The Primary-Secondary Care Partnership to Improve Outcomes in Chronic Kidney Disease (PSP-CKD) Study: A Cluster Randomised Trial and Economic Model in Primary Care

Supplementary Material

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A Primary-Secondary Care Partnership to Prevent Adverse Outcomes in Chronic Kidney Disease

The PSP-CKD Study

A Cluster Randomised Clinical Trial

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INTRODUCTION AND BACKGROUND

Chronic kidney disease (CKD) is a major public health problem with a UK prevalence of 8-10% (1). The Renal NSF - Part Two (2) mandated seamless care pathways to allow identification of individuals with early CKD through the standardised measurement of kidney function by a formula based estimation of GFR (eGFR), in order that people at increased risk of developing or having undiagnosed CKD, especially those with diabetes or hypertension, are identified, assessed and their condition managed to preserve their kidney function. Recently introduced changes in renal function measurement using eGFR, and the incorporation of financially incentivised CKD clinical indicators in the Quality and Outcomes Framework (QOF) have driven the establishment of primary care CKD registers and provided a platform for the introduction of community-based approaches to the care of patients with CKD (3). The severity of CKD is classified into 5 stages according to eGFR – CKD 1-5 – where CKD 5 represents the most advanced stage of renal functional loss. The majority of patients on CKD registers have CKD 3 (eGFR 30-59 ml/min/1.72m^2), and this category of disease has been sub-classified into CKD 3a (eGFR 45-59 ml/min/1.72m^2) and CKD 3b (eGFR 30-44 ml/min/1.72m^2), with or without the suffix 'p' for proteinuric patients (eg. CKD 3bp), in the belief that these groups have different risks for adverse clinical outcomes (4,5).

The number of randomised controlled trials (RCTs) published in nephrology over the last 40 years is less than for any other speciality area of general medicine (6,7). The evidence base for treatment (6) in CKD is derived largely from young, heavily proteinuric, intensively investigated and well clinically phenotyped patients

in secondary care. However the bulk of patients on CKD registers are elderly with absent or minimal proteinuria and no clear cause for their CKD, thus differing from those previously studied in nephrology RCTs. Recently published guidelines for the management of CKD necessarily rely heavily on this existing evidence base, or on extrapolations from evidence derived from non-CKD populations. Whether these guidelines, together with nascent primary care CKD management pathways, can be effectively delivered and reduce morbidity/mortality in CKD has not been studied.

Patients with CKD are at risk of progressive loss of renal excretory function and excess mortality due to cardiovascular disease (CVD). Cohort studies suggest that although some patients with CKD progress to end stage renal failure and the need for renal replacement therapy, this risk is greatly outweighed by the risk of CVD (8,9,10). In patients with CKD5, some traditional CVD risk factors may be associated with better survival (11). Whilst confounding due to associated co-morbid conditions in CKD5 patients with complex metabolic disease may partially explain this "reverse causality", CVD in CKD may also relate to risk factors distinct from those associated with CVD in a non-CKD population. If these risk factors shift from traditional to non-traditional as CKD progresses through stage 3 this has important implications for the clinical management of patients on CKD registers

Many clinicians in primary care are uncomfortable with the concept of CKD and find this area of patient management challenging and difficult. CKD QOF indicators focusing on the establishment of CKD registers, emphasising blood pressure control and encouraging documentation of proteinuria help to address key issues relating to CKD management but whether this will ultimately lead to improved patient outcomes remains uncertain. There is much CKD expertise in secondary care that could support and nurture the institution of management

programmes for CKD in primary care, but communication between primary and secondary care is at best variable and often absent.

The National Institute for Health Research Collaboration in Applied Health Research and Care for Leicestershire, Northamptonshire and Rutland (LNR CLAHRC) is an ambitious new venture that aims to bring researchers, practitioners and managers together to address long term conditions (LTCs) of major public health importance. It is funded through £10m from the NIHR and a further £10m matched funding provided by the University of Leicester, the acute and primary care NHS Trusts in LNR, the East Midlands Deanery, and by industry. LNR CLAHRC seeks to encourage collaboration to initiate and evaluate new programmes to prevent, detect and manage LTCs. Using innovative approaches, LNR CLAHRC works with health care teams to translate research into practice to improve health in LNR.

