BMJ Open

A Randomised Controlled Trial of High versus Ad Libitum Water Intake in Patients with Autosomal Dominant Polycystic Kidney Disease: Rationale and Design of the DRINK Feasibility Trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022859
Article Type:	Protocol
Date Submitted by the Author:	13-Mar-2018
Complete List of Authors:	El-Damanawi, Ragada; Division of Experimental Medicine and Immunotherapeutics, Department of Medicine, University of Cambridge; Cambridge Clinical Trials Unit, Lee, Michael; Division of Anaesthesia, Department of Medicine, University of Cambridge Harris, Tess; PKD Charity, London, United Kingdom Mader, Laura; Cambridge Clinical Trials Unit, ; Patient Led Research Hub Bond, Simon; Cambridge Clinical Trials Unit, Pavey, Holly; Cambridge Clinical Trials Unit, Sandford, Richard; Department of Medical Genetics, University of Cambridge Wilkinson, Ian; Division of Experimental Medicine and Immunotherapeutics, Department of Medicine, University of Cambridge; Cambridge Clinical Trials Unit, Burrows, Alison; University of Bristol Woznowski, Przemyslaw; University of Bristol Ben-Shlomo, Yoav; University of Bristol Karet Frankl, Fiona; Department of Medical Genetics, University of Cambridge Hiemstra, Thomas; Division of Experimental Medicine and Immunotherapeutics, Department of Medicine, University of Cambridge; Cambridge Clinical Trials Unit,
Keywords:	Autosomal Dominant Polcystic Kidney Disease, Vasopressin, Water, Osmolality, Urine specific gravity, Feasibility

A Randomised Controlled Trial of High versus Ad Libitum Water Intake in Patients with Autosomal Dominant Polycystic Kidney Disease: Rationale and Design of the DRINK Feasibility Trial

Ragada El-Damanawi[1,4], Michael Lee[2], Tess Harris[3], Laura B Mader [4,5], Simon Bond[4], Holly Pavey[4], Richard N Sandford[6], Ian B Wilkinson[1,4], Alison Burrows[7], Przemyslaw Woznowski[7], Yoav Ben-Shlomo[7], Fiona E Karet Frankl[6], Thomas F Hiemstra[1,4]

[1]Division of Experimental Medicine and Immunotherapeutics, Department of Medicine, University of Cambridge; [2]Division of Anaesthesia, Department of Medicine, University of Cambridge; [3]PKD Charity, London, United Kingdom; [4]Cambridge Clinical Trials Unit, Cambridge UK; [5]Patient Led Research Hub, Cambridge UK, [6]Department of Medical Genetics, University of Cambridge; [7]University of Bristol, UK.

Corresponding Author:

Thomas F Hiemstra
tfh24@cam.ac.uk
Cambridge Clinical Trials Unit
Box 401 Cambridge Biomedical Campus,
Hills Road,
Cambridge,
CB2 0QQ,
United Kingdom

ABSTRACT

Introduction

Vasopressin stimulates cyst growth in Autosomal Dominant Polycystic Kidney Disease (ADPKD) leading to enlarged kidneys, hypertension and renal failure. Vasopressin receptor blockade slows disease progression. Physiological suppression of vasopressin secretion through high water intake could achieve a similar effect, necessitating a definitive large-scale trial of high water intake in ADPKD. The objective of the DRINK trial is to answer the key design and feasibility questions required to deliver a successful definitive water intake trial.

Methods and Analysis

We describe the design of a single-centre, open label, prospective, randomised controlled trial. DRINK aims to enroll 50 ADPKD patients, over the age 16years with an eGFR≥20ml/min/1.73m2. Participants will be randomised 1:1 to high water (HW) intake based on an individualised water intake prescription, or to ad libitum(AW) water intake. The HW group will aim for a dilute urine (urine osmolality≤270mOsmo/kg) as a surrogate marker of vasopressin suppression, and those in the AW group will target more concentrated urine. Participants will have an 8week treatment period, and will be seen at week 0, 2,4 and 8, undergoing assessments of fluid status, renal function and serum and urine osmolalities. They will receive dietary advice, and self-monitor urine specific gravity and fluid intake. The trial employs smartphone technology to permit home monitoring and remote direct data capture. The primary feasibility endpoints are recruitment rate and separation between arms in measured urinary osmolality. Key secondary assessments include acceptability, adherence, health-related quality of life, acute effects of high water intake on measured (^{51}Cr-EDTA) and estimated glomerular filtration rate, and ADPKD-related pain.

Ethics and Dissemination

Ethical approval was awarded by the East of England Essex Research Ethics Committee (16/EE/0026). The results of DRINK will be submitted to peer reviewed journals, and presented to patients via the PKD Charity.

Trial Registration Details: NCT02933268 and ISCRTN16794957

Strengths and Limitations

- The use of a randomised controlled feasibility trial designed to determine adherence and adequate separation between treatment arms will provide crucial data on the practical and biological feasibility of a definitive global high water trial
- Self-monitoring and recording of results using smartphone technology will aid compliance and allow remote data capture, thereby reducing the burden of trial visits on participants and facilitate recruitment and streamlining of future trials
- The effect of high water intake in ADPKD was identified as a research priority by ADPKD patients. The trial was designed and is being conducted in partnership with the PKD Charity.
- DRINK will include those with more advanced kidney disease (CKD3 and 4), representative of typical patients under hospital care
- DRINK is limited by the relatively short duration of follow-up, thus not providing data on the long-term sustainability of fluid prescription adherence.

INTRODUCTION

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the commonest human inherited renal disorder affecting 12 million people worldwide[1]. Kidney cyst growth throughout the life span leads to enlarged kidneys, hypertension and impaired kidney function. More than two thirds of those affected will develop kidney failure by a median age of 58 years[2], approximately 10 years earlier than for most other primary kidney diseases[3]. Interventions that slow the progression of ADPKD are urgently needed.

ADPKD is usually caused by mutations in PKD1, PKD2 or, rarely, GANAB[4]. Its pathogenesis is incompletely understood. PKD1 and PKD2 encode the polycystins PC1and PC2 respectively. PKD1 or PKD2 mutations lead to reductions in intracellular calcium, accumulation and impaired destruction of cAMP and reduced intracellular ATP. This promotes sensitivity of collecting duct epithelial cells for the tonic effects of vasopressin[5]. Since vasopressin promotes cyst growth, it has emerged as a therapeutic target for ADPKD[6]. Recent evidence has confirmed efficacy of vasopressin receptor blockade with the V_2 receptor antagonist Tolvaptan in slowing ADPKD progression, reducing the annual increase in total kidney volume by 2.7%[7] and slowing the rate of eGFR decline[8]. However, the utility of Tolvaptan is limited by cost and side effects, with up to 25% of patients intolerant of the drug[7].

Vasopressin release from the posterior pituitary is driven by plasma osmolality[9], and is readily suppressed by drinking beyond thirst. It is therefore plausible that high water intake could slow the progression of ADPKD through reduced exposure of the kidneys to vasopressin. Congruent with this hypothesis, studies in the PCK rat have shown slowing of cystic kidney disease and vasopressin suppression with high water consumption[10,11]. In humans, Amro et al[12] showed significant reductions in copeptin concentration and urine osmolality after two weeks of solute restriction and high water intake compared in 34 patients with ADPKD. In a prospective observational study, high water intake in 13 patients with ADPKD resulted in reduced urine osmolality and increased urine volume compared to healthy controls after 7 days[13]. However, in a non-randomised prospective study of 30 ADPKD patients, high water intake resulted in a more rapid decline in eGFR and increase in TKV despite a significant reduction in urine osmolality and plasma copeptin level compared to controls[14]. Uncertainty therefore remains over the effectiveness and safety of high water

intake in preserving kidney function in patients with ADPKD. Adequately powered randomised trials are urgently needed.

One other trial of high water intake is currently underway (PREVENT-ADPKD ACTRN12614001216606), with the aim of recruiting 180 ADPKD patients who will be randomised to high or standard water intake[15]. However, PREVENT-ADPKD has several important limitations. First, patients with eGFR < 30 ml/min are excluded from the trial. Second, the primary outcome change in height-adjusted total kidney volume (htTKV), a surrogate for kidney function decline. Powered (87%) to detect a relatively large difference in htTKV increase, there is a very real risk that clinically meaningful effect may exist but might not be detected in a trial of this size. Third, the validity of htTKV as a surrogate for disease progression is disputed.[16 7]. PREVENT-ADPKD will therefore not determine the effect of high water intake on kidney function. Finally, PREVENT-ADPKD will not assess the acute effects of increased hydration in eGFR. Acute effects are of high importance in selecting the most appropriate kidney function endpoint for interventional trials in CKD[17]. It is apparent that, irrespective of the outcome of this trial, a large randomised comparison of the effect of high water intake versus standard of care on kidney function will remain necessary.

We report the design and set-up of a randomised feasibility trial of high versus ad libitum water intake, developed to rigorously assess the feasibility of a definitive trial powered to detect a difference in kidney function decline in patients with ADPKD. This trial was initiated by patient members of the PKD Charity through a research proposal to the Patient Led Research Hub during 2016, and has been co-designed and produced (and part funded) by the PKD charity.

METHODS AND ANALYSIS

Objectives

The primary feasibility objectives are 1) recruitment rate, and 2) achievement of target urine osmolality in ≥ 85% of study participants in the HW group. Secondary endpoints include separation in urine osmolality between trial arms, the completeness of self-monitored uSG data (adherence to the self-monitoring regimen), serious adverse event rate, changes in quality of life (EQ5D) scores from baseline to 8 weeks, change in pain scores between

groups, change in measured GFR between baseline and 4 weeks, and change in eGFR between baseline and 4 weeks (Table 1).

Primary Endpoints
The number of patients eligible for, and randomised to the trial
The proportion of patients in the high water intake group achieving a urine osmolality < 270 mOsmo/kg
Secondary Endpoints
The proportion in each of the high and ad libitum water intake groups achieving their target urine osmolality (between group separation)
The proportion of participants that can self-monitor and report urine SG reliably
Acceptability and usability of the SPLASH app (qualitative questionnaires and interviews)
Incidence of serious adverse event
Change between baseline and 8wk in quality of life scores (measured using EQ-5D)
Change between baseline and 8wk pain scores (measured using Pain Questionnaire)
Change in measured GFR between baseline and 4wks (acute GFR effects in high water intake group)
Change in estimated GFR between baseline and 4 weeks (both interventional groups)
Acute GFR effects measured as the change in ^{51}CR-EDTA measured GFR from week 0 to week 4

Table 1: DRINK trial primary and secondary endpoints

Trial Design

This prospective, open label, randomised trial was designed to assess the feasibility of a large definitive randomised controlled trial comparing the effectiveness and safety of high water intake in patients with ADPKD to a control arm of ad libitum water intake. Participants were randomly assigned (1:1) to receive either a prescribed (high) fluid intake sufficient to achieve vasopressin suppression, or to ad libitum water intake (Figure 1). Following an 8 week treatment period where participants will undertake all the trial assessments, they will undergo a four week washout and have one final end of trial visit at week 12. The trial was first proposed by the Polycystic Kidney Disease (PKD) Charity, and was developed through and

supported by the Cambridge Patient Led Research Hub, and run by the Cambridge Clinical Trials Unit.

Two nested substudies will be conducted: 1) Substudy A includes ^{51}CR-EDTA measured GFR and is designed to assess the acute effects on GFR of high water intake in the HW group. This substudy aims to enroll a minimum of 8 participants. 2) Substudy B is designed to assess the impact of a novel smartphone-based fluid intake monitoring device (termed SPLASH)[18] in promoting adherence to fluid prescriptions (Figure 2). Substudy B aims to enroll at least 10 participants.

Trial population, eligibility criteria and recruitment

Patients with a confirmed diagnosis of ADPKD aged 16 years or older are eligible for enrolment in the trial (Table 2). Patients are deemed ineligible if they have advanced renal impairment (defined as an estimated GFR < 20 ml/min/1.73m^2), are unable to provide informed consent, are unable or unwilling to comply with study procedures including self-monitoring of urinary specific gravity (SG), have evidence of fluid excess (defined as peripheral oedema, pulmonary oedema, heart failure, liver cirrhosis) or are receiving treatment with diuretics for such states, have concomitant renal diseases other than ADPKD, are pregnant or breastfeeding, or are receiving treatment with Tolvaptan within 4 weeks of screening.

In this single-center trial, participants will be recruited from the renal genetics and tubular disorders clinic at Addenbrooke's Hospital, Cambridge. Patients from other centers are eligible for entry, but have to attend Addenbrooke's Hospital for screening, enrolment and study procedures. Patients will be reimbursed for travel and other expenses, but will not receive any other payment or incentives for trial participation.

The DRINK trial was advertised nationally on the PKD charity and RaDAR websites and presented at PKD Patient Information days. Recruitment commenced in September 2016. The trial aims to enroll up to 50 participants. The trial steering committee may recommend halting recruitment at any point after 30 patients have been enrolled if it is clear that the feasibility questions have been adequately addressed.

Inclusion criteria

Diagnosis of ADPKD (radiological and or genetic evidence of PKD1 or PKD2 mutations) Aged 16 years or older Ability to provide informed consent eGFR ≥ 20ml/min/1.73m^2 Able to self-monitor uSG
Exclusion criteria
Fluid overload states e.g. heart failure, cirrhosis, or requirement for fluid restriction Confounding illness impacting on renal disease e.g. concomitant diabetes or glomerulonephritis Treatment with diuretics for fluid overload (those on diuretics for hypertension may participate in the trial after a run-in period of 2 weeks) Treatment with tolvaptan in the last 4 weeks Pregnancy or breastfeeding

Table 2: Eligibility Criteria

Randomisation:

Participants will be randomly assigned (1:1) to high (HW) or ad libitum (AW) water intake using a manual sealed envelope system prepared by the Cambridge Clinical Trials Unit statistician and to which the trial team will be blinded.

Although we have chosen patient level randomisation, the autosomal dominant inheritance pattern of ADPKD raises the particular challenge that multiple members of the same family or household may participate in a trial. In the context of high water intake, this may result in contamination between trial arms since fluid consumption patterns of one family member may be influenced by that of another. This is particularly relevant given that we have previously reported that up to 80% of ADPKD patients regularly discuss their condition and treatments with family members them[19]. The ability to draw inferences on contamination between trial arms within family clusters will be dependent on the number of related participants enrolled into the trial. Were contamination between arms apparent within family clusters, this may need to be taken into account in the randomisation strategy for a definitive trial

Intervention

Participants allocated to the high water intake (HW) arm will receive an individualised daily fluid intake prescription based on the free water clearance formula (Figure 3) and designed to achieve suppression of vasopressin.

The fluid prescription will be titrated to response against uSG (Table 3), since a uSG ≤1.010 correlates with vasopressin suppression and is easily assessable by urine indicator strip testing[20]. Urine osmolality will also be measured during study visits, and fluid prescription titrated in order to achieve a urine osmolality of ≤270mOsmo/kg. Participants are required to self-monitor uSG twice weekly to ensure that their fluid intake is sufficient to maintain the dilution target. Remote monitoring of home uSG values will be facilitated through the use of a bespoke smartphone application (app) that allows participants to input and monitor their uSG values. Titration instructions are embedded within the app. Participants will be encouraged to preferentially consume water, but consumption of other beverages is not restricted and will contribute to calculation of the daily fluid consumption total. Participants will undergo regular dietary evaluation encouraging them to maintain moderate sodium (<2g/day) and protein (0.75-1g/kg/day) intake in order to facilitate adherence to the urinary dilution target.

Urine SG	HW Group Advice	AL Group Advice
1.005	Maintain	Reduce intake by 3 cups
1.010	Maintain	Reduce intake by 2 cups
1.015	Increase intake by 2 cups	Maintain
1.020	Increase intake by 3 cups	Maintain
1.025	Increase intake by 4 cups	Maintain
1.030	Increase intake by 5 cups	Maintain

Table 3: Advice given to participants based on urine SG and treatment group

Control

Participants allocated to the ad libitum arm (AW) will not be given any fluid intake target, but will be asked to drink according to their usual practice and guided by thirst. They will also be required to monitor uSG using as for the HW group, but with a uSG target of >1.010 (corresponding to a urine osmolality >300mOsmo/Kg) given that, above this threshold, vasopressin is not suppressed. If the uSG is below this threshold, fluid intake is to be titrated

to achieve the target (Table 3), requiring a reduction in fluid intake. Dietary advice will be as for the HW group.

Adherence

Any attempt to conduct a trial of high water intake will need to identify mechanism for, and demonstrate the feasibility of, achieving and maintaining separation between trial arms sufficient to realistically translate into a biologically meaningful effect. Studies of the effect of high water intake advice on renal stone disease have shown the majority of patients are non-adherent to fluid prescription[21] and, in ADPKD patients[19], often over-estimate daily fluid intake. Several methods have been used to increase water intake in adults including education and counselling, goal setting, self-monitoring or the provision of calibrated containers. A recent systematic review of 16 studies showed that self-monitoring (urine volume and uSG) were the most effective strategy to increase fluid intake, highlighting the importance for adherence promoting methods[21]. In order to maximise the likelihood of achieving separation between trial arms, the DRINK trial will employ several novel approaches that include home monitoring of uSG and the use of smartphone technology for both monitoring and direct feedback purposes. Given that these strategies will be combined with education and counseling and regular dietary review of solute intake, failure to achieve and maintain separation between arms using the DRINK trial design would cast serious doubt on the feasibility of a larger trial powered to detect effects on kidney function decline. Assessment of the potential for a biologically meaningful separation will be facilitated by the objective analysis of measured urine osmolality and plasma copeptin concentrations.

Determinations

Blood pressure will be assessed after 5 minutes rest whilst seated. Screening blood pressure will be assessed using the DINAMAP Carescape monitor in routine clinic use. Blood pressure measurements will be taken in triplicate, and the mean of the second and third measurement reported. Brachial blood pressure will be taken in the non-dominant arm with an appropriately sized cuff, according to British Hypertension Society guidance. Side room urinalysis will be carried out using Siemens Multistix® GP indicator strips, read by Siemens CliniTek Status^{+} auto-analyser. Urine specific gravity (uSG) will be measured as a surrogate for urine osmolality by automated analysis of colorimetric change on Siemens Multistix®.

Home measurement will be conducted by visual assessment of colorimetric change, read after 45 seconds against the manufacturer's standard reference colour chart. Urine volume and measured urine osmolality will be obtained by performing two 24h urine collections at baseline. Further 24h urine samples will be obtained at 2, 8 and 12 weeks. Spot urine samples will be collected for urine osmolality estimation at every visit. Urine and plasma osmolality is measured on the Advanced Instruments Micro-Osmometer, Model 3320 using the freezing point depression method.

