple questions' that could be easily understood by patients and capture relevant dimensions of pain. The measure should take the 'shortest amount of time as possible', so it would not be 'too onerous' for patients. It was suggested that pain should be assessed in real time 'because it's so immediate, there is no recall bias', and it could be captured, for example, through a mobile application 'that lets people register pain when it happens'. Others advised that the recall period 'depends on the length of the trial', but 'a month is probably a good period of time' to capture both chronic and acute episodes. They believed these two types of pain should be reported separately because they were often driven by different causes (e.g.

acute pain from cyst haemorrhage/infection; chronic pain from pressure effect from enlarged cysts).

Applicable across diverse populations. A 'composite measure' for pain in ADPKD should be 'reproducible, validated and consistent' across different populations and settings because 'pain has a million different sources, and we're going to be able to measure something that's going to be responsive to all of our different individuals'. The measure should be applicable and meaningful in different age groups and include questions that are relevant to everyone.

DISCUSSION

Pain is a critically important outcome for both patients with ADPKD and health professionals, but it remains inconsistently measured and reported. Because pain is a symptom that only a patient with ADPKD can report, discussions were focused mainly on patient experiences and perspectives of pain. Patients, caregivers and health professionals agreed that the impact of pain on life participation was the highest relevant and important dimension to include in the proposed core outcome measure. This is because pain in ADPKD largely interferes with both normal daily and social activities. Psychological distress, depression, sleep problems and impaired sex life were in part attributed to ADPKD-related pain, adding extra burden to the disease. The unpredictability, severity and frequency of pain episodes substantially impacted the patients' ability to participate in daily life activities. Some patients with ADPKD, even at younger ages, deliberately avoided activities that could exacerbate pain, felt stigmatized and refrained from social activities so they would not have to explain their condition to healthier peers. Others adapted to and accepted pain as a normal and inevitable symptom of ADPKD, strived to continue with their usual activities and refused to be limited by pain.

Previous studies have identified that the burden of pain, which is exacerbated by increased severity and frequency, imposes limitations on patients in terms of work, housework, daily activities and social participation [14, 15]. Pain was debilitating due to its unpredictability and intensity of episodes, thereby preventing the start, completion or planning of tasks until the pain had subsided [15]. In this workshop, life participation was directly linked to the extent of severity and frequency of pain, because if the impact of pain (in terms of severity or frequency) was higher it would impose greater limitations on the individual's ability to participate in life-related activities (e.g. activities of daily living and social activities). Several measures have been used to assess pain in ADPKD [18–21, 23–25, 27–30, 32, 34], although they were not validated in this population, focusing on the interference of pain with general activities, walking ability, work, relations with others, enjoyment of life, sleep and mood. We noted that the impact of pain on life participation was identified as the most important dimension because it captured all aspects of pain, including severity, frequency and implications for daily living, relations with others, sexual life, sleep and psychological distress. Patients also drew attention to the need to restrict activities to minimize pain, including decisions to limit social activities because of stigma and a lack of understanding, and denial of pain as a coping mechanism so they would not have to confront a diagnosis of ADPKD. Conversely, the location and type of pain were not considered as crucial dimensions, due to patient-reported inability to accurately identify the site and source of pain.