NENE commissioning is a practice based commissioning (PBC) group that acts on behalf of ~80 practices in Northamptonshire. The organisation is structured into 4 locality groups covering a population of ~650,000, has an active CKD lead and a desire to implement and evaluate innovative new approaches to CKD management in primary care in Northants. Based on UK epidemiological data suggesting a CKD 3-5 prevalence of ~8-10%, around 50,000 patients in the practices covered by this PBC group will have CKD 3-5 (1). NENE commissioning has expressed an interest in partnership working with LNR CLAHRC to assess and improve the primary care management of CKD in their locality areas.

Although patients with CKD are more likely to die than reach end-stage renal disease, significant decline in renal function may occur with time. Studies have reported only low numbers of individuals with CKD progressing to end-stage

renal disease; Hallan *et al* reported that <2% of patients (of >65,000 patients) with CKD 3 progressed to ESRD during 8 years of follow-up (12). Data from Keith *et al* derived from ~12,000 patients with CKD3-4 showed that the rate of renal replacement therapy over a 5-year period was 1.3%, and 19.9%, respectively for CKD 3 and 4, but that the corresponding mortality rates were 24.3%, and 45.7% (13). Brantsma *et al* reported an age and sex corrected hazard ratio of 1.3 for cardiovascular events in CKD 3 patients compared to non-CKD individuals, and observed a cardiovascular event rate of 20.9/1000 patient years (14).

However renal function does slowly decline in many CKD patients. O'Hare *et al* found that eGFR declines at >3 ml/min/1.73m^2 in about 25% of ~175,000 patients with CKD 3, and in about 35% of ~16,000 patients with CKD 4 (9). Therefore a study of even 10-15 years duration may not detect significant numbers of CKD 3 patients progressing to ESRD. Nonetheless slowing eGFR decline remains an important goal in CKD management, both to prolong the dialysis free period in those destined to progress through CKD 5, and to reduce the increasing cardiovascular morbidity and mortality associated with advancing CKD.

Very few studies have examined the impact of altered CKD management programmes on this rate of progression. Jones *et al* examined the effect of referral to secondary nephrology clinic on rate of eGFR decline in patients with CKD 3-5 (15). They found that eGFR decline was 5.4 ml/min/1.73m^2/yr prior to referral and 0.35 ml/min/1.73m^2/yr after referral. At the same time systolic BP fell from 155 to 149 mmHg and diastolic BP from 84 to 80 mmHg. Clearly these results may not be easily generalisable to primary care CKD since the patients had been selected for secondary care referral by their general practitioners presumably on account of more severe disease. However, in a small primary care observational

study of 483 patients with borderline CKD 3/4, CKD 4 and CKD 5, a similar reduction in the rate of decline in renal function at 9 months was demonstrated after the introduction of a disease management programme (DMP) comprising patient education, medicine management, dietetic advice and optimisation of clinical management to achieve clinical targets (16). The median fall in eGFR in the 9 months prior to joining the DMP was 3.69 (1.49-7.46) ml/min/1.73m^2 compared to 0.32 ml/min/1.73m^2 in the 12 months following entry into the DMP. Likewise systolic BP fell from 139 to 130 mmHg and diastolic BP from 76 to 71 mmHg. This study focused on individuals with more advanced CKD and was observational rather than randomised (16).

However randomised trials are urgently needed to further study implementation and effectiveness of CKD DMPs in primary care.

Hypothesis

Intensive primary care led disease management programmes for CKD, supported by input from secondary care specialists will improve blood pressure control, slow progression of CKD and reduce cardiovascular events in patients on CKD registers.

STUDY DESIGN AND OBJECTIVES

The design will be a pragmatic RCT of patients with a mixture of renal diagnoses on primary care CKD registers. This will be a cluster randomised trial of an intensive, secondary care supported, CKD management programme in primary care *vs* normal CKD care. Randomisation will be at the level of the individual general practice. All general practices associated with NENE commissioning locality groups will be invited to participate. If insufficient numbers of practices in

Northants consent to participation then practices from Leicestershire and Rutland will be invited to participate in order to supplement numbers. Randomisation of practices will be performed by the University of Leicester Clinical Trials Unit. The study will adhere to guidelines for undertaking randomised cluster trials (17).

The aims of the study are:

1. To determine whether reinforcement of best practice in the management of key aspects CKD care by clinical nurse specialists based in primary care, but with close links to colleagues from secondary care, improves clinical outcomes.

