Table S1. Various ways that individualized risk-based information may be used by different stakeholders involved in CKD care

Stakeholder group	Potential value, need, or use of risk information
Patients, family, and caregivers	Knowledge of risks for the outcomes deemed important Information explained in language that is understandable Care providers offer the insights with patient preferences and values considered in the development of the management plan Education, social class, literacy and beliefs all contribute to self-management
Primary care providers	Knowledge of risk provides confidence in referral, management, and communication with patients – especially patients at low risk, not requiring referral to specialist care Consistent, agreed upon messages from different specialists involved in a patient's care are desired Recognize that patients often underestimate risks, and specialist healthcare providers may overestimate benefits and under estimate harms of interventions[S1]
Specialists, CKD care providers	Risk prediction tools combined with clinical judgment help identify patients requiring transition to different modalities of care and help guide necessary interventions (including educational initiatives) Differing risk guides intensity of follow-up and appropriate timing of: education and discussion of conservative treatment versus KRT; type of KRT modality; planning for dialysis access; end-of-life decision making Differing risks may also guide decisions concerning investigations and therapies
Health system payers, policy makers	Appropriateness, efficiency and affordability of care Risk prediction tools for the key outcomes of advanced CKD, including mortality and cardiovascular complications (heart failure, myocardial ischemia and stroke) combined with good epidemiological data enables prioritization and planning of use of healthcare resource Getting services to remote areas and reaching high risk vulnerable populations, national priorities versus local

CKD, chronic kidney disease; KRT, kidney replacement therapy

Table S10. Challenges, potential solutions and suggested actions related to increasing the number and quality of clinical trials in CKD G4+ populations

Challenge	Potential solution	Suggested action	Actor
The clinical needs of CKD G4+ patients are apparent, but other elements of a business case for conducting trials in this population have not been well described	Build the "business case" for industry and other payers to support trials in this population	Work with large health care providers that have used such business cases to justify their own CKD G4+ programs (e.g., Mayo, Kaiser Permanente). Use this information to create a briefing document for payers	KDIGO, ISN, ASN Kidney Health Initiative, French CKD trial network and others
Recruitment and retention to trials is an ongoing challenge in CKD G4+ populations	Engage patients to lead and support clinical trials in this population	Commission and support a group to conduct scoping review and propose structures/processes to enable sustained patient engagement	KDIGO, ISN, ASN Kidney Heatlh Initiative, French CKD clinical trials network
Available trials often do not address the needs of CKD G4+ patients and families	Ensure that the findings of trials in CKD G4+ are maximally relevant for patients and families	Review existing lists of patient-centered research priorities and commission a new list for CKD G4+ if required	KDIGO
Available trials are often small or underpowered, and recruitment is challenging	Leverage collaborations between existing national CKD trial networks to facilitate multinational trials	Partner with ISN-ACT to conduct a multinational investigator-initiated clinical trial on common interventions such as bicarbonate, uric acid reduction, ACEi/ARB or phosphate binder therapies	ISN-Advancing Clinical Trials (ISN- ACT), ASN Kidney Health Initiative, French CKD clinical trials network and others
Little is known about how to manage symptoms of CKD G4+, which is a key treatment objective for patients	Do more studies of symptom management	Create a toolbox of validated instruments for common CKD G4+ symptoms that can be used in trials or in supporting studies	KDIGO*

* Although KDIGO could act as a catalyst to establish these initiatives, they will likely require the creation of a dedicated organization or structure to ensure sustainability. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CKD, chronic kidney disease; KDIGO, Kidney Disease: Improving Global Outcomes; ISN, International Society of Nephrology, ASN, American Society of Nephrology.