In terms of ensuring the feasibility of measuring pain as a core patient-reported outcome, aspects including the completion time, ease of administration and interpretation of the findings across a broad range of patients should be considered [47]. Participants emphasized that a simple, short, reproducible and validated measure would maximize uptake in ADPKD trials and clinical settings across regions. At the time of the workshop, only the ADPKD Impact Scale (ADPKD-IS) [48] and the Polycystic Liver Disease questionnaire (PLD-Q) [26] had been validated in people with ADPKD. However, both measures were not considered suitable to be used as a core outcome measure for pain. Although the ADPKD-IS [48] assessed the impact of pain on daily activity and the need to modify lifestyle due to discomfort, the measure reported only 3 of 18 items related to general pain and was not feasible due to the time required to complete the measure. The PLD-Q [26] included 13 items, none of which assessed the impact on life participation, and was developed to measure quality of life in PLD in people with ADPKD. Recently a new tool for ADPKD-related chronic pain has been validated through the DRINK (Determining feasibility of Randomisation to high vs ad libitum water Intake in Polycystic Kidney Disease) trial [49]. It is a comprehensive measurement tool that encompasses severity, impact on various dimensions (mood, sleep and function) and frequency. However, because it requires a device to open the application software and its length, it is not a suitable measure to capture pain as a core outcome for every trial in people with ADPKD. Some of the content and measurement dimensions important to patients with ADPKD are captured in other existing measures for pain, such as the Patient-Reported Outcomes Measurement Information System [50], which includes severity of pain [51] and interference with daily living, social activities, work and household chores [52]. However, these measures have not been validated in this population. Therefore, the usefulness of existing measures in their current form is limited because they do not capture all dimensions important to patients suffering from pain due to ADPKD, include an excessive number of response items impairing feasibility, require a paid license or have not been validated in this population [17]. To date, the available measures are not able to cover all critical aspects of pain for people with ADPKD. Further work needs to be conducted to develop a new and psychometrically robust core outcome measure for pain that can be used in trials in patients with ADPKD. The measure must be one that captures the aspects and impacts of pain that are important to patients and is responsive to meaningful changes in pain.

Recommendations emerging from this workshop are provided in Table 2 and will be used to inform the development and/or validation of a core outcome measure for pain in ADPKD. The workshop delegates agreed that the measure should include severity and frequency of pain, impact on life participation and psychological aspects to inform decision making in clinical practice. Some participants recommended that the selected measure should be applicable across different age groups and settings, using ideally a recall period of a month to capture patients' experiences of pain without being burdensome. As recommended by the IMMPACT (Initiative on Methods, Measurement and Pain Assessment in Clinical Trials) [53] and the COSMIN-COMET (Consensus-Based Standards for the Selection of Health Measurement Instruments-Core Outcome Measures in Effectiveness Trials Initiative) guidelines [47], before routine use in clinical trials, it is also necessary to establish the psychometric properties of the measure.

In this workshop we discussed in detail the development of a core outcome measure for pain that includes dimensions

considered important and meaningful to patients, caregivers and health professionals from different countries. Discussions were recorded and transcribed. Transcripts were coded using software to ensure that all concepts, experiences and issues were captured. The preliminary results were sent to all participants and contributors to cover the breadth and depth of the discussions. However, this workshop had some limitations. All participants attended the workshop as investigators and demographic information was not collected. We acknowledge that non-English-speaking patients and health professionals and those without access to the Internet were unable to participate in the workshop, which could limit the generalizability of outcomes.

Establishing a validated core outcome measure for pain will ensure that pain is measured and reported in a consistent way across all trials in ADPKD to inform decision making and identify effective interventions aimed at managing pain and minimizing its impact on patients with ADPKD.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

ACKNOWLEDGEMENTS

We acknowledge, with permission, all the attendees listed below who attended the consensus workshop. Health professionals: Ahsan Alam, Albert Ong, Aliza Thompson, Allison Tong, Amanda Baumgart, Andrea Matus Gonzalez, Andrea Viecelli, Angela Wang, Angela Ju, Chandana Guha, Charlotte Logeman, Craig Gordon, Dana Miskulin, David Johnson, Djalila Mekahli, Dorothee Oberdhan, Elyssa Hannan, Frank Czerwiec, Giovanni Strippoli, Gopi Rangan, Gregory Germino, Iris Koorevaar, Juliana Kao, Karine Manera, Kristen Nowak, Meyeon Park, Michael Chin Han Lee, Nicole Evangelidis, Noa Amir, Pamela Lopez-Vargas, Patrizia Natale, Reem Mustafa, Richard Sanford, Ron Gansevoort, Ronald Perrone, Roser Torra, Rudi Vennekens, Shigeo Horie and Yeoungjee Cho. Patients and caregivers: Amy Coffin, Bev Goldberg, Charmaine Green, Cheryl Ferris, David Baron, Dwight Odland, Eva Burnette, Francesco Messina, Helen Coolican, Jill Brown, Kevin Fowler, Klee Kleber, Leilani Johnston, Natasha O'Brien, Peggy Robinson, Richard Lee, Rob Burland, Samuel Durham, Sarah Easty, Tess Harris and Vincent Tam.