2. To foster excellence in CKD care.

3. To improve coding of CKD and prevalence on chronic disease registers.

4. To increase interest in, and capacity for primary care research in Northamptonshire.

5. To implement and evaluate a new model of partnership working between primary and secondary care.

Primary outcome measures:

- *difference in mean CKD register patient eGFRs between groups after 3.5 years of study*

Secondary outcome measures:

- *blood pressure control*

- *proteinuria*

- *incidence of cardiovascular events*

- other biochemical parameters

- referrals to secondary care and hospitalisations

- mortality

STUDY MANAGEMENT

The study will be managed and co-ordinated by investigators based at UHL NHS Trust, University of Leicester, Northants PCT, NENE Commissioning and Northampton General Hospital (NGH). The intervention will be performed within individual general practices. Clinical nurse specialists will be employed as 'outreach nurses' by Northampton General Hospital with letters of access provided by NHS Northamptonshire to allow clinical practice in individual GP surgeries. The clinical nurse specialists will be located alongside Nephrology clinical service at NGH where Dr Warren Pickering, Consultant Nephrologist, will provide a clinical lead. The primary care clinical lead will be Dr Kamal Sood, General Practitioner, Abington Park Surgery. The study will be supported by the University of Leicester Clinical trials Unit.

CLUSTER RANDOMISED CONTROLLED TRIAL - THE STUDY INTERVENTIONS

General Considerations

The study will be run by specialist nurses working between primary and secondary care. Anonymised laboratory and clinical data will be extracted from primary care IT systems using MIQUEST search methodology. After agreeing to

participate in the study, but prior to randomisation, practices will be visited by a member of the research team trained in MIQUEST methodology. This will be T=0, and data will be extracted to identify:

- all prevalent patients ≥18 years of age in the practice with measurement of serum creatinine and eGFR <60ml/min/1.73m^2
- for all prevalent patients with eGFR <60ml/min/1.73m^2 the following laboratory data will be extracted if available and obtained within 3 months of the relevant eGFR data:
    - *albumin, B12, blood glucose, ferritin, haemoglobin, HbA1c, total cholesterol, serum potassium, serum sodium, serum urea, serum bicarbonate, serum calcium, serum folate, serum phosphate, serum triglycerides, urine protein or albumin:creatinine ratio*
- for all prevalent patients with eGFR <60ml/min/1.73m^2 current medication data will be recorded focusing on:
    - *ACE inhibitor, ARB, alpha-blocker, aspirin, other anti-platelet drugs, beta-blocker, Ca^{2+} channel blocker, diuretic, other antihypertensive, erythropoietin, insulin, K^+ sparing diuretics, statins, lithium, metformin, NSAIDs, sulfonylurea, other oral hypoglycaemic, phosphate binders, steroids, vitamin D or its analogues*
- last recorded BP for all prevalent patients with eGFR <60ml/min/1.73m^2
- results of dipstick urinalysis
- smoking history
- medical history of:
    - anaemia, atrial fibrillation, cerebrovascular disease, diabetes (type 1 and 2) , diabetic nephropathy, glomerulonephritis, heart failure, hypertension, ischaemic heart disease, IHD, malignant disease,

obesity, peripheral vascular disease, polycystic kidney disease, prostatic hypertrophy, renal artery stenosis, CKD, urinary tract obstruction, recurrent UTI.

- for all prevalent patients with an eGFR <60ml/min/1.73m^2 at T=0, a retrospective search of eGFR data over the preceding 3 years will be performed (T=-12, -24, -36)

This data, with attached patient identifiers will be provided to the clinical staff in the practice, but exported anonymously for research analysis with all recognisable patient identifiers removed. Individual practices will then be randomised into control or intervention groups and the study will run for 42 months.

Further data extractions will be performed every 6 months from the records of all CKD patients with eGFR <60ml/min/1.73m^2 identified at T=0. On these occasions laboratory, urinalysis, and blood pressure data will be extracted, together with data on medications, mortality, all hospitalisations, cardiovascular events and the development of ESRD. This data, with attached patient identifiers will be provided to the clinical staff in the practice, but exported anonymously for research analysis with all recognisable patient identifiers removed

Control Group

Practices randomised to the control arm of the study will continue to provide 'usual' CKD care for patients on their CKD registers delivered according to published guidelines (10,18,19). This will include elements of blood pressure and cardiovascular risk management delivered either *ad hoc*, or to CKD patients cohorted into CKD clinics or cardiovascular risk clinics, according to individual practice preference and current practice.