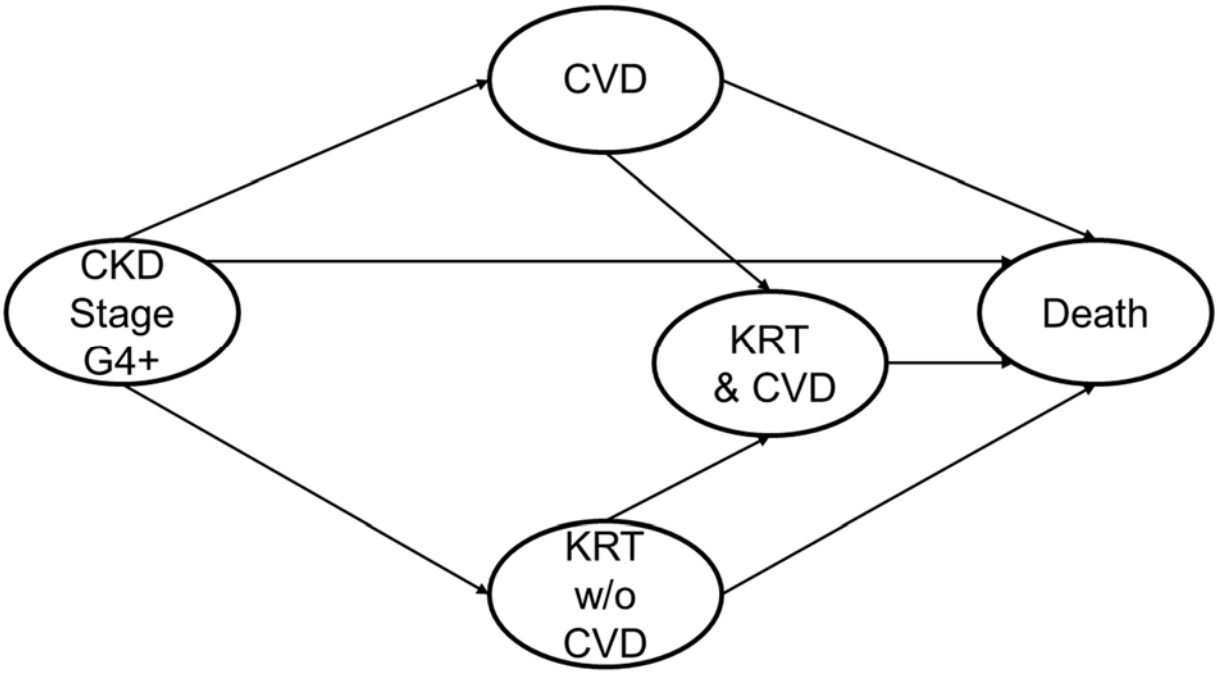


Figure S1. Markov Model – modified graph illustrating the different possible pathways Reproduced from Grams *et al.* [S25]