FUNDING

A.T. is supported by a National Health and Medical Research Council (NHMRC) fellowship (1106716). Y.C. is supported by an NHMRC Early Career Fellowship (1126256). A.K.V. is supported by a Jacquot Research Establishment fellowship. R.D.P. is supported in part by the National Center for Advancing Translational Sciences, National Institutes of Health (award UL1TR002544). The University of Cambridge has received salary support for R.S. from the National Health Service in the East of England through the Clinical Academic Reserve. The funding organizations had no role in the study design; collection, analysis and interpretation of data; writing the report or the decision to submit the report for publication.

AUTHORS' CONTRIBUTIONS

All authors were responsible for the research idea, study design and data analysis/interpretation. P.N. and A.T. were responsible for data acquisition. A.T., J.C.C. and Y.C. were responsible for supervision or mentorship. Each author contributed important intellectual content during manuscript drafting or revision, accepts personal accountability for the author's own contributions and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose. The results presented in this review have not been published previously in whole or part, except in abstract format.

DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article and in its online [Supplementary Material](#).

REFERENCES

- Bajwa ZH, Sial K, Malik AB et al. Pain patterns in patients with polycystic kidney disease. *Kidney Int* 2004; 66: 1561–1569
- Casteleijn NF, de Jager R, Neeleman MP et al. Chronic kidney pain in autosomal dominant polycystic kidney disease: a case report of successful treatment by catheter-based renal denervation. *Am J Kidney Dis* 2014; 63: 1019–1021
- Casteleijn NF, van Gastel M, Blankestijn PJ et al. Novel treatment protocol for ameliorating refractory, chronic pain in patients with autosomal dominant polycystic kidney disease. *Kidney Int* 2017; 91: 972–981
- Perrone RD, Malek A, Watnick T. Vascular complications in autosomal dominant polycystic kidney disease. *Nat Rev Nephrol* 2015; 11: 589–598
- Almeida EA, Oliveira EI, Lopes JA et al. Tissue Doppler imaging in the evaluation of left ventricular function in young adults with autosomal dominant polycystic kidney disease. *Am J Kidney Dis* 2006; 47: 587–592
- Boertien WE, Meijer E, de Jong PE et al. Short-term effects of tolvaptan in individuals with autosomal dominant polycystic kidney disease at various levels of kidney function. *Am J Kidney Dis* 2015; 65: 833–841
- Sallée M, Rafat C, Zahar JR et al. Cyst infections in patients with autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol* 2009; 4: 1183–1189
- Tellman MW, Bahler C, Shumate AM et al. Management of pain in autosomal dominant polycystic kidney disease and anatomy of renal innervation. *J Urol* 2015; 193: 1470–1478
- Rizk D, Jurkowitz C, Veledar E et al. Quality of life in autosomal dominant polycystic kidney disease patients not yet on dialysis. *Clin J Am Soc Nephrol* 2009; 4: 560–566
- Anderegg MA, Dhayat N, Sommer G et al. Quality of life in autosomal dominant polycystic kidney disease patients treated with tolvaptan. *Kidney Med* 2020; 2: 162–171