Creatinine will be measured using the Siemens Advia 2400 autoanalyser. Screening estimated GFR (eGFR) will be derived from the 4-variable MDRD GFR equation[22]. All within-trial eGFR measurements will be calculated using the CKD-EPI equation[23]. Serum copeptin (a surrogate for vasopressin concentrations)[24] will be analysed by the department of clinical chemistry at the Royal Victoria Infirmary, Newcastle, UK.

Plasma samples will be obtained on all participants at all time points for biobanking.

Measured GFR will be determined by ^{51}CR-EDTA. On the day preceding the test, participants will be asked to abstain from high protein meals and excessive caffeine, and to abstain from caffeine consumption after 10pm. They will be permitted a light breakfast on the day of the test. An intravenous injection of 2MBq Chromium-51 EDTA was administered via a 16G cannula. Venous blood (10mL) will be drawn from the contralateral arm at baseline, 2, 3 and 4 hours after the injection. Samples will be centrifuged for 15 minutes at 2000rpm to allow plasma separation, and read using a Wizard2 2480 gamma counter (PerkinElmer). The glomerular filtration rate will be derived from the area under the plasma clearance curve using the slope intercept method.

Health-related Quality of Life (HRQoL) will be assessed using the EQ-5D quality of life questionnaire (EUROQoL), administered at baseline and 8 weeks.

Secondary outcome data from the efficacy trial of tolvaptan suggests that the drug reduces the frequency of acute episodic pain in ADPKD[25]. Although the mechanism for pain relief is unclear, it was partly explained by the reduced incidence of urinary tract infection, stones, and cyst rupture and haemorrhage. As high water intake is associated with reduced incidences of urinary stones and infections in the general population[26] and the increasing recognition of chronic pain in the condition[27], we have chosen to assess pain in DRINK. This will be assessed using a bespoke pain assessment tool to collect longitudinal data on the nature, frequency and pattern of pain, and analgesic use (SUPPLEMENTARY APPENDIX I). To date, no questionnaires have been validated for the assessment of pain in ADPKD. We

employed two brief questionnaires, which are validated and widely used for a broad range of chronic pain disorders in the general population, which are Short-form Brief Pain Inventory (SF-BPI)[28] and McGill Pain Questionnaire (SF-MPQ-2)[28]. The questionnaire will be completed at baseline and week 8, but participants can also record any acute episodes of pain at any time during the study. This will be facilitated through provision of the pain assessment tool within the trial smartphone application. A separate paper will follow that describes the results and feasibility of use in the DRINK-cohort.

An acceptability questionnaire, adapted from that used by Torres et al[7], will be administered at the end of the trial to determine the sustainability and acceptability of long term adherence to the trial fluid intake prescription. All questionnaire based assessments (EQ5D, Pain, Acceptability) can be completed on paper, via email or via smartphone application. The trial smartphone application has been developed in collaboration with FatFractile Ltd. The app will be used to record home uSG results, capture questionnaire data as described above, allow messaging and reminder functionality, and to direct participants to help and additional information if required (SUPPLEMENTARY APPENDIX II). In order to avoid contamination between trial arms, two distinct versions of the app were developed, each specific to one of the trial arms. Identification of the version of the app used by participants could be monitored centrally to avoid use of the incorrect version.

Run in period

Eligible patients who are prescribed either diuretics or Tolvaptan will be allowed to enter a two-week run-in period after enrolment during which these drugs will be withdrawn. At the end of the run-in period, these participants will be reassessed to ensure that they still met the eligibility criteria before commencing the trial. Diuretics will only be withdrawn if the indication is hypertension, and which case alternative anti-hypertensives will be prescribed. Alternatives that would result in acute effects on GFR will be avoided (ACE inhibitors and Angiotensin Receptor Blockers).

Participant Timeline

The trial design is represented graphically in Figure 1 and the schedule of events in Table 4.

Screening

Patients who are potentially eligible will be invited for a screening visit. Screening will include a medical history and a targeted ADPKD-related history that captures data on the

timing and nature of the diagnosis, kidney size and function, and the presence of any complications such as pain, haemorrhage, nephrolithiasis or infections. Comorbidities and medications will be recorded. A full physical examination will be conducted that includes assessment of blood pressure. Indicator strip side room urinalysis will be performed. Blood analysis will include a full blood count, liver function tests, electrolytes and creatinine, and paired serum and spot urine osmolalities. Participants that are deemed eligible will be provided with two 24h urine collection bottles for return at the time of the baseline visit in order to measure osmolality and urine volume.

Baseline

Eligible participants who have provided informed consent will be randomised at the time of the baseline visit. A targeted physical examination to assess fluid status and vital signs will be conducted. Participants will be weighed, prescribed medications noted and blood and urine taken to measure electrolytes and creatinine, osmolality and urinalysis. A baseline quality of life EQ5D questionnaire will be completed. Participants will be instructed on how to conduct indicator strip uSG analysis, and asked to perform urinalysis twice weekly on Mondays and Thursdays between 16:00 and 20:00. They will be assisted in installing the DRINK trial smartphone application on their smartphone, and will be provided with a tutorial on its use. This will allow input of home uSG measurements. Participants who do not own a smartphone will be required to telephone, email or text uSG results to the trial team. Finally, participants will be required to complete the DRINK trial pain assessment tool (SUPPLEMENTARY APPENDIX I).

Follow-up (weeks 2, 4, 8):

Participants will be recalled for follow-up visits after 2, 4 and 8 weeks. During these visits, a physical examination will be carried out and weight and vital signs recorded. Blood and urine samples will be taken to measure electrolytes and creatinine, osmolality and urinalysis. Urine for 24h urine osmolality will be collected at weeks 2 and 8 respectively. A dietary assessment will be carried out at weeks 4 and 8. A pain assessment and EQ5D questionnaire will be completed at the 8week visit.

Washout period and final visit:

After completion of the intervention period (week 8), participants will be asked to revert to their pre-enrolment fluid intake. After a further 4 weeks, a final visit will be conducted (week 12). This will include all assessments conducted at the 8week visit, with the exception of pain and quality of life questionnaires.

Study Period							
Time Point		Recruitment	Trial visits				
			Active				Washout
		W-24**	W0	W2	W4	W8	W12
Enrolment	Screening	X					
	Informed Consent	X					
	Randomisation	X					
Intervention	High water intake						
	Ad libitum water intake						
Assessment	Medical History	X					
	Medication review	X	X	X	X	X	X
	Physical Examination	X	X	X	X	X	X
	Vital Signs (Blood pressure, pulse rate and oximetry)	X	X	X	X	X	X
	Height	X					
	Weight	X	X	X	X	X	X
	Haematology (Full blood count)	X					
	Biochemistry (Urea, Creatinine, Electrolytes, Serum Osmolality)	X	X	X	X	X	X
	Biochemistry (Liver function and bone profile)	X					
	Measured GFR*		X	X	X		
	Urine SG	X	X	X	X	X	X
	Spot Urine Osmolality	X	X	X	X	X	X
	24 hour Urine Collection (volume and osmolality)	X		X		X	X
	Home uSG monitoring***		X	X	X	X	
	SPLASH Monitoring		X	X	X	X	
	Dietary Assessment	X	X		X		X
	Pain Questionnaire***		X			X	
	Acceptability Questionnaire***		X			X	
	EQ5D***		X			X	

Table 4: Schedule of enrolment, intervention and assessments

* ^{51}Cr-EDTA measured GFR performed as part of a sub-study in 8 participants in the HW group

** 24 week pre study recruitment period. *** Recorded using the DRINK Smartphone App

SUBSTUDY A

Effect of high water intake on ^{51}CR-EDTA GFR

Determining the acute effects of high water intake on GFR is a prerequisite to the definition of renal endpoints in any future trial[22]. We will conduct a substudy to determine the acute effect of high water intake on ^{51}CR-EDTA GFR, to allow a more rigorous assessment of GFR than that derived from estimation equations. Eight patients will be enrolled in this substudy, which will require a negative pregnancy test in addition to the eligibility criteria for the main trial.

Participants in substudy A will undergo ^{51}CR-EDTA GFR measurement at baseline, week 2 and week 4 in addition to all other trial measurements.

SUBSTUDY B

SPLASH smartphone fluid intake monitoring

Substudy B was designed to evaluate the feasibility and usability of a novel smartphone based fluid intake monitoring device termed SPLASH[18]. This Android based app uses reusable near field communication (NFC) adhesive tags that attach to drink holders (glasses, cups or bottles). Tags are calibrated before use by measuring the drinks container volume (using a standard measuring jug) and programing the app accordingly. The app is activated by holding the phone near the NFC tag, allowing the user to select the volume consumed by identifying the corresponding fraction of the container (e.g. full, ½, ¼ etc.). Ad hoc consumption of fluids from uncalibrated drinks holders is captured using customised credit card or keyring NFC tags pre-calibrated for most drinking scenarios. The app also allows input of daily fluid intake targets and displays progress towards this. Given that the system is android-specific, android phones will be provided to substudy B participants on loan where required.

At least 10 participants will be enrolled in Substudy B. Participants in both trial arms will be eligible for Substudy B enrolment. Training in the use of the SPLASH system will be provided in person, through provision of written information, and via an online training video (https://vimeo.com/208818645). Participants will be allowed to use the SPLASH system freely, but will be specifically required to use this for at least 24 hours at the time of the baseline, week 2 and week 8 visits (to coincide with measured 24h urine osmolality).

At the end of Substudy B, participants will be interviewed to provide qualitative data on their experience of using the SPLASH app.

Patient and Public Involvement

High water intake is an issue of great importance and was identified as a key research priority by patients with ADPKD. The DRINK trial was first proposed by the PKD charity in 2015 and, facilitated by the Patient Led Research Hub. Patient co-investigators have remained involved throughout the design and set-up, and are co-applicants on the awarded funding grants for the trial. The study design was presented at several PKD charity information days, and patients have provided valuable feedback on the intervention and the use smartphone applications.

The findings of the DRINK trial will be available to patients on the DRINK trial-specific and PKD websites. They will also be presented at the PKD information days that are run throughout the year by the charity.

Adverse Events and Safety

Adverse events will be assessed at each study visit. Additionally, a 24h trial participant helpline will be made available. Given the nature of the intervention, fluid retention, worsening hypertension and hyponatraemia are adverse events of special interest.

Participants will be withdrawn from the trial in the case of persistent hyponatraemia (< 132mmol/L on two consecutive samples), fluid retention defined by the presence of one of 1) pulmonary oedema, 2) significant lower limb swelling, or 3) uncontrolled hypertension on two consecutive visits despite optimal antihypertensive treatment (as judged by the responsible clinician). Participants will also be withdrawn for a decline in eGFR by ≥10ml/min/1.73m^2 or 25% from baseline, confirmed on two consecutive samples at separate time points.

All adverse events will be recorded from the point of informed consent on the appropriate case report forms. All serious adverse events will be assessed by the chief investigator in terms of seriousness and causality and reported to the sponsor in accordance with GCP guidance.

Sample size

Data from a small pilot study by Armo et al showed that using a low osmolar diet and high water intake, urine osmolality could be reduced from 426±193 to 258±147 (p=0.01) with a

non-significant change in the control group[29]. This is comparable to the reduction seen in the TEMPO3:4 trial (472 to 264 mOsmo/Kg), where 81% receiving Tolvaptan achieved a urine osmolality<300mOsmo/kg compared to 17% in the placebo group[30]. In order to observe a benefit of high water intake on the rate of kidney function decline, we estimate that a comparable proportion of the high water intake group should achieve a urine osmolality consistent with vasopressin suppression. We estimate that 28 participants would be required to detect 85% of the HW intervention group reaching their target urine osmolality and 15% of controls achieving a urine osmolality less than the target threshold (99% power, two sided α= 0.05). Assuming a 15% dropout rate, the minimum required sample size is 30.

Statistical Analysis

Analysis of the primary and secondary outcomes of the trial will utilise the intention-to-treat principle. All randomised participants will be included in the final analysis within their treatment group allocation regardless of compliance, withdrawal or protocol deviations. Data will be analysed as proportions/percentages, mean ± standard deviation and with linear mixed-level modelling for repeated measures (uSG, renal function and blood pressure). For non-parametric data median with interquartile range (25-75th) with minimum and maximum values will be reported as appropriate. We will be using a 95% CI and a significance level of ≤0.05. The analysis will be carried out using the STATA version 13.1 statistical software.

We will perform a qualitative assessment of SPLASH looking at ease and acceptability of use through participant questionnaires and face-to-face interviews. We will also collect exploratory data on the validity of SPLASH as a potential fluid intake-monitoring device, comparing the app-based intake volumes recorded to the coinciding urine osmolality results of 24 hour collections.

Data Management and monitoring

Data collection will be performed by trained local research staff at each of the trial visits in the form of case report forms. This will then be entered in to the DRINK trial database which is housed in the NIHR accredited Cambridge Clinical Trials Unit and supervised by the trial data manager. Data from the DRINK and SPLASH smartphone applications will be transferred securely to the N3 NHS Database where it can be accessed securely via a specialized administration panel by members of the research team using an encrypted password.

The DRINK study will undergo monitoring for regulatory compliance in accordance with the GCP Guidance via the trial steering committee which independently monitors progress and conduct of the trial and will also provide advice on the continuation, termination or amendments to the trial protocol. DRINK is sponsored by Cambridge University Hospital NHS Foundation Trust and will be subject to regular monitoring visits and audits.

Discussion

The DRINK trial will address the key feasibility issues facing future definitive high water intake trials in ADPKD. Importantly, it will determine the recruitment potential especially given the uptake of Tolvaptan, the optimal renal endpoint and effect size, the randomisation strategy, and demonstrate whether biological feasibility which is essential to any subsequent efficacy findings is achievable. Water as a disease modifying intervention could revolutionise the management of ADPKD, not only providing a low cost, widely available treatment option for those in developing countries, but also those with early disease for whom it is essential to target cyst development early. Yet the early stage of their condition and lack of renal function decline makes it difficult to justify the use of medications with potentially toxic side effects as the risk-benefit ratio in this group remains largely unknown.

Ethics and Dissemination

Ethical approval was awarded by the East of England Essex Research Ethics Committee in July 2016 (16/EE/0026). DRINK opened to recruitment in September 2016, and the last study visit is anticipated to be April 2018. The primary and secondary outcomes results will be published in peer-reviewed journals, this will include a separate paper on the use of smartphone technology in clinical trial design and the longitudinal ADPKD pain characteristics. A synopsis of the trial findings will also be made available to participants and the public through the trial specific website and the PKD charity. All the DRINK data will be shared through the Cambridge Data Repository.

Author Affiliations

[1]Division of Experimental Medicine and Immunotherapeutics, Department of Medicine, University of Cambridge
[2]Division of Anaesthesia, Department of Medicine, University of Cambridge
[3]PKD Charity, London, United Kingdom
[4]Cambridge Clinical Trials Unit, Cambridge UK
[5]Patient Led Research Hub, Cambridge UK
[6]Department of Medical Genetics, University of Cambridge

[7]University of Bristol, UK

Acknowledgments

We would like to thank the PKD charity for their input in the design and delivery of the DRINK trial and the British Renal Society for their grant towards the funding of DRINK. RED is supported by the PKD Charity, Kidney Research UK and the Addenbrooke's Charitable Trust. TFH and FEK are supported by the NIHR and the Cambridge Biomedical Research Centre. The DRINK smartphone application was developed in conjunction with FatFractile Ltd. and funded by the PKD charity. The SPLASH application was developed by SPHERE IRC and was funded by the UK Engineering and Physical Sciences Research Council (EPSRC) and the Addenbrookes Charitable Trust.

Contributors

TFH and TH originated the study. TFH, RED, SK, IBW, FEK and RNS designed the study. ML provided specific support with pain questionnaires. SB provided statistical expertise. All authors reviewed and approved the study protocol and manuscript

Funding Statement

The study is funded by the British Renal Society and Kidney Care UK (formerly British Kidney Patient Association) grant programme (15-004), the PKD Charity, the Addenbrooke's Charitable Trust (45/16), and Kidney Research UK (TF-009-20161125), and is supported by the UKCRC-registered Cambridge Clinical Trials Unit and the Cambridge NIHR Clinical Research Facility.

Conflict of interest

The authors declare that they have no competing interests

References

1 Chapman AB, Devuyst O, Eckardt K-U, *et al.* Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney International* 2015; **88**: 1–11.

2 Gansevoort RT, Arici M, Benzing T, *et al.* Recommendations for the use of tolvaptan in

autosomal dominant polycystic kidney disease: a position statement on behalf of the ERA-EDTA Working Groups on Inherited Kidney Disorders and European Renal Best Practice. *Nephrology Dialysis Transplantation* 2016; **31**: 337–48.

3 Shaw C, Simms RJ, Pitcher D, Sandford R. Epidemiology of patients in England and Wales with autosomal dominant polycystic kidney disease and end-stage renal failure. *Nephrol Dial Transplant* 2014; **29**: 1910–8.

4 Porath B, Gainullin VG, Gall EC-L, *et al.* Mutations in GANAB, Encoding the Glucosidase IIα Subunit, Cause Autosomal-Dominant Polycystic Kidney and Liver Disease. *The American Journal of Human Genetics* 2016; **98**: 1193–207.

5 Chebib FT, Sussman CR, Wang X, Harris PC, Torres VE. Vasopressin and disruption of calcium signalling in polycystic kidney disease. *Nat Rev Nephrol* 2015; **11**: 451–64.

6 Devuyst O, Torres VE. Osmoregulation, vasopressin, and cAMP signaling in autosomal dominant polycystic kidney disease. 2013; **22**: 459–70.

7 Torres VE, Chapman AB, Devuyst O, *et al.* Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease. *N Engl J Med* 2012; **367**: 2407–18.

8 Torres VE, Chapman AB, Devuyst O, *et al.* Tolvaptan in Later-Stage Autosomal Dominant Polycystic Kidney Disease. *N Engl J Med* 2017; : NEJMoa1710030–13.

9 van Gastel MDA, Torres VE. Polycystic Kidney Disease and the Vasopressin Pathway. *Ann Nutr Metab* 2017; **70**: 43–50.

10 Nagao S. Increased Water Intake Decreases Progression of Polycystic Kidney Disease in the PCK Rat. *Journal of the American Society of Nephrology* 2006; **17**: 2220–7.

11 Hopp K, Wang X, Ye H, Irazabal MV, Harris PC, Torres VE. Effects of hydration in rats and mice with polycystic kidney disease. *Am J Physiol Renal Physiol* 2015; **308**: F261–6.