The Intervention Group

Practices randomised to the intervention group will be offered an enhanced level of CKD disease management led by clinical nurse specialists based on an intervention previously piloted in high risk patients (16). Soon after randomisation to 'intervention' a clinical nurse specialist trained in CKD care will make contact with the CKD lead at the practice.

This clinical nurse specialist will:-

1. Be allocated their own portfolio of practices.
2. Encourage the practice to assess their barriers to the application of best practice in CKD care using a brief questionnaire and formulate ways to overcome these barriers. This may involve: exploring ways of integrating better CKD care into day to day practice with regular feedback to staff; explanation and assistance in implementing guidelines; clarification of existing algorithms for management of hypertension and cardiovascular risk factors; helping with medicines management; directly supporting the establishment of dedicated primary care CKD clinics and providing 'hands on' care as required.
3. In collaboration with practice CKD leads, assist practice clinical staff to identify 'high risk' CKD patients (those particularly at risk of progressive renal functional decline or CVD), with CKD 3b, CKD 4 and CKD 5, progressive CKD, proteinuria (PCR >50 and/or ACR >30) or poorly controlled BP. This identification will be based on the data previously extracted from the practice computer system. With regard to this group of patients, specialist nurses will encourage rigorous adherence to treatment guidelines, advising on patient recall intervals, liaising and encouraging dialogue with colleagues in secondary care for advice where necessary.

4. Make contact with the relevant CKD lead weekly by phone to identify any unresolved CKD management issues and to help formulate a management plan if necessary.
5. Visit their allocated practices at least twice monthly in person. On these visits the specialist nurse will meet with the practice CKD lead to discuss any ongoing CKD patient management problems and will focus on BP control in high risk patients. Comprehensive clinical guidelines now provide guidance for primary carers on the management of key aspects of CKD and blood pressure control guidance is particularly crucial. For example, NICE guidelines (10) suggest that for people with CKD a systolic blood pressure target below 140 mmHg (target range 120–139 mmHg) and the diastolic blood pressure below 90 mmHg is appropriate. In people with diabetes and CKD or when the ACR is ≥70 mg/mmol, or PCR ≥100 mg/mmol the systolic blood pressure should be maintained below 130 mmHg (target range 120–129 mmHg) and the diastolic blood pressure below 80 mmHg. Advice provided to the intervention group of practices will be in line with NICE CKD guidelines.
6. Provide a conduit for clinicians (nurses and/or physicians) in primary care to obtain management advice from secondary care at short notice. This may include advice regarding incremental BP medication changes, anaemia management or additional investigations and will be achieved either by telephoning the designated nephrologist or arranging an expedited out-patient clinic appointment if necessary. Whilst these secondary care services are already available, the specialist nurse will facilitate their use for the intervention group of practices. The aim, in addition to helping CKD patient

management, is to build a professional relationship between colleagues in primary and secondary care and facilitate collaborative working.

7. Provide the practice staff with personal diaries to distribute to patients on CKD patients to increase patient engagement in disease management.
8. Keep a diary of their interactions with each practice - both visits and phone contacts.

There is funding for 3 clinical nurse specialists, and at the time of submission of this protocol 48 practices have agreed to participate in the study and this will provide sufficient CKD patients to power the primary outcome (see below). Assuming 24 practices in a control group and 24 practices in an intervention group each nurse will be required to cover 8 practices. Therefore with these numbers the specialist nurse would be able to visit each practice 3 times per month, allowing half a day for each visit, and under these circumstances the intervention will not be too thinly spread. Regular contact with the clinical nurse specialist will raise the profile of CKD in the intervention practices, and the nurse specialist will be in a position to provide 'hands on' assistance with CKD management working closely with practice based staff who may already be providing care for other chronic conditions such as diabetes, hypertension *etc*. This pragmatic study design recognises that requirements of individual practices will differ, some requiring little input from the intervention and others requiring more.

CLUSTER RANDOMISED CONTROLLED TRIAL - OUTCOMES

Primary Outcome

Change in eGFR

CKD register patients in both control and intervention practices have eGFR measured as part of routine clinical care. The natural history of renal excretory

function in many patients with CKD is a gradual decline, but this is not well studied in primary care populations.