- Heiwe S, Bjuke M. "An evil heritage": interview study of pain and autosomal dominant polycystic kidney disease. *Pain Manag Nurs* 2009; 10: 134–141
- Hogan MC, Norby S. Evaluation and management of pain in autosomal dominant polycystic kidney disease. *Adv Chronic Kidney Dis* 2010; 17: e1–e16
- Cho Y, Rangan G, Logeman C et al. Core outcome domains for trials in autosomal dominant polycystic kidney disease: an international Delphi survey. *Am J Kidney Dis* 2020; 76: 361–373
- Cho Y, Tong A, Craig JC. 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. *Am J Kidney Dis* 2020; 77: 255–263
- Tong A, Rangan G, Ruospo M et al. A painful inheritance—patient perspectives on living with polycystic kidney disease: thematic synthesis of qualitative research. *Nephrol Dial Transplant* 2015; 30: 790–800
- Sawicki M, Walecka A, Rozanski J et al. Doppler sonography measurements of renal vascular resistance in autosomal-dominant polycystic kidney disease. *Med Sci Monitor* 2009; 15: MT101–MT104
- Sautenet B, Cho Y, Gutman T et al. Range and variability of outcomes reported in randomized trials conducted in polycystic kidney disease: a systematic review. *Am J Kidney Dis* 2020; 76: 213–223
- Chrispijn M, Gevers TJG, Hol JC et al. Everolimus does not further reduce polycystic liver volume when added to long acting octreotide: results from a randomized controlled trial. *J Hepatol* 2013; 59: 153–159
- D'Agnoilo HM, Kievit W, Takkenberg RB et al. Ursodeoxycholic acid in advanced polycystic liver disease: a phase 2 multicenter randomized controlled trial. *J Hepatol* 2016; 65: 601–607
- de Jager RL, Casteleijn NF, de Beus E et al. Catheter-based renal denervation as therapy for chronic severe kidney-related pain. *Nephrol Dial Transplant* 2018; 33: 614–619
- Delli Zotti GB, Sangiovanni E, Brioni E et al. Psychological assessment of a sample of women with ADPKD: quality of life, body image, anxiety and depression. *G Ital Nefrol* 2019; 36: 1–14
- El-Damanawi R, Lee M, Harris T et al. High water versus ad libitum water intake for autosomal dominant polycystic kidney disease: a randomised controlled feasibility trial. *QJM* 2019; 113: 258–265
- Eriksson D, Karlsson L, Eklund O et al. Health-related quality of life across all stages of autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant* 2017; 32: 2106–2111
- Gevers TJG, Hol JC, Monshouwer R et al. Effect of lanreotide on polycystic liver and kidneys in autosomal dominant polycystic kidney disease: an observational trial. *Liver Int* 2015; 35: 1607–1614
- Lai S, Petramala L, Muscaritoli M et al. α -lipoic acid in patients with autosomal dominant polycystic kidney disease. *Nutrition* 2020; 71: 110594
- Neijenhuis MK, Gevers TJ, Hogan MC et al. Development and validation of a disease-specific questionnaire to assess patient-reported symptoms in polycystic liver disease. *Hepatology* 2016; 64: 151–160
- Perico N, Ruggenenti P, Perna A et al. Octreotide-LAR in later-stage autosomal dominant polycystic kidney disease (ALADIN 2): a randomized, double-blind, placebo-controlled, multicenter trial. *PLoS Med* 2019; 16: e1002777
- Schrier RW, Abebe KZ, Perrone RD et al. Blood pressure in early autosomal dominant polycystic kidney disease. *N Engl J Med* 2014; 371: 2255–2266