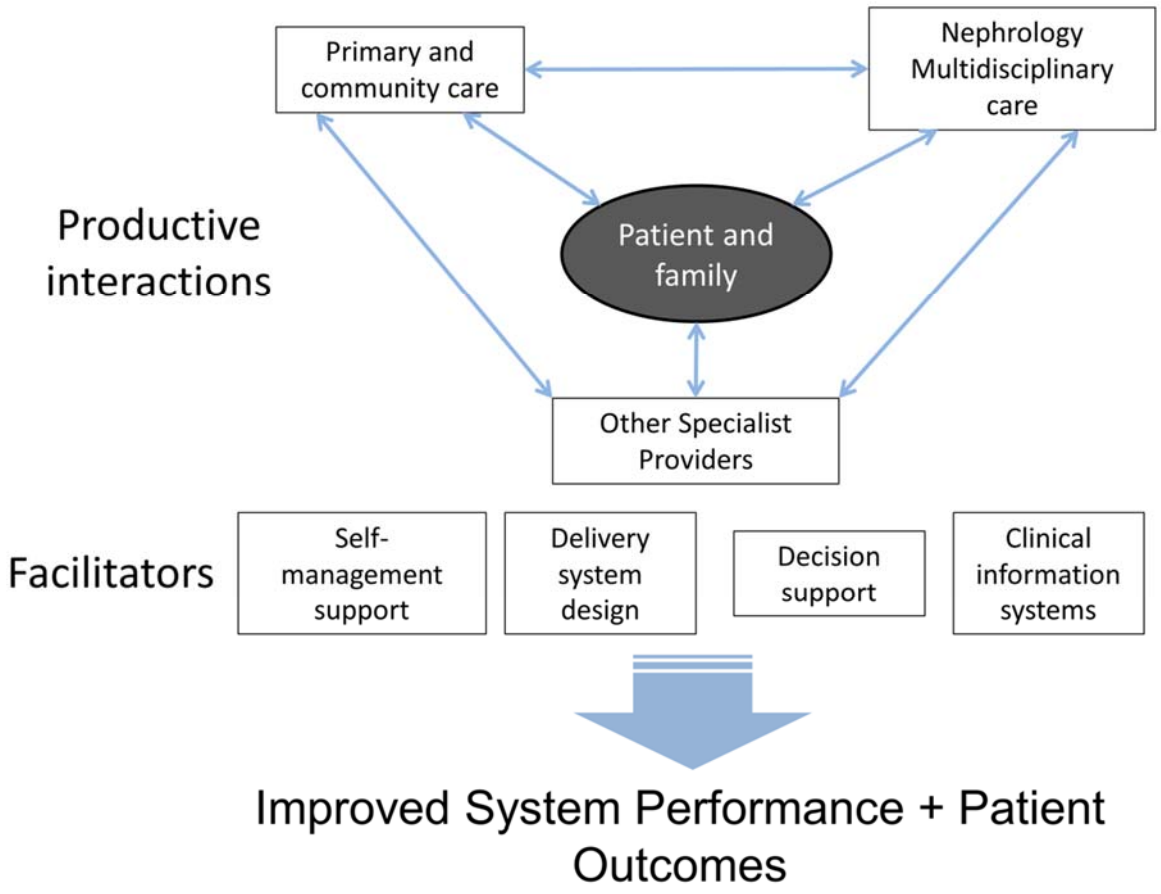
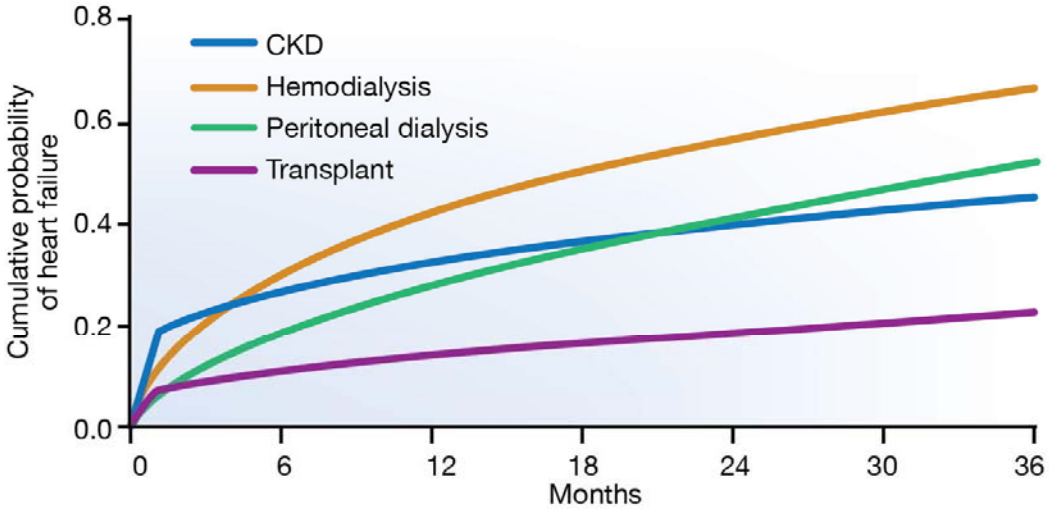


Figure S2. CKD Chronic Care Model



CKD: incident general Medicare CKD patients, age 66 & older, 2001–2003 combined.
ESRD: Incident ESRD patients, age 20 & older
Patients with CHF at baseline excluded. Probabilities unadjusted.

Figure S3. Cumulative probability of heart failure in incident patients
Reproduced from the USRDS ADR 2007[S26]

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Table S2. Key competencies required for delivery of CKD G4+ care

1. Diagnosis and categorizing CKD
   Assessment of prognosis; identification of kidney-related and non-kidney related complications; initiation of required interventions and determination of a care plan; identification of people with care needs despite prediction of low risk of progression of CKD
2. Education
   Education of patient/family/carer concerning CKD; explanation of competing risks of CKD progression and mortality; kidney failure treatment options; coordination of care between patient/family/carer(s) and other members of CKD multidisciplinary team and primary care physician
3. Planning for kidney failure
   Evaluation for kidney transplant including living transplantation options and transplant education; assessment of dialysis options (hemodialysis and peritoneal dialysis); creation of dialysis access; provision of end-of-life care, symptom control and palliation; setting goals of care with aligned treatment plans
4. Nutrition
   Dietary advice as required, including salt and fluid management
5. Medications
   Medicines reconciliation and education of potential harm of over-the-counter medicines; advice with respect to “tablet holidays” during severe intercurrent illness and strategies to avoid/ameliorate acute kidney injury; review of immunizations and implementation of vaccination programs
6. Psychosocial support
   Access to counselling; access to housing and transport support; insurance advice

CKD, chronic kidney disease.