Retrospective, anonymised eGFR data for all prevalent patients on CKD registers will be extracted from practice records for the period T=-36, -24, -12 and -6 months and at T=0 (at randomisation). Thereafter eGFR data will be extracted every 6 months until month 42 (T=42). At each time point median eGFR values for all CKD patients, and patients sub-divided into CKD3a, CKD3b, CKD4, and CKD5 patients will be calculated. Rate of decline of eGFR for patients on CKD registers in each practice cluster will be compared.

Secondary Outcomes

Changes in Blood Pressure Control

Blood pressure control is a crucial determinant of clinical outcomes in CKD, both in terms of cardiovascular co-morbidities and CKD progression, and will be measured according to the requirements of routine clinical care. Systolic and diastolic blood pressure readings of patients on CKD registers will be extracted anonymously from practice records at T=0, 6, 12, 18, 24, 30, 36 and 42 months of the study for practices in both control and intervention groups. Blood pressure will be measured and recorded using the techniques and equipment prevalent in each practice.

At each time point median BP values for patients on CKD registers will be calculated and results from each cluster compared. In addition results for each cluster will be and assessed against published BP targets for CKD patients as:-

1. % achieving QOF targets (20) – BP ≤140/85
2. % achieving NICE guideline targets (10) – BP <140/90

Cardiovascular Events

Cardiovascular event rates of 20.9/1000 patient years have been described for patients with CKD (14). Assuming 25,000 patients accrue a total of 87,500 patient years in each arm of the study, then ~1,830 cardiovascular events would be expected in each group.

Laboratory and Biochemical Data

- *urine protein excretion (albumin:creatinine ratio or protein:creatinine ratio according to local practice)*
- *total cholesterol*
- *triglyceride*
- *haemoglobin*

Clinical Outcomes

In addition, at T=12, 24, 36 and 42 months, data relating to hospital referral, cardiovascular events and mortality for patients on CKD registers will be extracted from practice databases. At T=36 months a general reminder will be issued to all participating practices reminding practice CKD leads to ensure that eGFRs of all CKD register patients have been appropriately recorded in a timely manner according to published guidelines (2).

DATA EXTRACTION AND HANDLING

Data will be extracted from practice computers by MIQUEST search at T=0 using the following strategy to identify patients with CKD:

1) find total population over 17
2) find those with eGFR <60 ml/min/1.73m^2 ever
3) find those with read code of renal impairment

4) 2 OR 3

5) find in 4 those with RRT

6) 4 NOT 5 to get the target population minus exclusions

7) Search 6 for the data needed

Search tools for data downloads will be available online to practice staff who will require a username and password for access. Extracted data will be provided to clinical staff in the practice with patients identified by NHS number. Before the data is removed by the CLAHRC researcher the NHS number will be scrambled and thus the data will be completely anonymous to researchers. The formula for NHS number scrambling will be embedded within the data extraction tool and it will be impossible for CLAHRC researchers to unscramble the exported scrambled NHS numbers thus preserving patient anonymity.

Anonymised data will be collated and stored by a dedicated CLAHRC data handler within the University of Leicester Clinical Trials Unit team.

SAMPLE SIZE

(see sample size addendum page 30-31)

We predict, given the described 8-10% prevalence of CKD 3-5, that ~50,000 patients in 75 practices will be available for study and that over a 3.5 year study 87,500 patient years will accrue in each study group.

In order to have 90% power to find a difference in eGFR of 3ml per minute at the end of three years (follow up time) significant at the 5% level (2-tailed test), assuming a within subject standard deviation of 7, 116 patients per group would be required before taking into account the design effect.

The design effect is calculated as 1 + (600-1) x ICC

Here we anticipate having ~600 eligible patients per practice on average, and we conservatively estimate the ICC to be 0.2 based on the work of Campbell *et al* (21) demonstrating that the maximum ICC for a continuous variable in a sub-group of primary care is 0.201.

Our design effect is thus:

1 + (599 x 0.201) = 1 + 121 = 122.

So we need:

116 x 122 = 14,152 patients per group.

However we anticipate that we will lose 20% of patients per group through death, and therefore adjusting for this will need: 14,152/0.80 = 17,690 patients per group (35,380 in total).