29. van Aerts RMM, Kievit W, D'Agnolo HMA et al. Lanreotide reduces liver growth in patients with autosomal dominant polycystic liver and kidney disease. *Gastroenterology* 2019; 157: 481–491.e7
30. van KL, Nevens F, Vanslembrouck R et al. Lanreotide reduces the volume of polycystic liver: a randomized, double-blind, placebo-controlled trial. *Gastroenterology* 2009; 137: 1661–1668
31. Natale P, Hannan E, Sautenet B et al. Patient-reported outcome measures for pain in autosomal dominant polycystic kidney disease: a systematic review. *PLoS One* 2021; 16: e0252479 10.1371/journal.pone.0252479.PMC: 34043715.
32. Kim H, Park HC, Ryu H et al. Clinical correlates of mass effect in autosomal dominant polycystic kidney disease. *PLoS One* 2015; 10: e0144526
33. Meijer E, Visser FW, Van Aerts RMM et al. Effect of lanreotide on kidney function in patients with autosomal dominant polycystic kidney disease the DIPAK 1 randomized clinical trial. *JAMA* 2018; 320: 2010–2019
34. Miskulin DC, Abebe KZ, Chapman AB et al. Health-related quality of life in patients with autosomal dominant polycystic kidney disease and CKD stages 1–4: a cross-sectional study. *Am J Kidney Dis* 2014; 63: 214–226
35. Haseebuddin M, Tanagho YS, Millar M et al. Long-term impact of laparoscopic cyst decortication on renal function, hypertension and pain control in patients with autosomal dominant polycystic kidney disease. *J Urol* 2012; 188: 1239–1244
36. Iliuta IA, Shi B, Pourafkari M et al. Foam sclerotherapy for cyst volume reduction in autosomal dominant polycystic kidney disease: a prospective cohort study. *Kidney Med* 2019; 1: 366–375
37. Sakuhara Y, Nishio S, Morita K et al. Transcatheter arterial embolization with ethanol injection in symptomatic patients with enlarged polycystic kidneys. *Radiology* 2015; 277: 277–285
38. Tavira B, Gomez J, Malaga S et al. A labor and cost effective next generation sequencing of PKHD1 in autosomal recessive polycystic kidney disease patients. *Gene* 2015; 561: 165–169
39. Abraham GP, Siddaiah AT, Das K et al. Laparoscopic nephrectomy for autosomal dominant polycystic kidneys in patients with end-stage renal disease on maintenance hemodialysis: 10-year single surgeon experience from an Indian center. *J Min Access Surg* 2015; 11: 187–192
40. Walsh N, Sarria JE. Management of chronic pain in a patient with autosomal dominant polycystic kidney disease by sequential celiac plexus blockade, radiofrequency ablation, and spinal cord stimulation. *Am J Kidney Dis* 2012; 59: 858–861
41. Suwabe T, Ubara Y, Mise K et al. Quality of life of patients with ADPKD-Toranomon PKD QOL study: cross-sectional study. *BMC Nephrol* 2013; 14: 179
42. Suwabe T, Ubara Y, Sekine A et al. Effect of renal transcatheter arterial embolization on quality of life in patients with autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant* 2017; 32: 1176–1183
43. Torres VE, Chapman AB, Devuyst O et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med* 2012; 367: 2407–2418
44. D'Agnolo HMA, Casteleijn NF, Gevers TJG et al. The association of combined total kidney and liver volume with pain and gastrointestinal symptoms in patients with later stage autosomal dominant polycystic kidney disease. *Am J Nephrol* 2017; 46: 239–248
45. Standardized Outcome in Nephrology (SONG). <https://songinitiative.org/> (July 2020, date last accessed)
46. Cho Y, Sautenet B, Gutman T et al. Identifying patient-important outcomes in polycystic kidney disease: an international nominal group technique study. *Nephrology (Carlton)* 2019; 24: 1214–1224
47. Prinsen CAC, Vohra S, Rose MR et al. How to select outcome measurement instruments for outcomes included in a “Core Outcome Set” – a practical guideline. *Trials* 2016; 17: 449
48. Oberdhan D, Cole J, Krasa HB et al. Development of the autosomal dominant polycystic kidney disease impact scale: a new health-related quality-of-life instrument. *Am J Kidney Dis* 2018; 71: 225–235
49. El-Damanawi R, Lee M, Harris T et al. Developing a patient-centred tool for pain measurement and evaluation in autosomal dominant polycystic kidney disease. *Clin Kidney J* 2021; doi: 10.1093/ckj/sfaa259
50. PROMIS Pain Measures. <https://www.healthmeasures.net/search-view-measures> (December 2020, date last accessed)
51. Pain Intensity 3a. <https://www.healthmeasures.net/search-view-measures> (December 2020, date last accessed)
52. Pain Interference 4a. <https://www.healthmeasures.net/search-view-measures> (December 2020, date last accessed)
53. Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials. <http://www.impact.org/> (February 2021, date last accessed)