12 Amro OW, Paulus JK, Noubary F, Perrone RD. Low-Osmolar Diet and Adjusted Water Intake for Vasopressin Reduction in Autosomal Dominant Polycystic Kidney Disease: A Pilot Randomized Controlled Trial. *American Journal of Kidney Diseases* 2016; **68**: 882–91.

13 Barash I, Ponda MP, Goldfarb DS, Skolnik EY. A pilot clinical study to evaluate changes in urine osmolality and urine cAMP in response to acute and chronic water loading in autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol* 2010; **5**: 693–7.

14 Higashihara E, Nutahara K, Tanbo M, *et al.* Does increased water intake prevent disease progression in autosomal dominant polycystic kidney disease? *Nephrology Dialysis Transplantation* 2014; **29**: 1710–9.

15 Wong ATY, Mannix C, Grantham JJ, *et al.* Randomised controlled trial to determine the efficacy and safety of prescribed water intake to prevent kidney failure due to autosomal dominant polycystic kidney disease (PREVENT-ADPKD). *BMJ Open* 2018; **8**. DOI:10.1136/bmjopen-2017-018794.

16 Yu ASL, Shen C, Landsittel DP, *et al.* Baseline total kidney volume and the rate of kidney growth are associated with chronic kidney disease progression in Autosomal Dominant Polycystic Kidney Disease. *Kidney International* 2018; **93**: 691–9.

17 MD ASL, MS LAIM, PhD KMM, *et al.* GFR Decline as an End Point for Clinical Trials in CKD: A Scientific Workshop Sponsored by the National Kidney Foundation and the US Food and Drug Administration. *American Journal of Kidney Diseases* 2014; **64**: 821–35.

18 Luo X, Woznowski P, Burrows A, Haghighi M, Craddock I. SPLASH. New York, New York, USA: ACM Press, 2016: 1526–32.

19 El-Damanawi R, Harris T, Sandford RN, Karet Frankl FE, Hiemstra TF. Patient Survey of current water Intake practices in autosomal dominant Polycystic kidney disease: the SIPs survey. *Clinical Kidney Journal* 2017; : 1–5.

20 Imran S, Eva G, Christopher S, Flynn E, Henner D. Is specific gravity a good estimate of urine osmolality? *J Clin Lab Anal* 2010; **24**: 426–30.

21 Chua TXW, Prasad NS, Rangan GK, Allman-Farinelli M, Rangan AM. A systematic review to determine the most effective interventions to increase water intake. *Nephrology* 2015; : n/a–n/a.

22 Levey AS, Greene T, Schluchter MD, *et al.* Glomerular Filtration Rate Measurements in Clinical Trials. *J Am Soc Nephrol* 1993; **4**: 1159–71.

23 Levey AS, Stevens LA, Schmid CH, *et al.* A New Equation to Estimate Glomerular Filtration Rate. *Ann Intern Med* 2009; **150**: 604–12.

24 Bolignano D, Cabassi A, Fiaccadori E, *et al.* Copeptin (CTproAVP), a new tool for understanding the role of vasopressin in pathophysiology. *Clinical Chemistry and Laboratory Medicine (CCLM)* 2014; **52**: 1–10.

25 Casteleijn NF, Blais JD, Chapman AB, *et al.* Tolvaptan and Kidney Pain in Patients With Autosomal Dominant Polycystic Kidney Disease: Secondary Analysis From a Randomized Controlled Trial. *American Journal of Kidney Diseases* 2017; **69**: 210–9.

26 Lotan Y, Daudon M, Bruyère F, *et al.* Impact of fluid intake in the prevention of urinary system diseases. *Current Opinion in Nephrology and Hypertension* 2013; **22**: S1–S10.

27 Hogan MC, Norby SM. Evaluation and Management of Pain in Autosomal Dominant Polycystic Kidney Disease. *Advances in Chronic Kidney Disease* 2010; **17**: e1–e16.

28 Dworkin RH, Turk DC, Trudeau JJ, *et al.* Validation of the Short-Form McGill Pain Questionnaire-2 (SF-MPQ-2) in Acute Low Back Pain. *The Journal of Pain* 2015; **16**: 357–66.

29 Amro OW, Paulus JK, Noubary F, Perrone RD. Low-Osmolar Diet and Adjusted Water Intake for Vasopressin Reduction in Autosomal Dominant Polycystic Kidney Disease: A Pilot Randomized Controlled Trial. *American Journal of Kidney Diseases* 2016; **68**: 882–91.

30 Devuyst O, Chapman AB, Gansevoort RT, *et al.* Urine Osmolality, Response to Tolvaptan, and Outcome in Autosomal Dominant Polycystic Kidney Disease: Results from the TEMPO 3:4 Trial. *Journal of the American Society of Nephrology* 2017; **28**: 1592–602.

Legends for figures

Figure 1: Schematic of the DRINK trial design. Participants are randomised 1:1 to the High water (HW) or Ad libitum (AW) water intake groups. Each participant in the HW group is given an individualised daily water prescription with urinary dilution targets consistent with vasopressin suppression. The AW group has more concentrated urinary targets.

Figure 2: Smartphone technology used during the DRINK study. The SPLASH app uses near field communication technology to automate fluid intake monitoring (left). The DRINK app will be used to record urine specific gravity results allowing remote data collection and monitoring of progress (right).

Figure 3: Calculation of fluid prescription using the free water clearance equation. Insensible losses were arbitrarily set at 500mls as an average

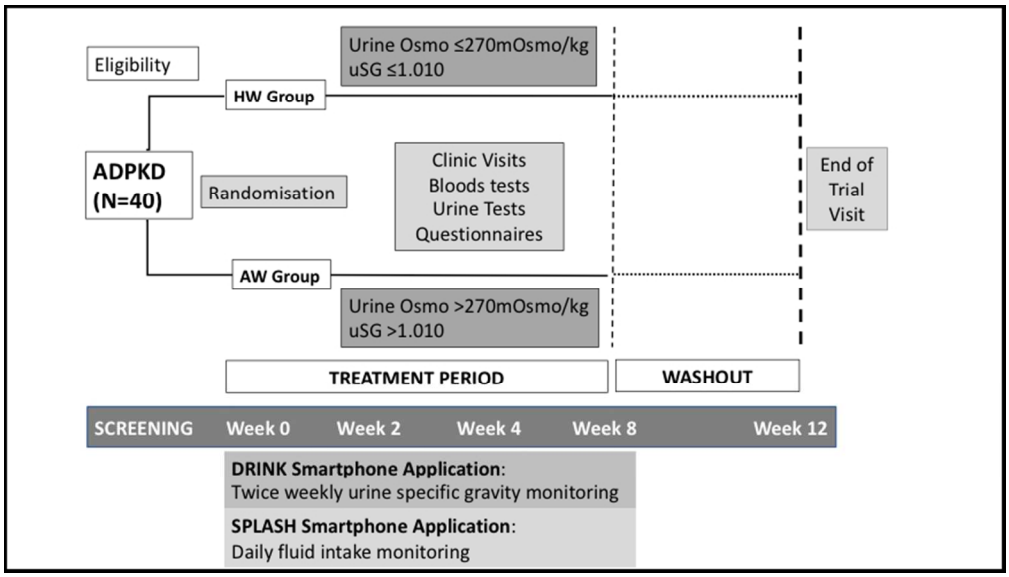


Figure 1: Schematic of the DRINK trial design. Participants are randomised 1:1 to the High water (HW) or Ad libitum (AW) water intake groups. Each participant in the HW group is given an individualised daily water prescription with urinary dilution targets consistent with vasopressin suppression. The AW group has more concentrated urinary targets.

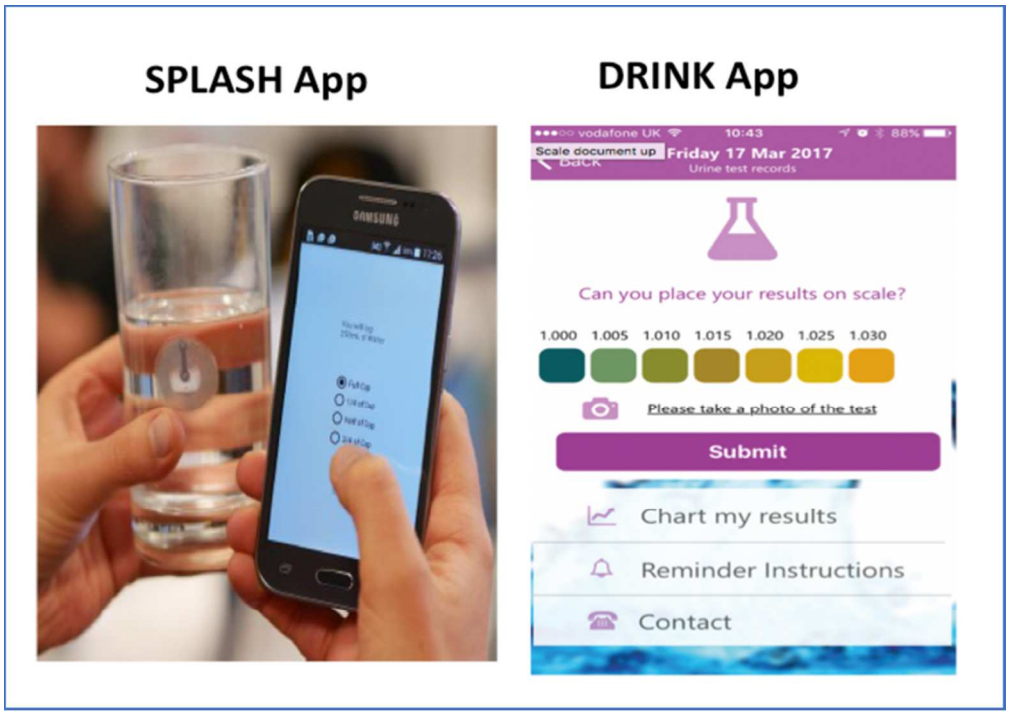


Figure 2: Smartphone technology used during the DRINK study. The SPLASH app uses near field communication technology to automate fluid intake monitoring (left). The DRINK app will be used to record urine specific gravity results allowing remote data collection and monitoring of progress (right).

Calculation is shown for a hypothetical patient

Average of 2x 24 hours collections:
Total Solute = Urine Osmolality (mOsmo/Kg) x Urine Volume (mls)

Free Water Clearance Formula:
Fluid intake = {Total Solute (moSmo)/270} + Insensible Losses*

Example
The average 24 hour urine collection results for a participant in the HW group show the following;
Urine Osmolality 400mOsmo/Kg
Urine Volume 1500mls

Thus….
Total solute = 400 x 1500 = 600000
Fluid intake = (600000/270) + 500 = 2722 mls

A minimum of 2722 milliliters of fluid/day is required to achieve the target urine osmolality ≤270mOsmo/kg

Figure 3: Calculation of fluid prescription using the free water clearance equation. Insensible losses were arbitrarily set at 500mls as an average

Appendix I - Pain Questionnaire

BASELINE/ SCREENING +/- other visits too.

Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain? **YES/NO**

If YES,
Body Map:

Please shade using **horizontal** lines in the areas where all your pain(s) are.

Now shade using **vertical** lines where you feel that your **kidney** problems are causing pain.

Put X on **where pain** it hurts (bothers) you the most.

For area marked X,

*Please rate your pain by marking the box beside the number that best describes your pain at its **WORST** in the **last 2 weeks***

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No pain — *Pain as Bad As You Can Imagine*

*Please rate your pain by marking the box beside the number that best describes your pain at its **LEAST** in the **last 2 weeks***

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No pain — *Pain as Bad As You Can Imagine*

*Please rate your pain by marking the box beside the number that best describes your pain **ON AVERAGE***

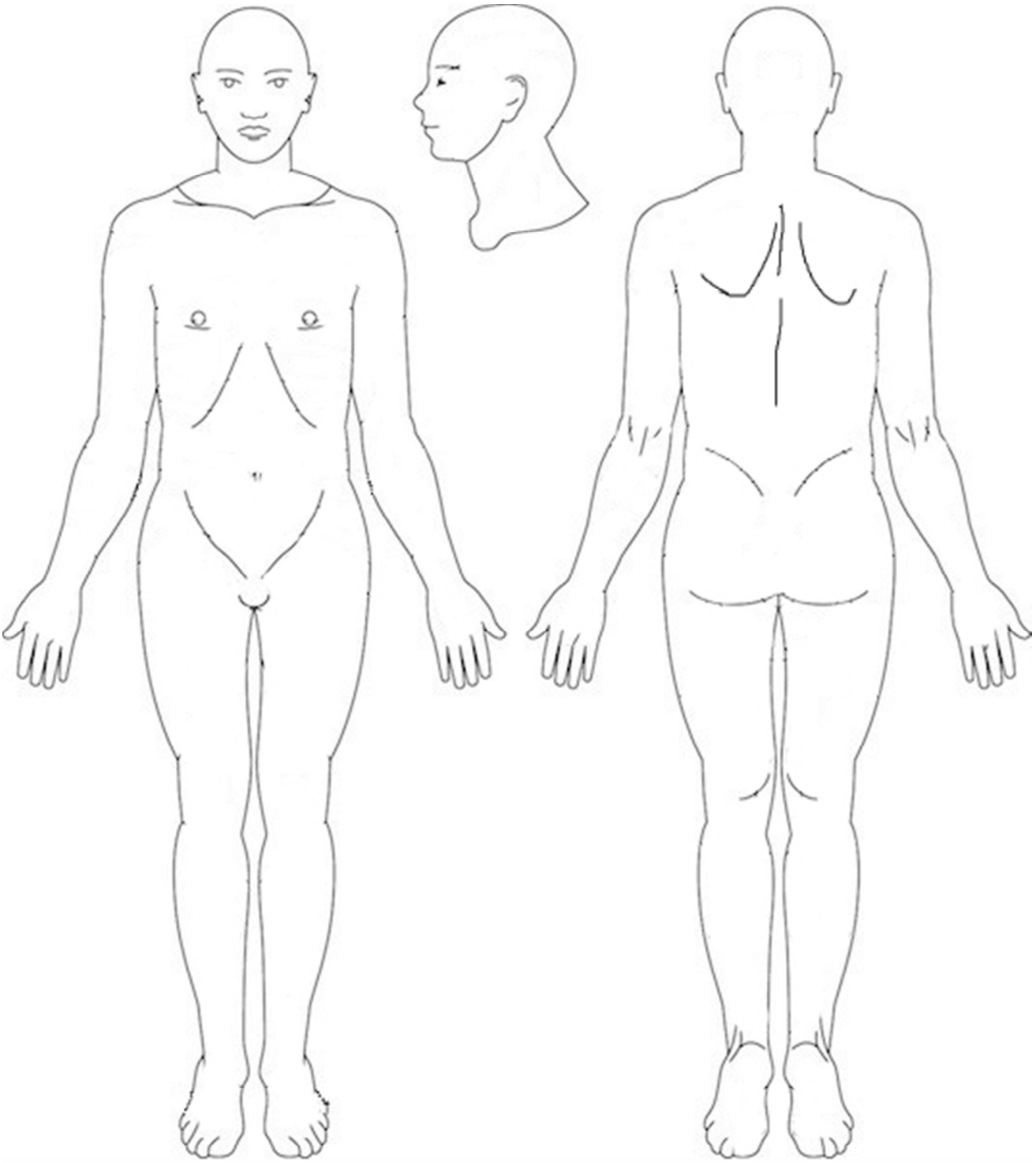
☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

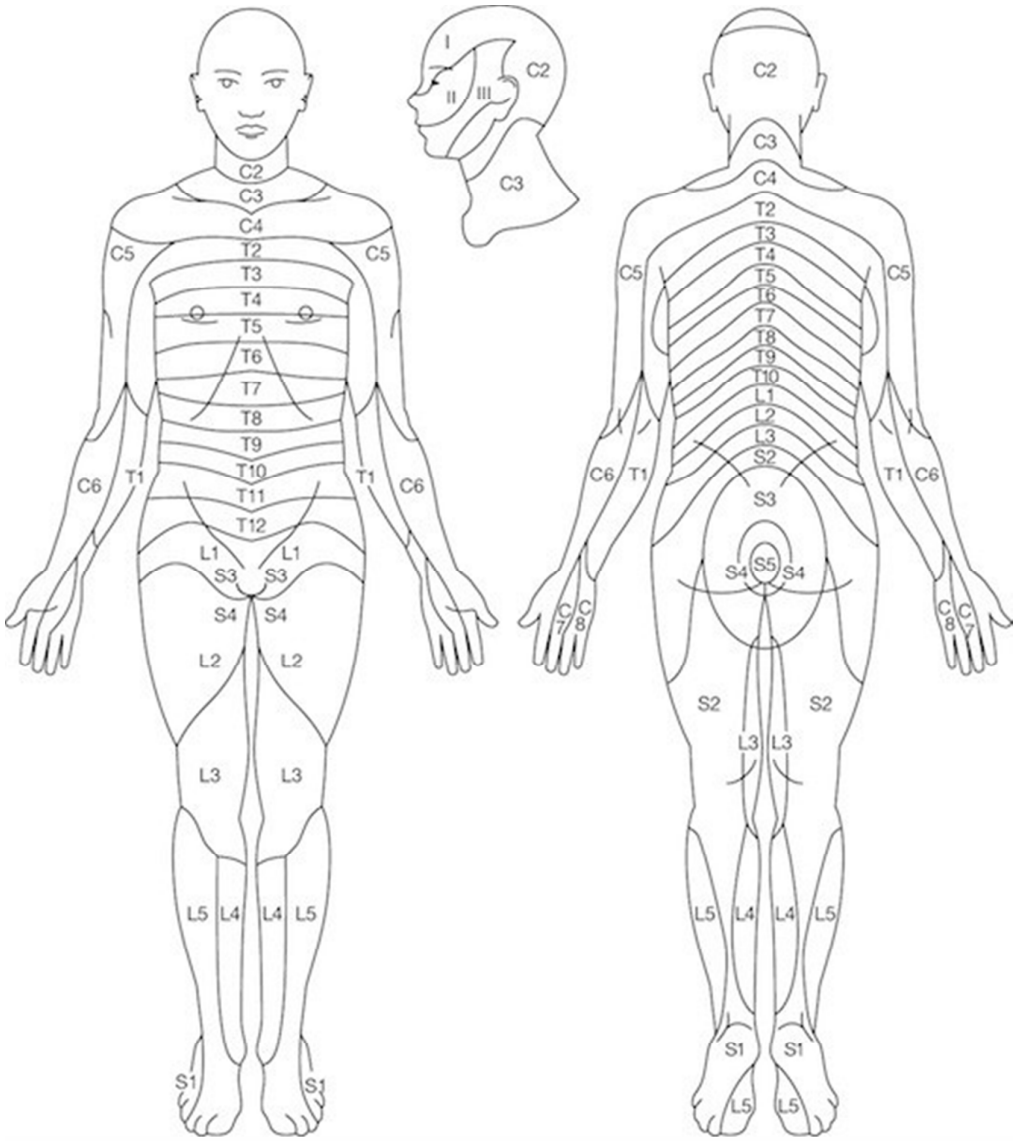
No pain — *Pain as Bad As You Can Imagine*