Given number of practices interested in being involved it is likely that the study will be significantly overpowered for this outcome. However for CLAHRC purposes studying the ability to deliver the partnership intervention to large numbers of practices is also important.

STATISTICS

The primary outcome is change in eGFR over 3.5 years (continuous). We will analyse using a two-level model (change score within practices will be the level 1 variable, and practices will be the level 2 variable). We assume the change score will be approximately normally distributed. SAS Proc Mixed (SAS version 9.1.3) will be used to analyse the data, with the comparison of mean change score being adjusted for the effects of the clustering (GP practice) as well as any potential confounders.

Alternatively, we will compare eGFR scores at the end of three years, after adjusting for baseline scores. We expect baseline scores to be equivalent between the two groups. The two groups will also be checked for equivalence for other demographic variables. If there are any significant differences between the groups for any variable, this will be adjusted for in the analysis.

We will also measure mortality within each group. If the group with the worst eGFR has a higher mortality, and if this higher mortality is related to the eGFR score, then any effect we were hoping to record may be diluted as a consequence. We do not expect the mortality rates to be significantly different in the two groups.

ETHICAL ISSUES

Main Research Ethics Committee approval and University Hospitals of Leicester Trust R&D Approval will be sought for the study before it commences. This will ensure that all ethical and indemnity issues are dealt with.

An internal Data Safety Monitoring Committee will be established to oversee all activities required to determine safe and effective conduct and to recommend conclusion of the trial when significant benefits or risks have developed or the trial is unlikely to be concluded successfully. The committee will meet on a regular scheduled basis to review data collection. Issues raised will be addressed with the Principal Investigators and reports and recommendations will be provided.

POTENTIAL BENEFITS, DISSEMINATION AND IMPLEMENTATION OF FINDINGS

The project will establish whether intensivised management of CKD at the practice level will improve renal, and possibly other, outcomes for patients with CKD. In addition, the potential for partnership working between primary and secondary

care will be established with the possibility of new commissioning arrangements. Infrastructure and interest in primary care research in Northamptonshire will be enhanced. Research findings will be disseminated via general and CLAHRC specific meetings by oral presentation and posters. All results will be submitted for publication. Significant findings will be presented to Kidney Research UK for consideration of further research support if appropriate. Local press will be informed of headline results. If the intervention leads to improved outcomes for CKD patients, results will be presented to PCTs and PBC groups for consideration of service commissioning.

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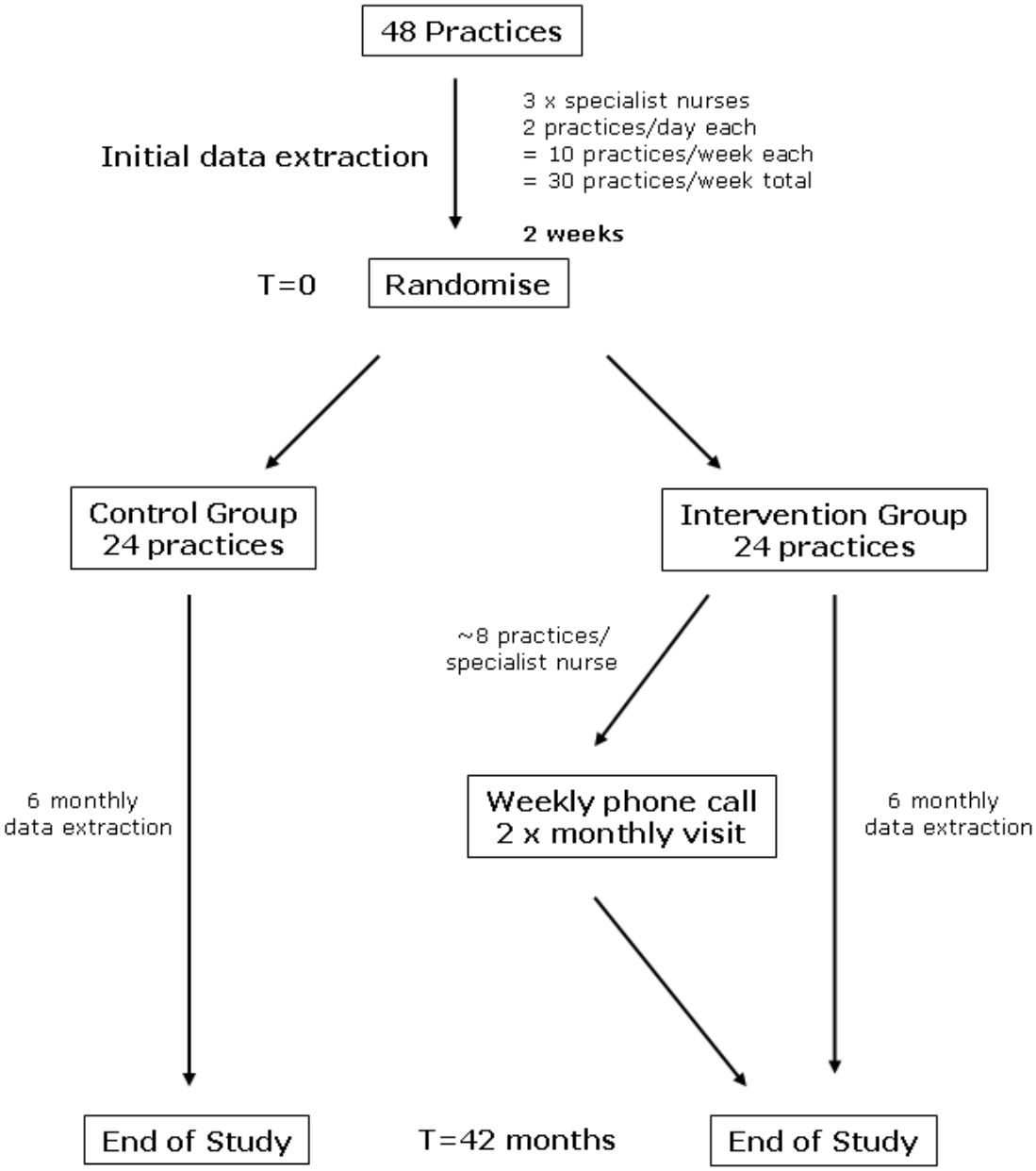