Table S3. Selected therapies for future research in CKD G4+

Therapy	Evidence	Current Guidance
Aspirin for prevention of cardiovascular disease	In secondary prevention low-dose aspirin therapy reduces the incidence of adverse cardiovascular events and all-cause mortality.[S2] In primary prevention the evidence does not support the universal use or avoidance of aspirin. A systematic review (3 studies, n=4468) found no clear benefit of aspirin for the primary prevention of cardiovascular events in CKD and no statistically significant reduction in mortality. Major bleeding events were significantly increased with aspirin.[S3]	Both KDIGO[S4] and NICE[S5] recommend that aspirin is indicated for secondary but not primary prevention. NICE have recommended future research to address this question for those at highest risk of cardiovascular disease (What is the clinical effectiveness of low-dose aspirin compared with placebo for primary prevention of cardiovascular disease?)
Bicarbonate therapy in CKD G4+	A meta-analysis of 6 studies (n=312) concluded that bicarbonate therapy was associated with improvement in kidney function and possibly a reduction in progression of CKD.[S6] However, differences in study protocols and small sample sizes precluded definitive conclusions.	KDIGO suggest treatment with oral bicarbonate supplementation in people with CKD and serum bicarbonate concentrations < 22 mmol/l; NICE suggest considering oral sodium bicarbonate supplementation in people with CKD G4+ and a serum bicarbonate concentration of < 20 mmol/l.
Treatment of asymptomatic hyperuricemia	A systematic review (24 studies n=25,453) found that elevated serum uric acid levels were significantly associated with risk of mortality in patients with CKD.[S7] Another systematic review (13 studies, n=190,718) found a significant positive association with new-onset CKD at follow-up.[S8] However there is little evidence to justify uric acid-lowering in CKD G4+. Recent systematic review and RCT evidence on allopurinol use are inconsistent in terms of the potential benefits of lowering uric acid.[S9-S13]	KDIGO suggested there is insufficient evidence to support or refute the use of agents to lower serum uric acid concentrations in people with CKD and either symptomatic or asymptomatic hyperuricemia in order to delay progression of CKD. NICE make no recommendation but suggested that in people with CKD who are at high risk of progression, the clinical and cost effectiveness of uric acid-lowering agents on the progression of CKD and on mortality should be the subject of further research.

Metformin therapy in people with diabetes and CKD G4+	Metformin is widely prescribed given evidence suggesting it reduces the risk of myocardial infarction, stroke, atrial fibrillation and all-cause mortality.[S14] However its use in CKD has been limited because of the perceived increased risk of lactic acidosis. A Cochrane analysis of 347 controlled studies covering 70,490 patient-years of metformin use revealed no cases of lactic acidosis and no significant change in plasma lactate.[S15] A Swedish Diabetes Registry study suggested that metformin was well tolerated in people with CKD G3, and its use was associated with 13% lower all-cause mortality in this population.[S16] Blood levels of metformin are influenced by kidney function and the main problem for metformin treatment in CKD G4+ is the prevention of intoxication. Recently published dosage guidelines suggest a maximum of 1 g daily in CKD G4+.[S17]	Recent diabetes management guidelines from the American Association of Clinical Endocrinologists/American College of Endocrinology recommended discontinuing metformin at eGFR < 45 mL/min/1.73 m^2 [S18] KDIGO recommended that metformin be discontinued in people with eGFR < 30 ml/min/1.73 m^2.

CKD, chronic kidney disease; KDIGO, Kidney Disease: Improving Global Outcomes; NICE, National Institute for Health and Nutrition Examination

Table S4. Definition of heart failure (HF) according to ACCF/AHA and ESC

Heart failure (HF) Classification	Left ventricular ejection fraction (LVEF)	Description from ACCF/AHA	Description from ESC
HF with reduced ejection fraction (HFrEF)	LVEF ≤ 40%†	Also referred to as systolic HF. Randomized controlled trials have mainly enrolled patients with HFrEF, and it is only in these patients that efficacious therapies have been demonstrated to date.	Symptoms ± signs[a]
HF with preserved ejection fraction (HFpEF)	LVEF ≥ 50%	Also referred to as diastolic HF. Several different criteria have been used to further define HFpEF. The diagnosis of HFpEF is challenging because it is largely one of excluding other potential non-cardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified.	Symptoms ± signs[a] Elevated levels of natriuretic peptides[b]; At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction
HFpEF, borderline‡	LVEF 41-49%	These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patients with HFpEF.	Symptoms ± signs[a] Elevated levels of natriuretic peptides[b]; At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction
HFpEF, improved	LVEF > 40%	It has been recognized that a subset of patients with HFpEF previously had HFrEF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients.	