*Please rate your pain by marking the box beside the number that tells us how much pain you have **RIGHT NOW***

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No pain — *Pain as Bad As You Can Imagine*





BASELINE & FOLLOW-UP VISITS

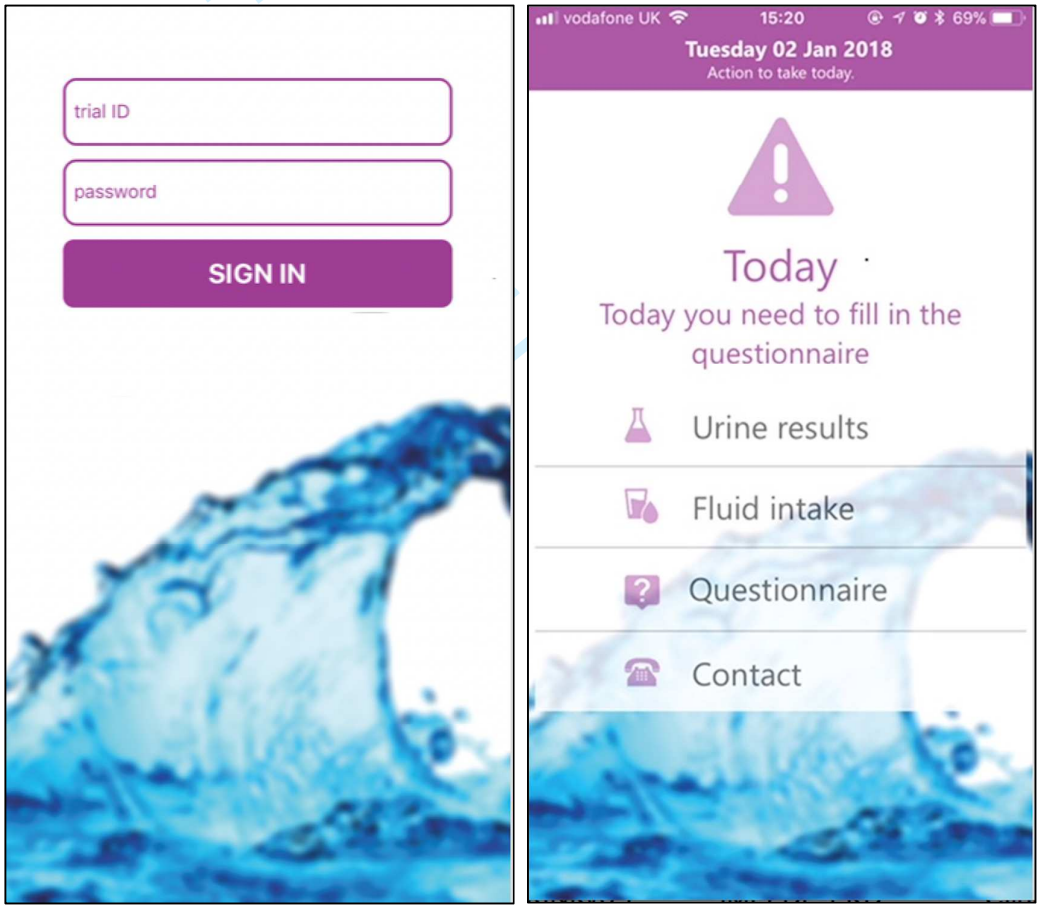
McGill Pain Questionnaire:

This questionnaire provides you with a list of words that describe some of the different qualities of pain and related symptoms.
Please put an **X** through the numbers that best describe the intensity of each of the pain and related symptoms you felt during the past **TWO WEEKS**.
Use **0** if the word does not describe your pain or related symptoms

1. Throbbing pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
2. Shooting pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
3. Stabbing pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
4. Sharp pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
5. Cramping pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
6. Gnawing pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
7. Hot-burning pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
8. Aching pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
9. Heavy pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
10. Tender	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
11. Splitting pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
12. Tiring-exhausting	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
13. Sickening	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
14. Fearful	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
15. Punishing-cruel	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
16. Electric-shock pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
17. Cold-freezing pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
18. Piercing	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
19. Pain caused by light touch	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
20. Itching	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
21. Tingling or 'pins and needles'	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
22. Numbness	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*

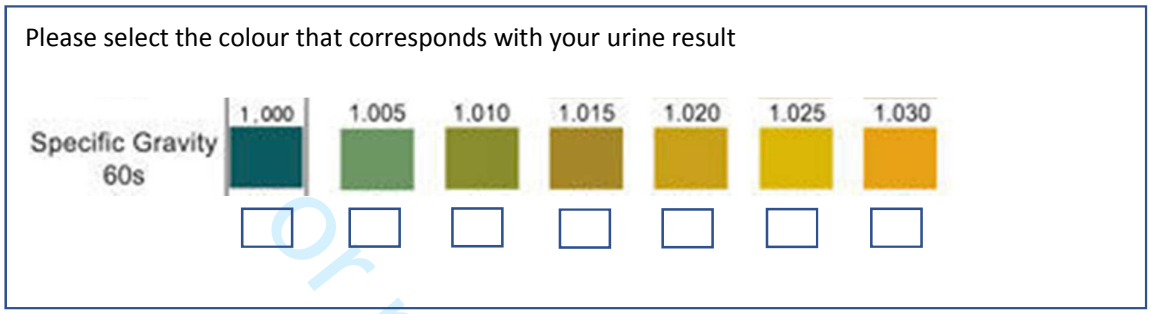
Appendix II – DRINK Smartphone Application

The smartphone application will be used by participants to record the results of their urine specific gravity (SG) measurement, pain and EQ 5D quality of life questionnaire and the participant acceptability question. Each participant will be given a unique trial ID number. When accessing the application for the first time, they will need to register and select a unique password. After this, each access to the application will require participants to input their unique trial ID and password. The information inputted is transferred and stored securely on the NHS N3 server. This is facilitated by FatFractile Ltd. Below is a picture of the login screen and the home screen that participants can use to navigate through the application.

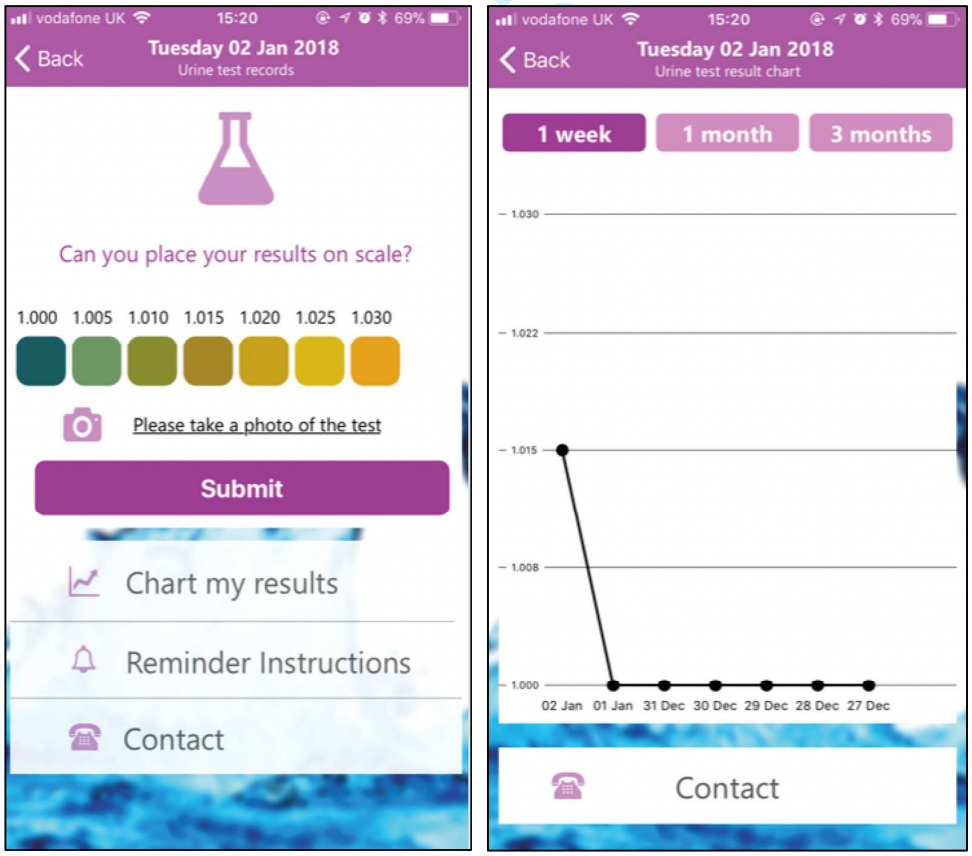


1) Home monitoring of urine SG

Every Monday and Thursday morning between 9am-12pm participants will receive a push notification from the reminding them that today a urine SG dipstick test is required and that this should be done between 4-8pm. Once they have the urine test result participants will be asked to input the urine SG result, see below.



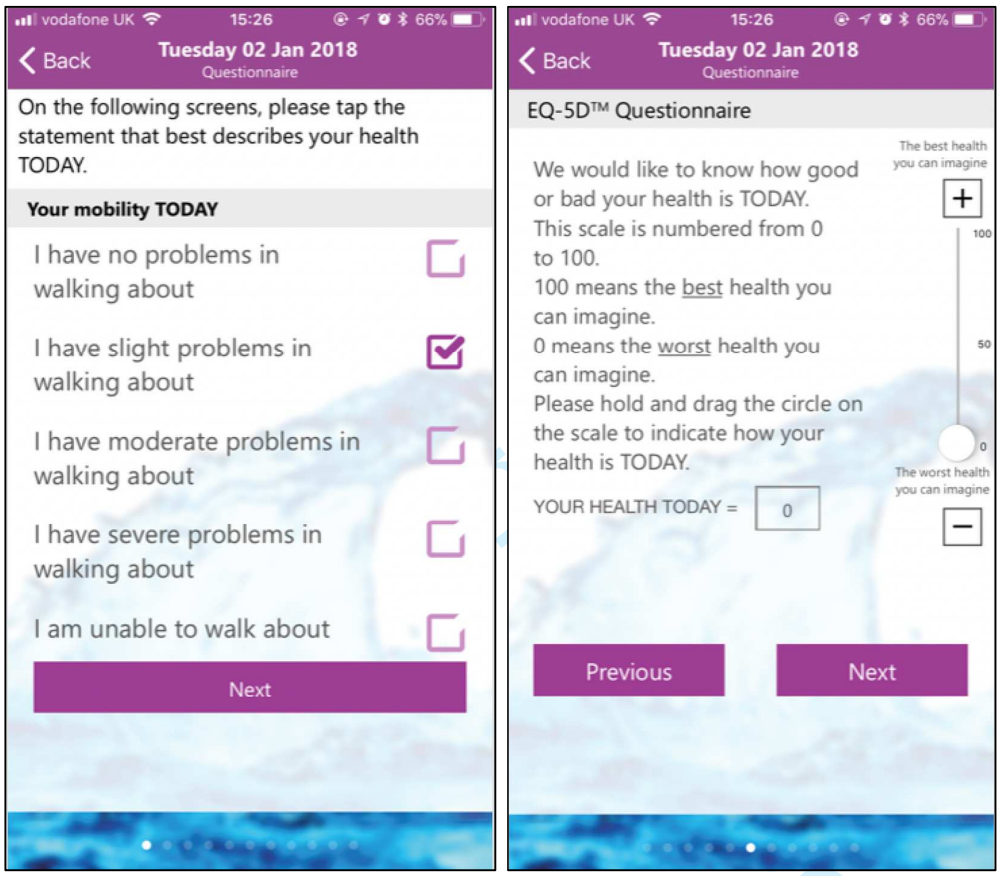
Once they make a selection this data can be transferred securely to the N3 database. A link is also available that will direct the participants to the trial specific website if they require further information or advice. Participants can also view their previous results in chart format to monitor their own progress. A picture of the urine results page as seen in the app is seen below.



2) EQ 5D Questionnaire

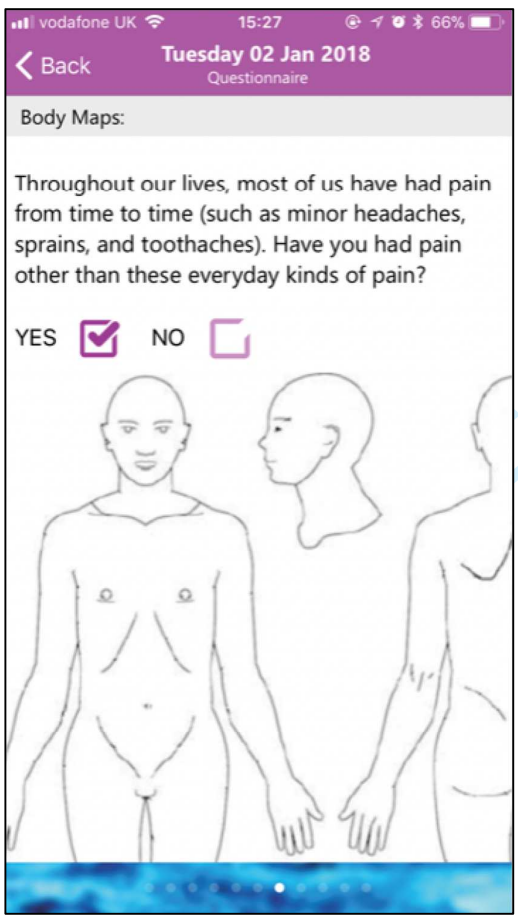
Participants will be reminded to fill out this questionnaire on the smartphone application at the screening visit and again at week 8. The results will be securely transferred to the NHS N3 server.

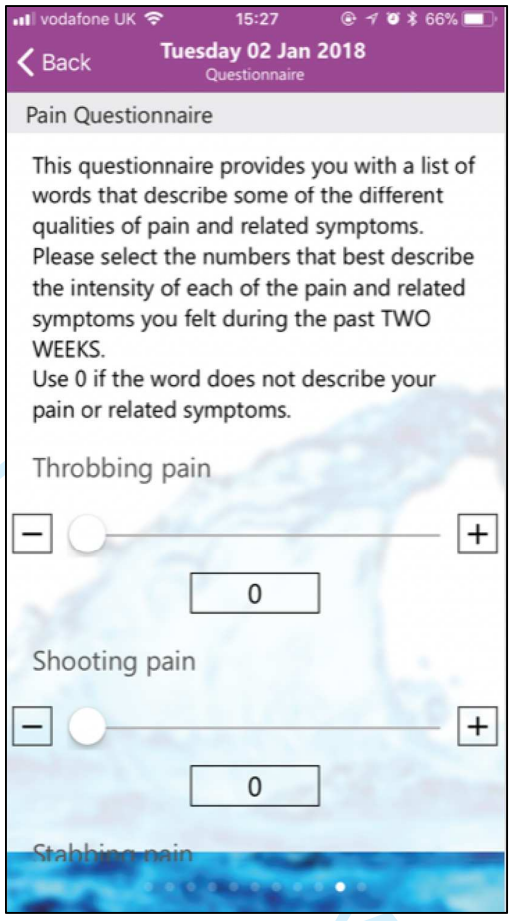
Examples of the questionnaire as seen in the smartphone app are demonstrated below.



3) Pain Questionnaire

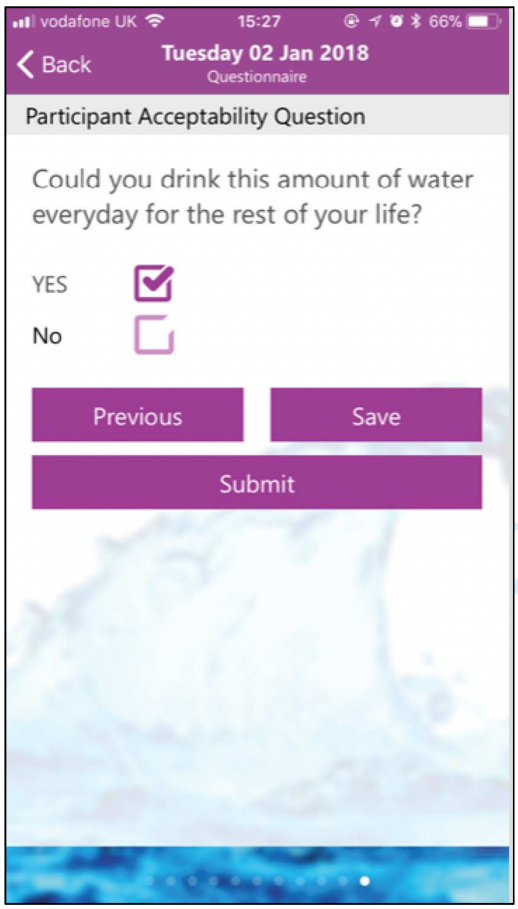
Participants will be reminded to fill out their pain questionnaire on the smartphone application at the screening and at the end of the treatment period at week 8. The data will be securely transferred to the NHS N3 database. Examples of the questionnaire from the app are demonstrated here.





4) Participant Acceptability Question

Participants will be reminded to answer the acceptability question on the smartphone application at weeks 0 and then again at week 8. An example of the question as seen in the app is shown below.