PSP-CKD Study – Schematic Representation

-----Original Message-----

From: Bankart, John (Dr.) [mailto:mjb65@leicester.ac.uk]

Sent: 09 February 2011 16:18

To: 'Brunskill, Nigel (Prof.)' <njb18@leicester.ac.uk>; 'philip shelton' <pas37@leicester.ac.uk>; 'Kirby, Danny' <dk13@leicester.ac.uk>

Subject: New sample Size Calculations

Hi Nigel,

I have re-done the sample size calculations for the CKD study based on the data given to me by Danny on December 18th.

Please see the attached file for revised calculations.

Basically, the SD we used from Jo Mason's data of 7 looks to be too low (bad news), but the ICC we used (conservatively we chose the highest one likely = 0.2) is too high (good news).

What this means, is that assuming the worst case scenario,

SD=12, we will need 25,985 in total, after 20% attrition.

If the SD is 11 we will need 21,418 after attrition.

If the SD is 10 we will need 17,683 after attrition.

All of these are for a difference of 3, 80% power, 5% significance (2-tailed), and take into account the newly calculated ICC and newly calculated SD.

If we are happy (retrospectively and hence not as satisfactorily) with a difference of 4 then we are fine (see attached table 2).

I suggest we have a meeting to discuss these new figures and what they mean for recruitment purposes, and also the relevance of the data given to me by Danny, and the way I have used it.

Given that we could potentially be 6,000 short, we may want to recruit more practices. That would be my advice.

John.

CKD Study

New sample size calculations

9th February 2011

John Bankart

Table 1: If difference = 3

Standard Deviation	Basic Sample Size Calculation based on difference of 3	Multiplied by Design effect of 40.6 (based on ICC of 0.1) = n per group	Number in total (*2)	Total after attrition (divide by expected completion rate of 0.8)
12	256	10,394	20,788	25,985
11.5	230	9,338	18,676	23,345
11	211	8,567	17,134	21,418
11	174	7,073	14,146	17,683

Table 2: If difference = 4

Standard Deviation	Basic Sample Size Calculation based on difference of 4	Multiplied by Design effect of 40.6 (based on ICC of 0.1) = n per group	Number in total (*2)	Total after attrition (divide by expected completion rate of 0.8)
12	141	5,725	11,450	14,313
11.5	130	5,278	10,556	13,195
11	119	4,832	9,664	12,080
11	98	3,979	7,958	9,948