BMJ Open

A Randomised Controlled Trial of High versus Ad Libitum Water Intake in Patients with Autosomal Dominant Polycystic Kidney Disease: Rationale and Design of the DRINK Feasibility Trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022859.R1
Article Type:	Protocol
Date Submitted by the Author:	26-Mar-2018
Complete List of Authors:	El-Damanawi, Ragada; Division of Experimental Medicine and Immunotherapeutics, Department of Medicine, University of Cambridge; Cambridge Clinical Trials Unit, Lee, Michael; Division of Anaesthesia, Department of Medicine, University of Cambridge Harris, Tess; PKD Charity, London, United Kingdom Mader, Laura; Cambridge Clinical Trials Unit, ; Patient Led Research Hub Bond, Simon; Cambridge Clinical Trials Unit, Pavey, Holly; Cambridge Clinical Trials Unit, Sandford, Richard; Department of Medical Genetics, University of Cambridge Wilkinson, Ian; Division of Experimental Medicine and Immunotherapeutics, Department of Medicine, University of Cambridge; Cambridge Clinical Trials Unit, Burrows, Alison; University of Bristol Woznowski, Przemyslaw; University of Bristol Ben-Shlomo, Yoav; University of Bristol Karet Frankl, Fiona; Department of Medical Genetics, University of Cambridge Hiemstra, Thomas; Division of Experimental Medicine and Immunotherapeutics, Department of Medicine, University of Cambridge; Cambridge Clinical Trials Unit,
Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Renal medicine, Genetics and genomics, Health economics, Health informatics, Research methods
Keywords:	Autosomal Dominant Polcystic Kidney Disease, Vasopressin, Water, Osmolality, Urine specific gravity, Feasibility

A Randomised Controlled Trial of High versus Ad Libitum Water Intake in Patients with Autosomal Dominant Polycystic Kidney Disease: Rationale and Design of the DRINK Feasibility Trial

Ragada El-Damanawi[1,4], Michael Lee[2], Tess Harris[3], Laura B Mader [4,5], Simon Bond[4], Holly Pavey[4], Richard N Sandford[6], Ian B Wilkinson[1,4], Alison Burrows[7], Przemyslaw Woznowski[7], Yoav Ben-Shlomo[7], Fiona E Karet Frankl[6], Thomas F Hiemstra[1,4]

[1]Division of Experimental Medicine and Immunotherapeutics, Department of Medicine, University of Cambridge; [2]Division of Anaesthesia, Department of Medicine, University of Cambridge; [3]PKD Charity, London, United Kingdom; [4]Cambridge Clinical Trials Unit, Cambridge UK; [5]Patient Led Research Hub, Cambridge UK, [6]Department of Medical Genetics, University of Cambridge; [7]University of Bristol, UK.

Corresponding Author:

Thomas F Hiemstra
tfh24@cam.ac.uk
Cambridge Clinical Trials Unit
Box 401 Cambridge Biomedical Campus,
Hills Road,
Cambridge,
CB2 0QQ,
United Kingdom

ABSTRACT

Introduction

Vasopressin stimulates cyst growth in Autosomal Dominant Polycystic Kidney Disease (ADPKD) leading to enlarged kidneys, hypertension and renal failure. Vasopressin receptor blockade slows disease progression. Physiological suppression of vasopressin secretion through high water intake could achieve a similar effect, necessitating a definitive large-scale trial of high water intake in ADPKD. The objective of the DRINK trial is to answer the key design and feasibility questions required to deliver a successful definitive water intake trial.

Methods and Analysis

We describe the design of a single-centre, open label, prospective, randomised controlled trial. DRINK aims to enroll 50 ADPKD patients, over the age 16years with an eGFR≥20ml/min/1.73m2. Participants will be randomised 1:1 to high water (HW) intake based on an individualised water intake prescription, or to ad libitum(AW) water intake. The HW group will aim for a dilute urine (urine osmolality≤270mOsmo/kg) as a surrogate marker of vasopressin suppression, and those in the AW group will target more concentrated urine. Participants will have an 8week treatment period, and will be seen at week 0, 2,4 and 8, undergoing assessments of fluid status, renal function and serum and urine osmolalities. They will receive dietary advice, and self-monitor urine specific gravity and fluid intake. The trial employs smartphone technology to permit home monitoring and remote direct data capture. The primary feasibility endpoints are recruitment rate and separation between arms in measured urinary osmolality. Key secondary assessments include acceptability, adherence, health-related quality of life, acute effects of high water intake on measured (^{51}Cr-EDTA) and estimated glomerular filtration rate, and ADPKD-related pain.

Ethics and Dissemination

Ethical approval was awarded by the East of England Essex Research Ethics Committee (16/EE/0026). The results of DRINK will be submitted to peer reviewed journals, and presented to patients via the PKD Charity.

Trial Registration Details: NCT02933268 and ISCRTN16794957

Strengths and Limitations

- The use of a randomised controlled feasibility trial designed to determine adherence and adequate separation between treatment arms will provide crucial data on the practical and biological feasibility of a definitive global high water trial
- Self-monitoring and recording of results using smartphone technology will aid compliance and allow remote data capture, thereby reducing the burden of trial visits on participants and facilitate recruitment and streamlining of future trials
- The effect of high water intake in ADPKD was identified as a research priority by ADPKD patients. The trial was designed and is being conducted in partnership with the PKD Charity.
- DRINK will include those with more advanced kidney disease (CKD3 and 4), representative of typical patients under hospital care
- DRINK is limited by the relatively short duration of follow-up, thus not providing data on the long-term sustainability of fluid prescription adherence.

INTRODUCTION

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the commonest human inherited renal disorder affecting 12 million people worldwide[1]. Kidney cyst growth throughout the life span leads to enlarged kidneys, hypertension and impaired kidney function. More than two thirds of those affected will develop kidney failure by a median age of 58 years[2], approximately 10 years earlier than for most other primary kidney diseases[3]. Interventions that slow the progression of ADPKD are urgently needed.

ADPKD is usually caused by mutations in PKD1, PKD2 or, rarely, GANAB[4]. Its pathogenesis is incompletely understood. PKD1 and PKD2 encode the polycystins PC1and PC2 respectively. PKD1 or PKD2 mutations lead to reductions in intracellular calcium, accumulation and impaired destruction of cAMP and reduced intracellular ATP. This promotes sensitivity of collecting duct epithelial cells for the tonic effects of vasopressin[5]. Since vasopressin promotes cyst growth, it has emerged as a therapeutic target for ADPKD[6]. Recent evidence has confirmed efficacy of vasopressin receptor blockade with the V_2 receptor antagonist Tolvaptan in slowing ADPKD progression, reducing the annual increase in total kidney volume by 2.7%[7] and slowing the rate of eGFR decline[8]. However, the utility of Tolvaptan is limited by cost and side effects, with up to 25% of patients intolerant of the drug[7].

Vasopressin release from the posterior pituitary is driven by plasma osmolality[9], and is readily suppressed by drinking beyond thirst. It is therefore plausible that high water intake could slow the progression of ADPKD through reduced exposure of the kidneys to vasopressin. Congruent with this hypothesis, studies in the PCK rat have shown slowing of cystic kidney disease and vasopressin suppression with high water consumption[10,11]. In humans, Amro et al[12] showed significant reductions in copeptin concentration and urine osmolality after two weeks of solute restriction and high water intake compared in 34 patients with ADPKD. In a prospective observational study, high water intake in 13 patients with ADPKD resulted in reduced urine osmolality and increased urine volume compared to healthy controls after 7 days[13]. However, in a non-randomised prospective study of 30 ADPKD patients, high water intake resulted in a more rapid decline in eGFR and increase in TKV despite a significant reduction in urine osmolality and plasma copeptin level compared to controls[14]. Uncertainty therefore remains over the effectiveness and safety of high water

intake in preserving kidney function in patients with ADPKD. Adequately powered randomised trials are urgently needed.

One other trial of high water intake is currently underway (PREVENT-ADPKD ACTRN12614001216606), with the aim of recruiting 180 ADPKD patients who will be randomised to high or standard water intake[15]. However, PREVENT-ADPKD has several important limitations. First, patients with eGFR < 30 ml/min are excluded from the trial. Second, the primary outcome change in height-adjusted total kidney volume (htTKV), a surrogate for kidney function decline. Powered (87%) to detect a relatively large difference in htTKV increase, there is a very real risk that clinically meaningful effect may exist but might not be detected in a trial of this size. Third, the validity of htTKV as a surrogate for disease progression is disputed.[16 7]. PREVENT-ADPKD will therefore not determine the effect of high water intake on kidney function. Finally, PREVENT-ADPKD will not assess the acute effects of increased hydration in eGFR. Acute effects are of high importance in selecting the most appropriate kidney function endpoint for interventional trials in CKD[17]. It is apparent that, irrespective of the outcome of this trial, a large randomised comparison of the effect of high water intake versus standard of care on kidney function will remain necessary.

We report the design and set-up of a randomised feasibility trial of high versus ad libitum water intake, developed to rigorously assess the feasibility of a definitive trial powered to detect a difference in kidney function decline in patients with ADPKD. This trial was initiated by patient members of the PKD Charity through a research proposal to the Patient Led Research Hub during 2016, and has been co-designed and produced (and part funded) by the PKD charity. A full version of the trial protocol can be found at the following link http://cctu.medschl.cam.ac.uk/Trials/Drink/Materials.htm on the DRINK trial website.

METHODS AND ANALYSIS

Objectives

The primary feasibility objectives are 1) recruitment rate, and 2) achievement of target urine osmolality in ≥ 85% of study participants in the HW group. Secondary endpoints include separation in urine osmolality between trial arms, the completeness of self-monitored uSG data (adherence to the self-monitoring regimen), serious adverse event rate, changes in quality of life (EQ5D) scores from baseline to 8 weeks, change in pain scores between

groups, change in measured GFR between baseline and 4 weeks, and change in eGFR between baseline and 4 weeks (Table 1).

Primary Endpoints
The number of patients eligible for, and randomised to the trial
The proportion of patients in the high water intake group achieving a urine osmolality < 270 mOsmo/kg
Secondary Endpoints
The proportion in each of the high and ad libitum water intake groups achieving their target urine osmolality (between group separation)
The proportion of participants that can self-monitor and report urine SG reliably
Acceptability and usability of the SPLASH app (qualitative questionnaires and interviews)
Incidence of serious adverse event
Change between baseline and 8wk in quality of life scores (measured using EQ-5D)
Change between baseline and 8wk pain scores (measured using Pain Questionnaire)
Change in measured GFR between baseline and 4wks (acute GFR effects in high water intake group)
Change in estimated GFR between baseline and 4 weeks (both interventional groups)
Acute GFR effects measured as the change in ^{51}CR-EDTA measured GFR from week 0 to week 4

Table 1: DRINK trial primary and secondary endpoints

Trial Design

This prospective, open label, randomised trial was designed to assess the feasibility of a large definitive randomised controlled trial comparing the effectiveness and safety of high water intake in patients with ADPKD to a control arm of ad libitum water intake. Participants were randomly assigned (1:1) to receive either a prescribed (high) fluid intake sufficient to achieve vasopressin suppression, or to ad libitum water intake (Figure 1). Following an 8 week treatment period where participants will undertake all the trial assessments, they will undergo a four week washout and have one final end of trial visit at week 12. The trial was first proposed by the Polycystic Kidney Disease (PKD) Charity, and was developed through and

supported by the Cambridge Patient Led Research Hub, and run by the Cambridge Clinical Trials Unit.

Two nested substudies will be conducted: 1) Substudy A includes ^{51}CR-EDTA measured GFR and is designed to assess the acute effects on GFR of high water intake in the HW group. This substudy aims to enroll a minimum of 8 participants. 2) Substudy B is designed to assess the impact of a novel smartphone-based fluid intake monitoring device (termed SPLASH)[18] in promoting adherence to fluid prescriptions (Figure 2). Substudy B aims to enroll at least 10 participants.

Trial population, eligibility criteria and recruitment

Patients with a confirmed diagnosis of ADPKD aged 16 years or older are eligible for enrolment in the trial (Table 2). Patients are deemed ineligible if they have advanced renal impairment (defined as an estimated GFR < 20 ml/min/1.73m^2), are unable to provide informed consent, are unable or unwilling to comply with study procedures including self-monitoring of urinary specific gravity (SG), have evidence of fluid excess (defined as peripheral oedema, pulmonary oedema, heart failure, liver cirrhosis) or are receiving treatment with diuretics for such states, have concomitant renal diseases other than ADPKD, are pregnant or breastfeeding, or are receiving treatment with Tolvaptan within 4 weeks of screening.

In this single-center trial, participants will be recruited from the renal genetics and tubular disorders clinic at Addenbrooke's Hospital, Cambridge. Patients from other centers are eligible for entry, but have to attend Addenbrooke's Hospital for screening, enrolment and study procedures. Patients will be reimbursed for travel and other expenses, but will not receive any other payment or incentives for trial participation.

The DRINK trial was advertised nationally on the PKD charity and RaDAR websites and presented at PKD Patient Information days. Recruitment commenced in September 2016. The trial aims to enroll up to 50 participants. The trial steering committee may recommend halting recruitment at any point after 30 patients have been enrolled if it is clear that the feasibility questions have been adequately addressed.

Inclusion criteria

Diagnosis of ADPKD (radiological and or genetic evidence of PKD1 or PKD2 mutations) Aged 16 years or older Ability to provide informed consent eGFR ≥ 20ml/min/1.73m^2 Able to self-monitor uSG
Exclusion criteria
Fluid overload states e.g. heart failure, cirrhosis, or requirement for fluid restriction Confounding illness impacting on renal disease e.g. concomitant diabetes or glomerulonephritis Treatment with diuretics for fluid overload (those on diuretics for hypertension may participate in the trial after a run-in period of 2 weeks) Treatment with tolvaptan in the last 4 weeks Pregnancy or breastfeeding

Table 2: Eligibility Criteria

Randomisation:

Participants will be randomly assigned (1:1) to high (HW) or ad libitum (AW) water intake using a manual sealed envelope system prepared by the Cambridge Clinical Trials Unit statistician and to which the trial team will be blinded.

Although we have chosen patient level randomisation, the autosomal dominant inheritance pattern of ADPKD raises the particular challenge that multiple members of the same family or household may participate in a trial. In the context of high water intake, this may result in contamination between trial arms since fluid consumption patterns of one family member may be influenced by that of another. This is particularly relevant given that we have previously reported that up to 80% of ADPKD patients regularly discuss their condition and treatments with family members them[19]. The ability to draw inferences on contamination between trial arms within family clusters will be dependent on the number of related participants enrolled into the trial. Were contamination between arms apparent within family clusters, this may need to be taken into account in the randomisation strategy for a definitive trial

Intervention

Participants allocated to the high water intake (HW) arm will receive an individualised daily fluid intake prescription based on the free water clearance formula (Figure 3) and designed to achieve suppression of vasopressin.

The fluid prescription will be titrated to response against uSG (Table 3), since a uSG ≤1.010 correlates with vasopressin suppression and is easily assessable by urine indicator strip testing[20]. Urine osmolality will also be measured during study visits, and fluid prescription titrated in order to achieve a urine osmolality of ≤270mOsmo/kg. Participants are required to self-monitor uSG twice weekly to ensure that their fluid intake is sufficient to maintain the dilution target. Remote monitoring of home uSG values will be facilitated through the use of a bespoke smartphone application (app) that allows participants to input and monitor their uSG values. Titration instructions are embedded within the app. Participants will be encouraged to preferentially consume water, but consumption of other beverages is not restricted and will contribute to calculation of the daily fluid consumption total. Participants will undergo regular dietary evaluation encouraging them to maintain moderate sodium (<2g/day) and protein (0.75-1g/kg/day) intake in order to facilitate adherence to the urinary dilution target.

Urine SG	HW Group Advice	AW Group Advice
1.005	Maintain	Reduce intake by 3 cups
1.010	Maintain	Reduce intake by 2 cups
1.015	Increase intake by 2 cups	Maintain
1.020	Increase intake by 3 cups	Maintain
1.025	Increase intake by 4 cups	Maintain
1.030	Increase intake by 5 cups	Maintain

Table 3: Advice given to participants based on urine SG and treatment group

Control

Participants allocated to the ad libitum arm (AW) will not be given any fluid intake target, but will be asked to drink according to their usual practice and guided by thirst. They will also be required to monitor uSG using as for the HW group, but with a uSG target of >1.010 (corresponding to a urine osmolality >300mOsmo/Kg) given that, above this threshold, vasopressin is not suppressed. If the uSG is below this threshold, fluid intake is to be titrated

to achieve the target (Table 3), requiring a reduction in fluid intake. Dietary advice will be as for the HW group.

Adherence

Any attempt to conduct a trial of high water intake will need to identify mechanism for, and demonstrate the feasibility of, achieving and maintaining separation between trial arms sufficient to realistically translate into a biologically meaningful effect. Studies of the effect of high water intake advice on renal stone disease have shown the majority of patients are non-adherent to fluid prescription[21] and, in ADPKD patients[19], often over-estimate daily fluid intake. Several methods have been used to increase water intake in adults including education and counselling, goal setting, self-monitoring or the provision of calibrated containers. A recent systematic review of 16 studies showed that self-monitoring (urine volume and uSG) were the most effective strategy to increase fluid intake, highlighting the importance for adherence promoting methods[21]. In order to maximise the likelihood of achieving separation between trial arms, the DRINK trial will employ several novel approaches that include home monitoring of uSG and the use of smartphone technology for both monitoring and direct feedback purposes. Given that these strategies will be combined with education and counseling and regular dietary review of solute intake, failure to achieve and maintain separation between arms using the DRINK trial design would cast serious doubt on the feasibility of a larger trial powered to detect effects on kidney function decline. Assessment of the potential for a biologically meaningful separation will be facilitated by the objective analysis of measured urine osmolality and plasma copeptin concentrations.

Determinations

Blood pressure will be assessed after 5 minutes rest whilst seated. Screening blood pressure will be assessed using the DINAMAP Carescape monitor in routine clinic use. Blood pressure measurements will be taken in triplicate, and the mean of the second and third measurement reported. Brachial blood pressure will be taken in the non-dominant arm with an appropriately sized cuff, according to British Hypertension Society guidance. Side room urinalysis will be carried out using Siemens Multistix® GP indicator strips, read by Siemens CliniTek Status^{+} auto-analyser. Urine specific gravity (uSG) will be measured as a surrogate for urine osmolality by automated analysis of colorimetric change on Siemens Multistix®.

Home measurement will be conducted by visual assessment of colorimetric change, read after 45 seconds against the manufacturer's standard reference colour chart. Urine volume and measured urine osmolality will be obtained by performing two 24h urine collections at baseline. Further 24h urine samples will be obtained at 2, 8 and 12 weeks. Spot urine samples will be collected for urine osmolality estimation at every visit. Urine and plasma osmolality is measured on the Advanced Instruments Micro-Osmometer, Model 3320 using the freezing point depression method.

Creatinine will be measured using the Siemens Advia 2400 autoanalyser. Screening estimated GFR (eGFR) will be derived from the 4-variable MDRD GFR equation[22]. All within-trial eGFR measurements will be calculated using the CKD-EPI equation[23]. Serum copeptin (a surrogate for vasopressin concentrations)[24] will be analysed by the department of clinical chemistry at the Royal Victoria Infirmary, Newcastle, UK.

Plasma samples will be obtained on all participants at all time points for biobanking.

Measured GFR will be determined by ^{51}CR-EDTA. On the day preceding the test, participants will be asked to abstain from high protein meals and excessive caffeine, and to abstain from caffeine consumption after 10pm. They will be permitted a light breakfast on the day of the test. An intravenous injection of 2MBq Chromium-51 EDTA was administered via a 16G cannula. Venous blood (10mL) will be drawn from the contralateral arm at baseline, 2, 3 and 4 hours after the injection. Samples will be centrifuged for 15 minutes at 2000rpm to allow plasma separation, and read using a Wizard2 2480 gamma counter (PerkinElmer). The glomerular filtration rate will be derived from the area under the plasma clearance curve using the slope intercept method.

Health-related Quality of Life (HRQoL) will be assessed using the EQ-5D quality of life questionnaire (EUROQoL), administered at baseline and 8 weeks.

Secondary outcome data from the efficacy trial of tolvaptan suggests that the drug reduces the frequency of acute episodic pain in ADPKD[25]. Although the mechanism for pain relief is unclear, it was partly explained by the reduced incidence of urinary tract infection, stones, and cyst rupture and haemorrhage. As high water intake is associated with reduced incidences of urinary stones and infections in the general population[26] and the increasing recognition of chronic pain in the condition[27], we have chosen to assess pain in DRINK. This will be assessed using a bespoke pain assessment tool to collect longitudinal data on the nature, frequency and pattern of pain, and analgesic use (SUPPLEMENTARY APPENDIX I). To date, no questionnaires have been validated for the assessment of pain in ADPKD. We

employed two brief questionnaires, which are validated and widely used for a broad range of chronic pain disorders in the general population, which are Short-form Brief Pain Inventory (SF-BPI)[28] and McGill Pain Questionnaire (SF-MPQ-2)[28]. The questionnaire will be completed at baseline and week 8, but participants can also record any acute episodes of pain at any time during the study. This will be facilitated through provision of the pain assessment tool within the trial smartphone application. A separate paper will follow that describes the results and feasibility of use in the DRINK-cohort.

An acceptability questionnaire, adapted from that used by Torres et al[7], will be administered at the end of the trial to determine the sustainability and acceptability of long term adherence to the trial fluid intake prescription. All questionnaire based assessments (EQ5D, Pain, Acceptability) can be completed on paper, via email or via smartphone application. The trial smartphone application has been developed in collaboration with FatFractile Ltd. The app will be used to record home uSG results, capture questionnaire data as described above, allow messaging and reminder functionality, and to direct participants to help and additional information if required (SUPPLEMENTARY APPENDIX II). In order to avoid contamination between trial arms, two distinct versions of the app were developed, each specific to one of the trial arms. Identification of the version of the app used by participants could be monitored centrally to avoid use of the incorrect version.

Run in period

Eligible patients who are prescribed either diuretics or Tolvaptan will be allowed to enter a two-week run-in period after enrolment during which these drugs will be withdrawn. At the end of the run-in period, these participants will be reassessed to ensure that they still met the eligibility criteria before commencing the trial. Diuretics will only be withdrawn if the indication is hypertension, and which case alternative anti-hypertensives will be prescribed. Alternatives that would result in acute effects on GFR will be avoided (ACE inhibitors and Angiotensin Receptor Blockers).

Participant Timeline

The trial design is represented graphically in Figure 1 and the schedule of events in Table 4.

Screening

Patients who are potentially eligible will be invited for a screening visit. Screening will include a medical history and a targeted ADPKD-related history that captures data on the

timing and nature of the diagnosis, kidney size and function, and the presence of any complications such as pain, haemorrhage, nephrolithiasis or infections. Comorbidities and medications will be recorded. A full physical examination will be conducted that includes assessment of blood pressure. Indicator strip side room urinalysis will be performed. Blood analysis will include a full blood count, liver function tests, electrolytes and creatinine, and paired serum and spot urine osmolalities. Participants that are deemed eligible will be provided with two 24h urine collection bottles for return at the time of the baseline visit in order to measure osmolality and urine volume.

Baseline

Eligible participants who have provided informed consent will be randomised at the time of the baseline visit. A targeted physical examination to assess fluid status and vital signs will be conducted. Participants will be weighed, prescribed medications noted and blood and urine taken to measure electrolytes and creatinine, osmolality and urinalysis. A baseline quality of life EQ5D questionnaire will be completed. Participants will be instructed on how to conduct indicator strip uSG analysis, and asked to perform urinalysis twice weekly on Mondays and Thursdays between 16:00 and 20:00. They will be assisted in installing the DRINK trial smartphone application on their smartphone, and will be provided with a tutorial on its use. This will allow input of home uSG measurements. Participants who do not own a smartphone will be required to telephone, email or text uSG results to the trial team. Finally, participants will be required to complete the DRINK trial pain assessment tool (SUPPLEMENTARY APPENDIX I).

Follow-up (weeks 2, 4, 8):

Participants will be recalled for follow-up visits after 2, 4 and 8 weeks. During these visits, a physical examination will be carried out and weight and vital signs recorded. Blood and urine samples will be taken to measure electrolytes and creatinine, osmolality and urinalysis. Urine for 24h urine osmolality will be collected at weeks 2 and 8 respectively. A dietary assessment will be carried out at weeks 4 and 8. A pain assessment and EQ5D questionnaire will be completed at the 8week visit.

Washout period and final visit:

After completion of the intervention period (week 8), participants will be asked to revert to their pre-enrolment fluid intake. After a further 4 weeks, a final visit will be conducted (week 12). This will include all assessments conducted at the 8week visit, with the exception of pain and quality of life questionnaires.

Study Period							
Time Point		Recruitment	Trial visits				
			Active				Washout
		W-24**	W0	W2	W4	W8	W12
Enrolment	Screening	X					
	Informed Consent	X					
	Randomisation	X					
Intervention	High water intake						
	Ad libitum water intake						
Assessment	Medical History	X					
	Medication review	X	X	X	X	X	X
	Physical Examination	X	X	X	X	X	X
	Vital Signs (Blood pressure, pulse rate and oximetry)	X	X	X	X	X	X
	Height	X					
	Weight	X	X	X	X	X	X
	Haematology (Full blood count)	X					
	Biochemistry (Urea, Creatinine, Electrolytes, Serum Osmolality)	X	X	X	X	X	X
	Biochemistry (Liver function and bone profile)	X					
	Measured GFR*		X	X	X		
	Urine SG	X	X	X	X	X	X
	Spot Urine Osmolality	X	X	X	X	X	X
	24 hour Urine Collection (volume and osmolality)	X		X		X	X
	Home uSG monitoring***		X	X	X	X	
	SPLASH Monitoring		X	X	X	X	
	Dietary Assessment	X	X		X		X
	Pain Questionnaire***		X			X	
	Acceptability Questionnaire***		X			X	
	EQ5D***		X			X	

Table 4: Schedule of enrolment, intervention and assessments

* ^{51}Cr-EDTA measured GFR performed as part of a sub-study in 8 participants in the HW group

** 24 week pre study recruitment period. *** Recorded using the DRINK Smartphone App

SUBSTUDY A

Effect of high water intake on ^{51}CR-EDTA GFR

Determining the acute effects of high water intake on GFR is a prerequisite to the definition of renal endpoints in any future trial[22]. We will conduct a substudy to determine the acute effect of high water intake on ^{51}CR-EDTA GFR, to allow a more rigorous assessment of GFR than that derived from estimation equations. Eight patients will be enrolled in this substudy, which will require a negative pregnancy test in addition to the eligibility criteria for the main trial.

Participants in substudy A will undergo ^{51}CR-EDTA GFR measurement at baseline, week 2 and week 4 in addition to all other trial measurements.

SUBSTUDY B

SPLASH smartphone fluid intake monitoring

Substudy B was designed to evaluate the feasibility and usability of a novel smartphone based fluid intake monitoring device termed SPLASH[18]. This Android based app uses reusable near field communication (NFC) adhesive tags that attach to drink holders (glasses, cups or bottles). Tags are calibrated before use by measuring the drinks container volume (using a standard measuring jug) and programing the app accordingly. The app is activated by holding the phone near the NFC tag, allowing the user to select the volume consumed by identifying the corresponding fraction of the container (e.g. full, ½, ¼ etc.). Ad hoc consumption of fluids from uncalibrated drinks holders is captured using customised credit card or keyring NFC tags pre-calibrated for most drinking scenarios. The app also allows input of daily fluid intake targets and displays progress towards this. Given that the system is android-specific, android phones will be provided to substudy B participants on loan where required.

At least 10 participants will be enrolled in Substudy B. Participants in both trial arms will be eligible for Substudy B enrolment. Training in the use of the SPLASH system will be provided in person, through provision of written information, and via an online training video (https://vimeo.com/208818645). Participants will be allowed to use the SPLASH system freely, but will be specifically required to use this for at least 24 hours at the time of the baseline, week 2 and week 8 visits (to coincide with measured 24h urine osmolality).

At the end of Substudy B, participants will be interviewed to provide qualitative data on their experience of using the SPLASH app.

Patient and Public Involvement

High water intake is an issue of great importance and was identified as a key research priority by patients with ADPKD. The DRINK trial was first proposed by the PKD charity in 2015 and, facilitated by the Patient Led Research Hub. Patient co-investigators have remained involved throughout the design and set-up, and are co-applicants on the awarded funding grants for the trial. The study design was presented at several PKD charity information days, and patients have provided valuable feedback on the intervention and the use smartphone applications.

The findings of the DRINK trial will be available to patients on the DRINK trial-specific and PKD websites. They will also be presented at the PKD information days that are run throughout the year by the charity.

Adverse Events and Safety

Adverse events will be assessed at each study visit. Additionally, a 24h trial participant helpline will be made available. Given the nature of the intervention, fluid retention, worsening hypertension and hyponatraemia are adverse events of special interest.

Participants will be withdrawn from the trial in the case of persistent hyponatraemia (< 132mmol/L on two consecutive samples), fluid retention defined by the presence of one of 1) pulmonary oedema, 2) significant lower limb swelling, or 3) uncontrolled hypertension on two consecutive visits despite optimal antihypertensive treatment (as judged by the responsible clinician). Participants will also be withdrawn for a decline in eGFR by ≥10ml/min/1.73m^2 or 25% from baseline, confirmed on two consecutive samples at separate time points.

All adverse events will be recorded from the point of informed consent on the appropriate case report forms. All serious adverse events will be assessed by the chief investigator in terms of seriousness and causality and reported to the sponsor in accordance with GCP guidance.

Sample size

Data from a small pilot study by Armo et al showed that using a low osmolar diet and high water intake, urine osmolality could be reduced from 426±193 to 258±147 (p=0.01) with a

non-significant change in the control group[29]. This is comparable to the reduction seen in the TEMPO3:4 trial (472 to 264 mOsmo/Kg), where 81% receiving Tolvaptan achieved a urine osmolality<300mOsmo/kg compared to 17% in the placebo group[30]. In order to observe a benefit of high water intake on the rate of kidney function decline, we estimate that a comparable proportion of the high water intake group should achieve a urine osmolality consistent with vasopressin suppression. We estimate that 28 participants would be required to detect 85% of the HW intervention group reaching their target urine osmolality and 15% of controls achieving a urine osmolality less than the target threshold (99% power, two sided α= 0.05). Assuming a 15% dropout rate, the minimum required sample size is 30.

Statistical Analysis

Analysis of the primary and secondary outcomes of the trial will utilise the intention-to-treat principle. All randomised participants will be included in the final analysis within their treatment group allocation regardless of compliance, withdrawal or protocol deviations. Data will be analysed as proportions/percentages, mean ± standard deviation and with linear mixed-level modelling for repeated measures (uSG, renal function and blood pressure). For non-parametric data median with interquartile range (25-75th) with minimum and maximum values will be reported as appropriate. We will be using a 95% CI and a significance level of ≤0.05. The analysis will be carried out using the STATA version 13.1 statistical software.

We will perform a qualitative assessment of SPLASH looking at ease and acceptability of use through participant questionnaires and face-to-face interviews. We will also collect exploratory data on the validity of SPLASH as a potential fluid intake-monitoring device, comparing the app-based intake volumes recorded to the coinciding urine osmolality results of 24 hour collections.

Data Management and monitoring

Data collection will be performed by trained local research staff at each of the trial visits in the form of case report forms. This will then be entered in to the DRINK trial database which is housed in the NIHR accredited Cambridge Clinical Trials Unit and supervised by the trial data manager. Data from the DRINK and SPLASH smartphone applications will be transferred securely to the N3 NHS Database where it can be accessed securely via a specialized administration panel by members of the research team using an encrypted password.

The DRINK study will undergo monitoring for regulatory compliance in accordance with the GCP Guidance via the trial steering committee which independently monitors progress and conduct of the trial and will also provide advice on the continuation, termination or amendments to the trial protocol. DRINK is sponsored by Cambridge University Hospital NHS Foundation Trust and will be subject to regular monitoring visits and audits.

Discussion

The DRINK trial will address the key feasibility issues facing future definitive high water intake trials in ADPKD. Importantly, it will determine the recruitment potential especially given the uptake of Tolvaptan, the optimal renal endpoint and effect size, the randomisation strategy, and demonstrate whether biological feasibility which is essential to any subsequent efficacy findings is achievable. Water as a disease modifying intervention could revolutionise the management of ADPKD, not only providing a low cost, widely available treatment option for those in developing countries, but also those with early disease for whom it is essential to target cyst development early. Yet the early stage of their condition and lack of renal function decline makes it difficult to justify the use of medications with potentially toxic side effects as the risk-benefit ratio in this group remains largely unknown.

Ethics and Dissemination

Ethical approval was awarded by the East of England Essex Research Ethics Committee in July 2016 (16/EE/0026). DRINK opened to recruitment in September 2016, and the last study visit is anticipated to be April 2018. The primary and secondary outcomes results will be published in peer-reviewed journals, this will include a separate paper on the use of smartphone technology in clinical trial design and the longitudinal ADPKD pain characteristics. A synopsis of the trial findings will also be made available to participants and the public through the trial specific website and the PKD charity. All the DRINK data will be shared through the Cambridge Data Repository.

Author Affiliations

[1]Division of Experimental Medicine and Immunotherapeutics, Department of Medicine, University of Cambridge
[2]Division of Anaesthesia, Department of Medicine, University of Cambridge
[3]PKD Charity, London, United Kingdom
[4]Cambridge Clinical Trials Unit, Cambridge UK
[5]Patient Led Research Hub, Cambridge UK
[6]Department of Medical Genetics, University of Cambridge

[7]University of Bristol, UK

Acknowledgments

We would like to thank the PKD charity and the Patient Led Research Hub for their input in the design and delivery of the DRINK trial and the British Renal Society for their grant towards the funding of DRINK. RED is supported by the PKD Charity, Kidney Research UK and the Addenbrooke's Charitable Trust. TFH and FEK are supported by the NIHR and the Cambridge Biomedical Research Centre. The DRINK smartphone application was developed in conjunction with FatFractile Ltd. and funded by the PKD charity. The SPLASH application was developed by SPHERE IRC and was funded by the UK Engineering and Physical Sciences Research Council (EPSRC) and the Addenbrookes Charitable Trust.

Contributors

All the authors contributed to the design and development of the study protocol, and have reviewed the manuscript. TFH and TH conceived the study. TFH, RED, IBW, FKF and RNS designed the study, and contributed to recruitment, trial oversight and implementation of the intervention. ML provided specific support with regards to the assessment of pain in trial participants. SB and HP provided statistical expertise and supported the development of the statistical analysis plan. LBM supported the development of the patient-led proposal through the Patient led research hub. AB, PW and YB developed the SPLASH app and contributed to development of the protocol for the SPLASH sub-study.

Funding Statement

The study is funded by the British Renal Society and Kidney Care UK (formerly British Kidney Patient Association) grant programme (15-004), the PKD Charity, the Addenbrooke's Charitable Trust (45/16), and Kidney Research UK (TF-009-20161125), and is supported by the UKCRC-registered Cambridge Clinical Trials Unit and the Cambridge NIHR Clinical Research Facility.

Conflict of interest

The authors declare that they have no competing interests

References

1 Chapman AB, Devuyst O, Eckardt K-U, *et al.* Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney International* 2015; **88**: 1–11.

2 Gansevoort RT, Arici M, Benzing T, *et al.* Recommendations for the use of tolvaptan in autosomal dominant polycystic kidney disease: a position statement on behalf of the ERA-EDTA Working Groups on Inherited Kidney Disorders and European Renal Best Practice. *Nephrology Dialysis Transplantation* 2016; **31**: 337–48.

3 Shaw C, Simms RJ, Pitcher D, Sandford R. Epidemiology of patients in England and Wales with autosomal dominant polycystic kidney disease and end-stage renal failure. *Nephrol Dial Transplant* 2014; **29**: 1910–8.

4 Porath B, Gainullin VG, Gall EC-L, *et al.* Mutations in GANAB, Encoding the Glucosidase IIα Subunit, Cause Autosomal-Dominant Polycystic Kidney and Liver Disease. *The American Journal of Human Genetics* 2016; **98**: 1193–207.

5 Chebib FT, Sussman CR, Wang X, Harris PC, Torres VE. Vasopressin and disruption of calcium signalling in polycystic kidney disease. *Nat Rev Nephrol* 2015; **11**: 451–64.

6 Devuyst O, Torres VE. Osmoregulation, vasopressin, and cAMP signaling in autosomal dominant polycystic kidney disease. 2013; **22**: 459–70.

7 Torres VE, Chapman AB, Devuyst O, *et al.* Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease. *N Engl J Med* 2012; **367**: 2407–18.

8 Torres VE, Chapman AB, Devuyst O, *et al.* Tolvaptan in Later-Stage Autosomal Dominant Polycystic Kidney Disease. *N Engl J Med* 2017; : NEJMoa1710030–13.

9 van Gastel MDA, Torres VE. Polycystic Kidney Disease and the Vasopressin Pathway. *Ann Nutr Metab* 2017; **70**: 43–50.

10 Nagao S. Increased Water Intake Decreases Progression of Polycystic Kidney Disease in the PCK Rat. *Journal of the American Society of Nephrology* 2006; **17**: 2220–7.

11 Hopp K, Wang X, Ye H, Irazabal MV, Harris PC, Torres VE. Effects of hydration in rats and mice with polycystic kidney disease. *Am J Physiol Renal Physiol* 2015; **308**: F261–6.

12 Amro OW, Paulus JK, Noubary F, Perrone RD. Low-Osmolar Diet and Adjusted Water Intake for Vasopressin Reduction in Autosomal Dominant Polycystic Kidney Disease: A Pilot Randomized Controlled Trial. *American Journal of Kidney Diseases* 2016; **68**: 882–91.

13 Barash I, Ponda MP, Goldfarb DS, Skolnik EY. A pilot clinical study to evaluate changes in urine osmolality and urine cAMP in response to acute and chronic water

loading in autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol* 2010; **5**: 693–7.

14 Higashihara E, Nutahara K, Tanbo M, *et al.* Does increased water intake prevent disease progression in autosomal dominant polycystic kidney disease? *Nephrology Dialysis Transplantation* 2014; **29**: 1710–9.

15 Wong ATY, Mannix C, Grantham JJ, *et al.* Randomised controlled trial to determine the efficacy and safety of prescribed water intake to prevent kidney failure due to autosomal dominant polycystic kidney disease (PREVENT-ADPKD). *BMJ Open* 2018; **8**. DOI:10.1136/bmjopen-2017-018794.

16 Yu ASL, Shen C, Landsittel DP, *et al.* Baseline total kidney volume and the rate of kidney growth are associated with chronic kidney disease progression in Autosomal Dominant Polycystic Kidney Disease. *Kidney International* 2018; **93**: 691–9.

17 MD ASL, MS LAIM, PhD KMM, *et al.* GFR Decline as an End Point for Clinical Trials in CKD: A Scientific Workshop Sponsored by the National Kidney Foundation and the US Food and Drug Administration. *American Journal of Kidney Diseases* 2014; **64**: 821–35.

18 Luo X, Woznowski P, Burrows A, Haghighi M, Craddock I. SPLASH. New York, New York, USA: ACM Press, 2016: 1526–32.

19 El-Damanawi R, Harris T, Sandford RN, Karet Frankl FE, Hiemstra TF. Patient Survey of current water Intake practices in autosomal dominant Polycystic kidney disease: the SIPs survey. *Clinical Kidney Journal* 2017; : 1–5.

20 Imran S, Eva G, Christopher S, Flynn E, Henner D. Is specific gravity a good estimate of urine osmolality? *J Clin Lab Anal* 2010; **24**: 426–30.

21 Chua TXW, Prasad NS, Rangan GK, Allman-Farinelli M, Rangan AM. A systematic review to determine the most effective interventions to increase water intake. *Nephrology* 2015; : n/a–n/a.

22 Levey AS, Greene T, Schluchter MD, *et al.* Glomerular Filtration Rate Measurements in Clinical Trials. *J Am Soc Nephrol* 1993; **4**: 1159–71.

23 Levey AS, Stevens LA, Schmid CH, *et al.* A New Equation to Estimate Glomerular Filtration Rate. *Ann Intern Med* 2009; **150**: 604–12.

24 Bolignano D, Cabassi A, Fiaccadori E, *et al.* Copeptin (CTproAVP), a new tool for understanding the role of vasopressin in pathophysiology. *Clinical Chemistry and Laboratory Medicine (CCLM)* 2014; **52**: 1–10.

25 Casteleijn NF, Blais JD, Chapman AB, *et al.* Tolvaptan and Kidney Pain in Patients With Autosomal Dominant Polycystic Kidney Disease: Secondary Analysis From a Randomized Controlled Trial. *American Journal of Kidney Diseases* 2017; **69**: 210–9.

26 Lotan Y, Daudon M, Bruyère F, *et al.* Impact of fluid intake in the prevention of urinary system diseases. *Current Opinion in Nephrology and Hypertension* 2013; **22**: S1–S10.

27 Hogan MC, Norby SM. Evaluation and Management of Pain in Autosomal Dominant Polycystic Kidney Disease. *Advances in Chronic Kidney Disease* 2010; **17**: e1–e16.

28 Dworkin RH, Turk DC, Trudeau JJ, *et al.* Validation of the Short-Form McGill Pain Questionnaire-2 (SF-MPQ-2) in Acute Low Back Pain. *The Journal of Pain* 2015; **16**: 357–66.

29 Amro OW, Paulus JK, Noubary F, Perrone RD. Low-Osmolar Diet and Adjusted Water Intake for Vasopressin Reduction in Autosomal Dominant Polycystic Kidney Disease: A Pilot Randomized Controlled Trial. *American Journal of Kidney Diseases* 2016; **68**: 882–91.

30 Devuyst O, Chapman AB, Gansevoort RT, *et al.* Urine Osmolality, Response to Tolvaptan, and Outcome in Autosomal Dominant Polycystic Kidney Disease: Results from the TEMPO 3:4 Trial. *Journal of the American Society of Nephrology* 2017; **28**: 1592–602.

Legends for figures

Figure 1: Schematic of the DRINK trial design. Participants are randomised 1:1 to the High water (HW) or Ad libitum (AW) water intake groups. Each participant in the HW group is given an individualised daily water prescription with urinary dilution targets consistent with vasopressin suppression. The AW group has more concentrated urinary targets.

Figure 2: Smartphone technology used during the DRINK study. The SPLASH app uses near field communication technology to automate fluid intake monitoring (left). The DRINK app will be used to record urine specific gravity results allowing remote data collection and monitoring of progress (right).

Figure 3: Calculation of fluid prescription using the free water clearance equation. Insensible losses were arbitrarily set at 500mls as an average

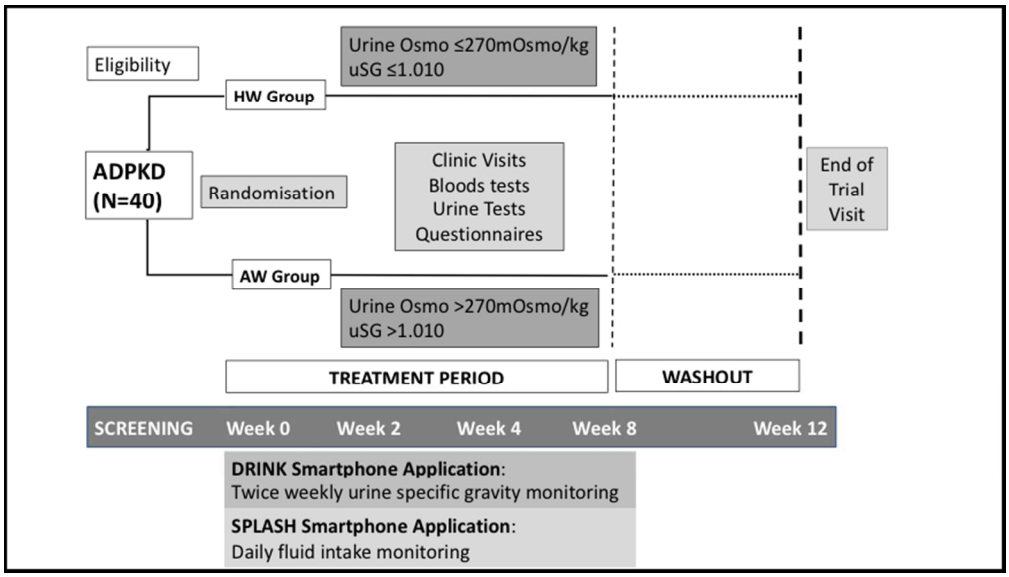


Figure 1: Schematic of the DRINK trial design. Participants are randomised 1:1 to the High water (HW) or Ad libitum (AW) water intake groups. Each participant in the HW group is given an individualised daily water prescription with urinary dilution targets consistent with vasopressin suppression. The AW group has more concentrated urinary targets.

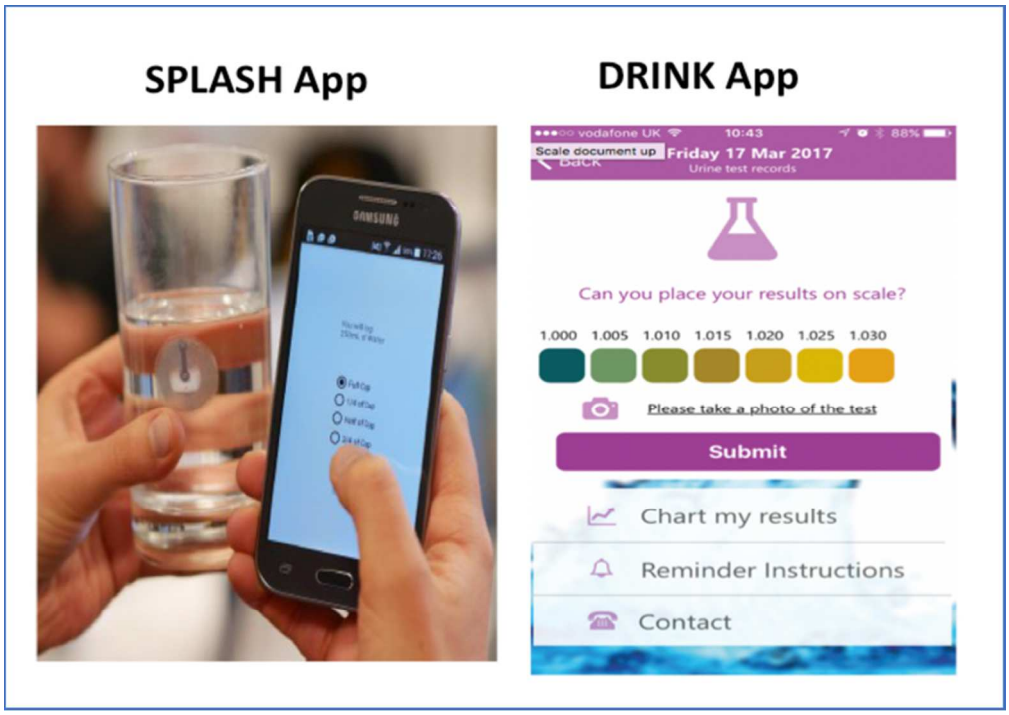


Figure 2: Smartphone technology used during the DRINK study. The SPLASH app uses near field communication technology to automate fluid intake monitoring (left). The DRINK app will be used to record urine specific gravity results allowing remote data collection and monitoring of progress (right).

Calculation is shown for a hypothetical patient

Average of 2x 24 hours collections:
Total Solute = Urine Osmolality (mOsmo/Kg) x Urine Volume (mls)

Free Water Clearance Formula:
Fluid intake = {Total Solute (moSmo)/270} + Insensible Losses*

Example
The average 24 hour urine collection results for a participant in the HW group show the following;
Urine Osmolality 400mOsmo/Kg
Urine Volume 1500mls

Thus….
Total solute = 400 x 1500 = 600000
Fluid intake = (600000/270) + 500 = 2722 mls

A minimum of 2722 milliliters of fluid/day is required to achieve the target urine osmolality ≤270mOsmo/kg

Figure 3: Calculation of fluid prescription using the free water clearance equation. Insensible losses were arbitrarily set at 500mls as an average

Appendix I - Pain Questionnaire

BASELINE/ SCREENING +/- other visits too.

Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain? **YES/NO**

If YES,
Body Map:

Please shade using **horizontal** lines in the areas where all your pain(s) are.

Now shade using **vertical** lines where you feel that your **kidney** problems are causing pain.

Put X on **where pain** it hurts (bothers) you the most.

For area marked X,

*Please rate your pain by marking the box beside the number that best describes your pain at its **WORST** in the **last 2 weeks***

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No pain — *Pain as Bad As You Can Imagine*

*Please rate your pain by marking the box beside the number that best describes your pain at its **LEAST** in the **last 2 weeks***

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No pain — *Pain as Bad As You Can Imagine*

*Please rate your pain by marking the box beside the number that best describes your pain **ON AVERAGE***

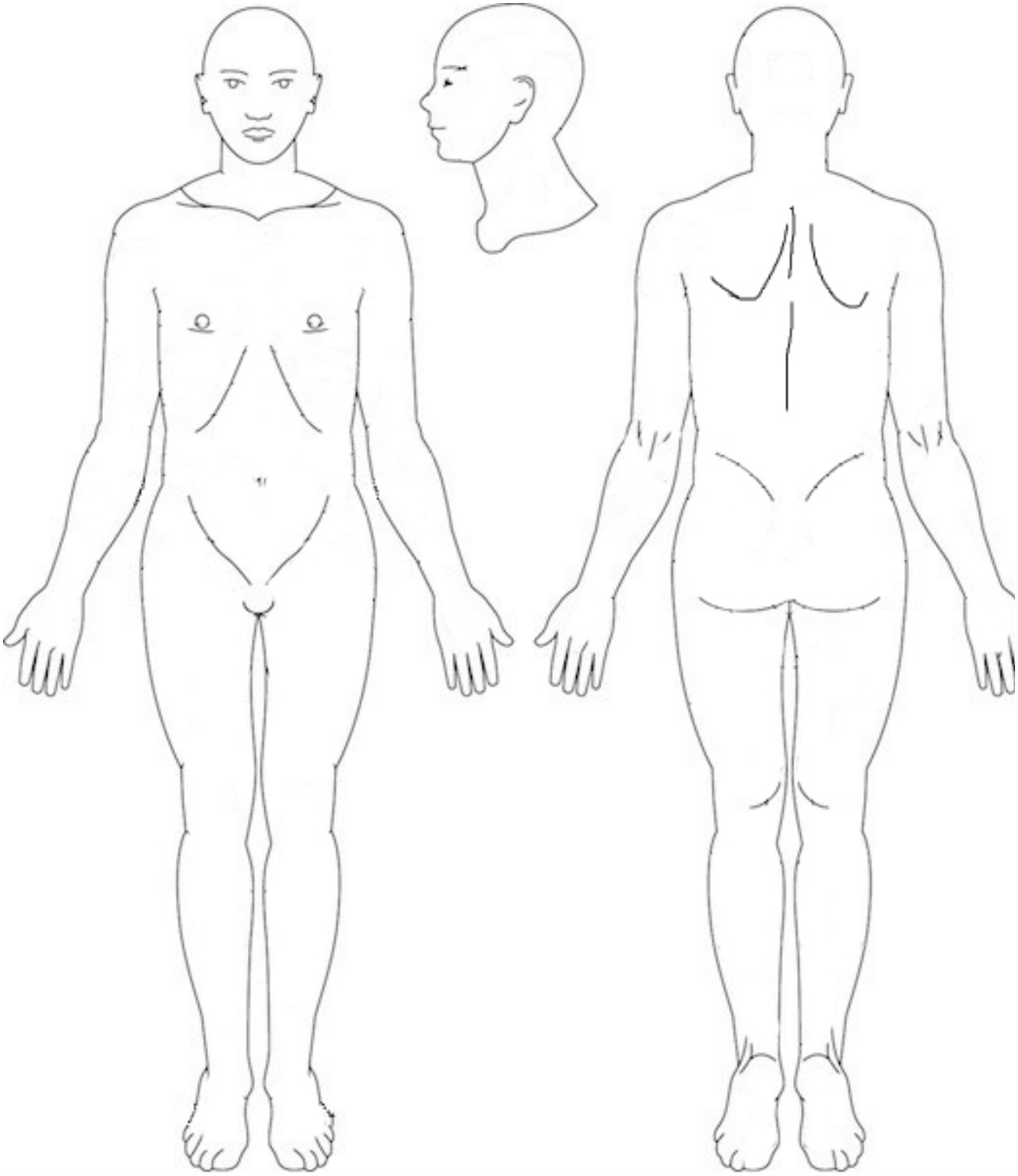
☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

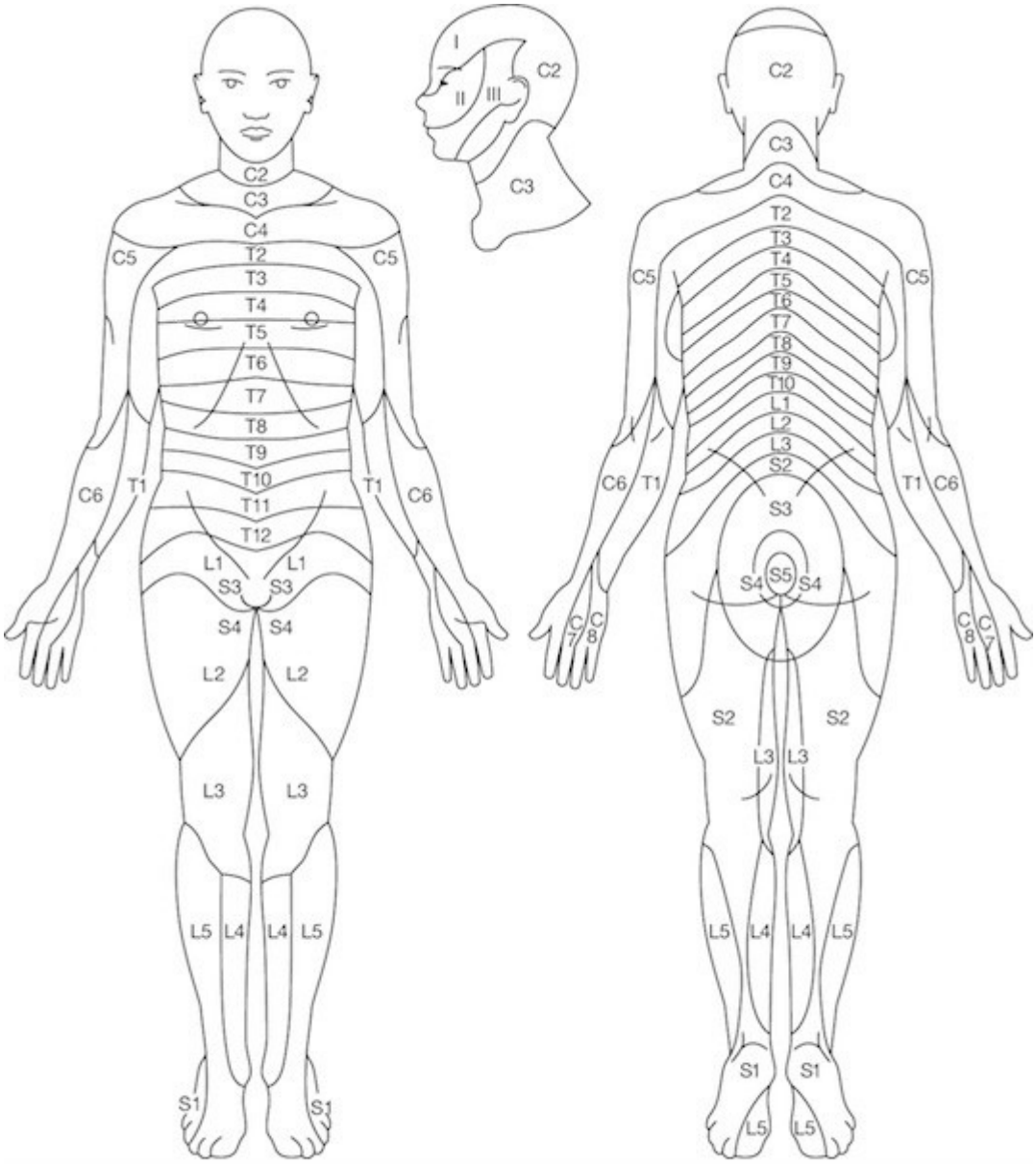
No pain — *Pain as Bad As You Can Imagine*

*Please rate your pain by marking the box beside the number that tells us how much pain you have **RIGHT NOW***

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No pain — *Pain as Bad As You Can Imagine*




I
II
III
C2
C3
C4
C5
T2
T3
T4
T5
T6
T7
T8
T9
T10
T11
T12
L1
L2
L3
L4
L5
S1
S2
S3
S4
S5
C6
C7
C8

BASELINE & FOLLOW-UP VISITS

McGill Pain Questionnaire:

This questionnaire provides you with a list of words that describe some of the different qualities of pain and related symptoms.

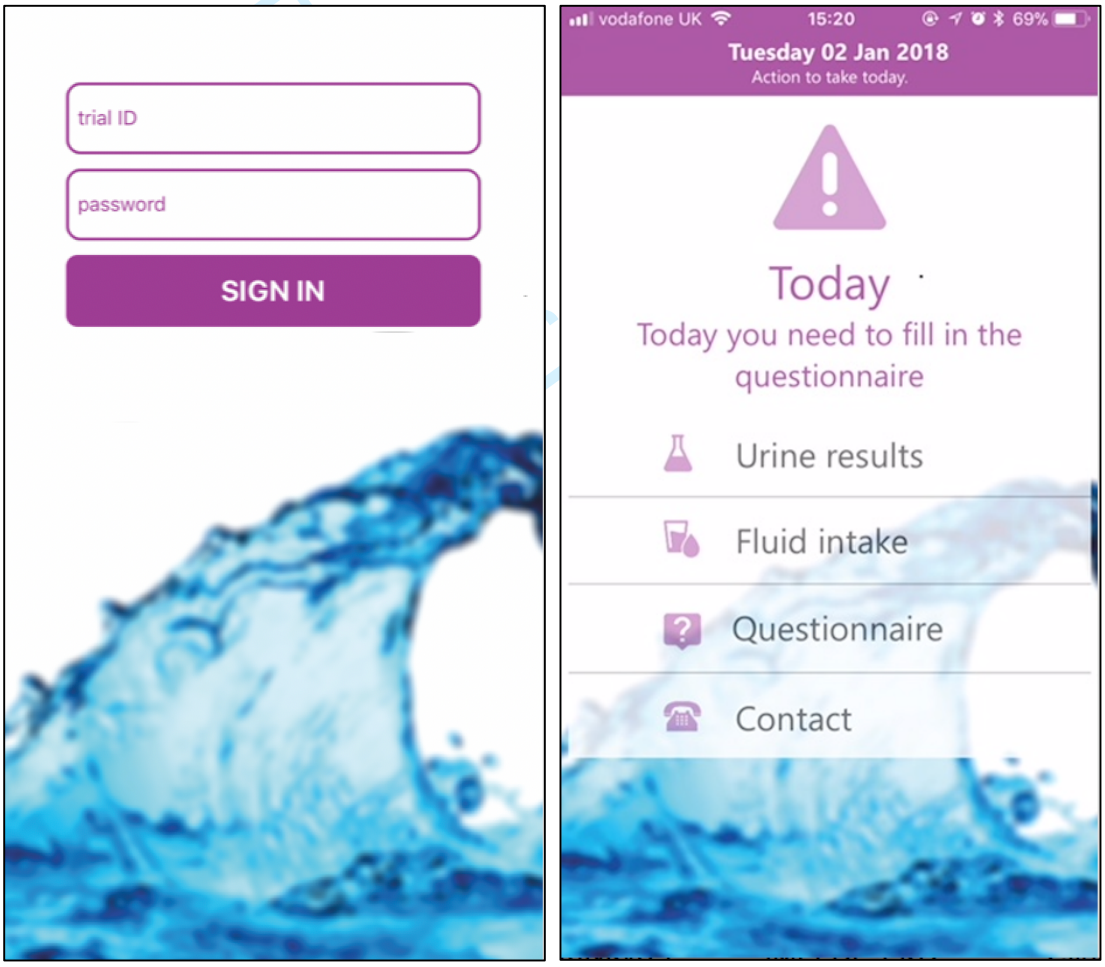
Please put an **X** through the numbers that best describe the intensity of each of the pain and related symptoms you felt during the past **TWO WEEKS**.

Use **0** if the word does not describe your pain or related symptoms

1. Throbbing pain	*none*	0	1	2	3	4	5	6	7	8	9	10 *worst possible*
2. Shooting pain	*none*	0	1	2	3	4	5	6	7	8	9	10 *worst possible*
3. Stabbing pain	*none*	0	1	2	3	4	5	6	7	8	9	10 *worst possible*
4. Sharp pain	*none*	0	1	2	3	4	5	6	7	8	9	10 *worst possible*
5. Cramping pain	*none*	0	1	2	3	4	5	6	7	8	9	10 *worst possible*
6. Gnawing pain	*none*	0	1	2	3	4	5	6	7	8	9	10 *worst possible*
7. Hot-burning pain	*none*	0	1	2	3	4	5	6	7	8	9	10 *worst possible*
8. Aching pain	*none*	0	1	2	3	4	5	6	7	8	9	10 *worst possible*
9. Heavy pain	*none*	0	1	2	3	4	5	6	7	8	9	10 *worst possible*
10. Tender	*none*	0	1	2	3	4	5	6	7	8	9	10 *worst possible*
11. Splitting pain	*none*	0	1	2	3	4	5	6	7	8	9	10 *worst possible*
12. Tiring-exhausting	*none*	0	1	2	3	4	5	6	7	8	9	10 *worst possible*
13. Sickening	*none*	0	1	2	3	4	5	6	7	8	9	10 *worst possible*
14. Fearful	*none*	0	1	2	3	4	5	6	7	8	9	10 *worst possible*
15. Punishing-cruel	*none*	0	1	2	3	4	5	6	7	8	9	10 *worst possible*
16. Electric-shock pain	*none*	0	1	2	3	4	5	6	7	8	9	10 *worst possible*
17. Cold-freezing pain	*none*	0	1	2	3	4	5	6	7	8	9	10 *worst possible*
18. Piercing	*none*	0	1	2	3	4	5	6	7	8	9	10 *worst possible*
19. Pain caused by light touch	*none*	0	1	2	3	4	5	6	7	8	9	10 *worst possible*
20. Itching	*none*	0	1	2	3	4	5	6	7	8	9	10 *worst possible*
21. Tingling or 'pins and needles'	*none*	0	1	2	3	4	5	6	7	8	9	10 *worst possible*
22. Numbness	*none*	0	1	2	3	4	5	6	7	8	9	10 *worst possible*

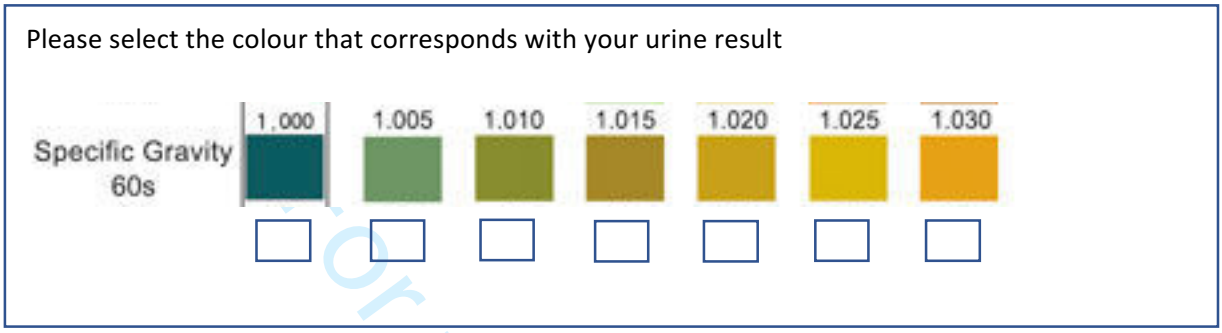
Appendix II – DRINK Smartphone Application

The smartphone application will be used by participants to record the results of their urine specific gravity (SG) measurement, pain and EQ 5D quality of life questionnaire and the participant acceptability question. Each participant will be given a unique trial ID number. When accessing the application for the first time, they will need to register and select a unique password. After this, each access to the application will require participants to input their unique trial ID and password. The information inputted is transferred and stored securely on the NHS N3 server. This is facilitated by FatFractile Ltd. Below is a picture of the login screen and the home screen that participants can use to navigate through the application.

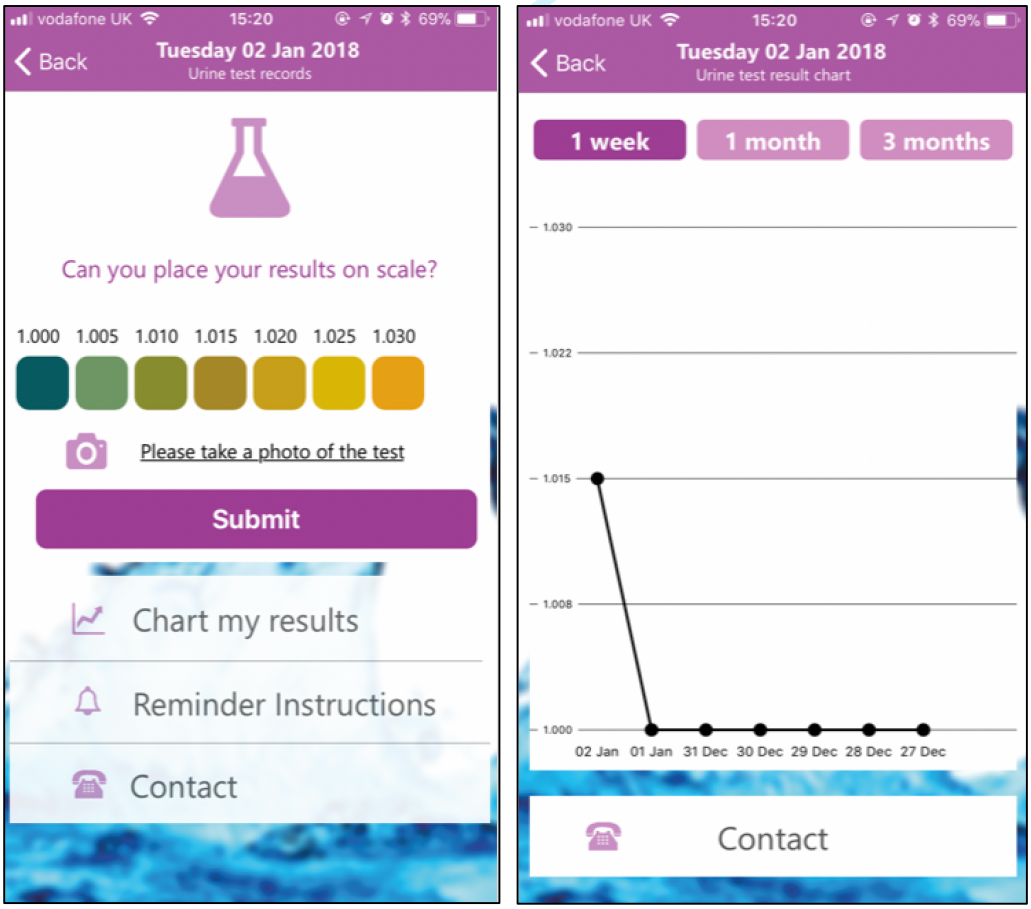


1) Home monitoring of urine SG

Every Monday and Thursday morning between 9am-12pm participants will receive a push notification from the reminding them that today a urine SG dipstick test is required and that this should be done between 4-8pm. Once they have the urine test result participants will be asked to input the urine SG result, see below.



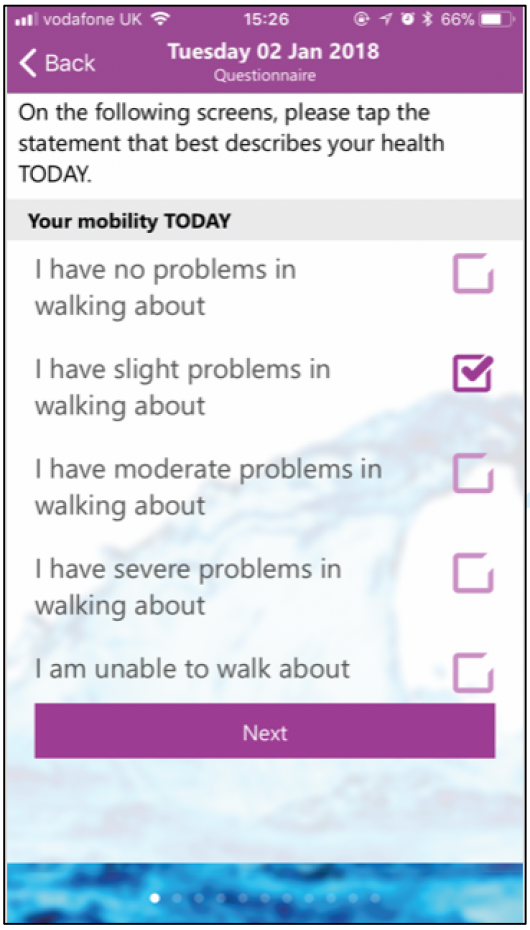
Once they make a selection this data can be transferred securely to the N3 database. A link is also available that will direct the participants to the trial specific website if they require further information or advice. Participants can also view their previous results in chart format to monitor their own progress. A picture of the urine results page as seen in the app is seen below.

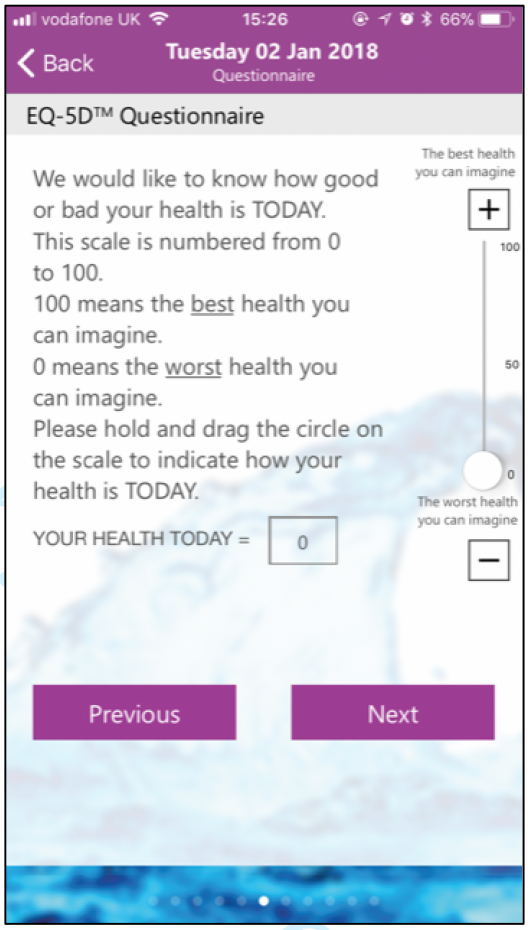


2) EQ 5D Questionnaire

Participants will be reminded to fill out this questionnaire on the smartphone application at the screening visit and again at week 8. The results will be securely transferred to the NHS N3 server.

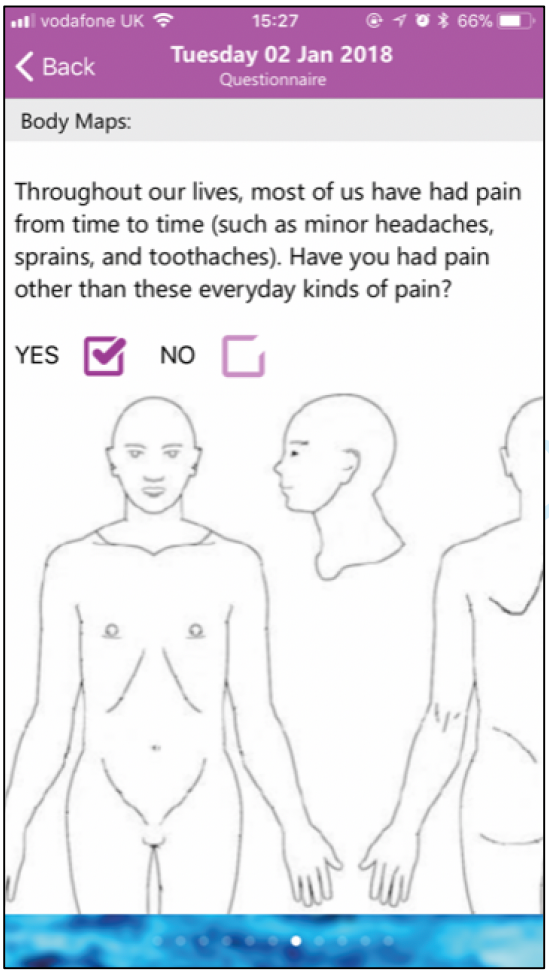
Examples of the questionnaire as seen in the smartphone app are demonstrated below.

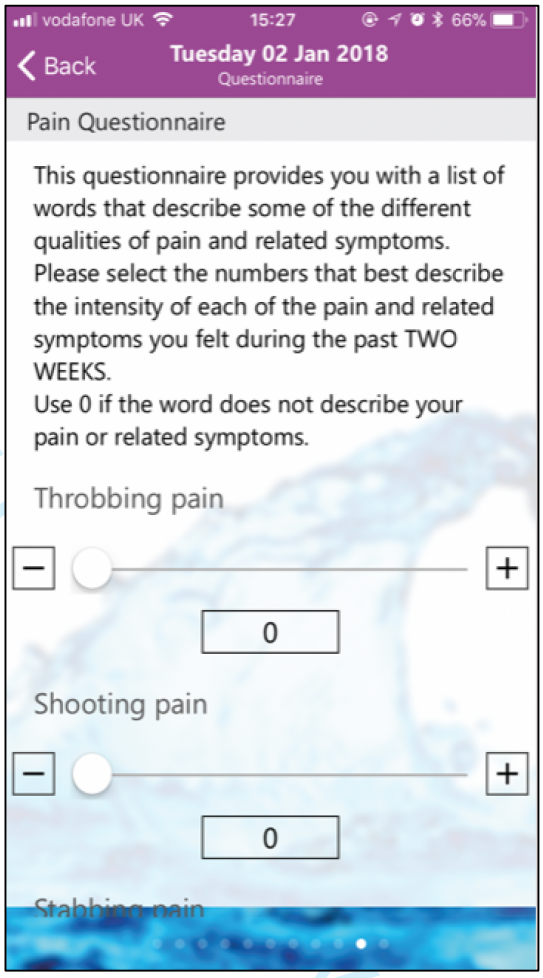




3) Pain Questionnaire

Participants will be reminded to fill out their pain questionnaire on the smartphone application at the screening and at the end of the treatment period at week 8. The data will be securely transferred to the NHS N3 database. Examples of the questionnaire from the app are demonstrated here.





4) Participant Acceptability Question

Participants will be reminded to answer the acceptability question on the smartphone application at weeks 0 and then again at week 8. An example of the question as seen in the app is shown below.