[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics.
[b]BNP >35 pg/ml and/or NT-proBNP >125 pg/ml.
†ESC defines HFrEF as LVEF < 40%
‡Also known as heart failure mid-range ejection fraction (HFmrEF) as coined by ESC whose LVEF is defined as 40-49%

ACCF, American College of Cardiology Foundation; AHA, American Heart Association; BNP, B-type natriuretic peptide; ESC, European Society of Cardiology; LAE, left atrial enlargement; LVH, left ventricular hypertrophy; NT-proBNP, N-terminal pro-B type natriuretic peptide. Adapted from ACCF/AHA[S19] and ESC[S20]

Table S5. Risk factors for HF in patients with CKD G4+

Traditional risk factors	Non-traditional risk factors
Age	Volume overload
Male sex	Anemia
Hypertension	Mineral metabolism abnormalities
Diabetes mellitus	Cause of CKD
Smoking	Aldosterone
Obesity	Inflammation
Coronary artery disease	Residual renal function
Left ventricular hypertrophy	Sympathetic overactivity
	Endogenous cardiac glycosides
	Uremic toxins
	Hyperkalemia
	Oxidative stress
	Malnutrition
	Myocardial stunning

Table S6. Adjusted hazard ratios of all-cause death in patients with heart failure, by CKD status, 2010-2011

	No CKD			CKD		
	Hazard ratio	CI	p-value	Hazard ratio	CI	p-value
Age: 66–69	reference					
70–74	1.36	1.33-1.40	<.0001	1.13	1.06-1.20	<.0001
75–84	2.62	2.55-2.68	<.0001	1.61	1.53-1.70	<.0001
85+	7.10	6.93-7.27	<.0001	3.14	2.98-3.31	<.0001
Male	reference					
Female	0.83	0.82-0.84	<.0001	0.89	0.87-0.92	<.0001
White	reference					
Black/Af Am	1.02	1.00-1.05	0.106	0.95	0.91-0.99	0.0152
Other	0.80	0.78-0.83	<.0001	0.85	0.80-0.90	<.0001
Diabetes	1.14	1.13-1.16	<.0001	1.09	1.06-1.12	<.0001
Hypertension	0.85	0.84-0.86	<.0001	0.73	0.70-0.77	<.0001
Other cause	reference					
Heart failure: none	reference					
Systolic	2.10	2.02-2.18	<.0001	2.34	2.24-2.44	<.0001
Diastolic	1.79	1.71-1.86	<.0001	1.93	1.83-2.02	<.0001
Both	2.02	1.88-2.17	<.0001	2.21	2.05-2.39	<.0001
Unspecifed	1.90	1.87-1.94	<.0001	1.80	1.73-1.86	<.0001

Reproduced from the USRDS ADR 2013, volume 1[S21]

Table S7. Consequences of arteriovenous fistula on the cardiovascular system

Immediate	Days-weeks	Weeks-months
Decrease in blood pressure	Increase in blood volume	Further increase in cardiac output
Reduced arterial stiffness	Increase in LV end diastolic volume	Increase in LV mass and LV size
Decrease in total peripheral resistance		Increase in atrial chamber size
Increase in heart rate and stroke volume		Diastolic and systolic dysfunction
Increase in cardiac output		Increase in pulmonary flows and later pulmonary hypertension

LV, left ventricular. Reproduced from Rao *et al.*[S22]

Table S8. Recommendations from the Renal Physicians Association regarding forgoing dialysis[S23]

If appropriate, forgo dialysis for patients with CKD or ESRD in certain, well-defined situations:

- Patients with decision-making capacity, who being fully informed and making voluntary choices, refuse dialysis
- Patients who no longer possess decision-making capacity who have previously indicated refusal of dialysis in an oral or written advance directive
- Patients who no longer possess decision-making capacity and whose properly appointed legal surrogates refuse dialysis
- Patients with irreversible, profound neurological impairment such that they lack signs of thought, sensation, purposeful behavior, and awareness of self and environment.

Consider forgoing dialysis for CKD or ESRD patients who have a very poor prognosis or for whom dialysis cannot be provided safely. Included in these categories of patients are the following:

- Those whose medical condition precludes the technical process of dialysis because the patient is unable to cooperate (e.g., advanced dementia patient who pulls out dialysis needles or profound hypotension)
- Those who have a terminal illness from non-renal causes (acknowledging that some in this condition may perceive benefit from and choose to undergo dialysis)
- Those with CKD G5 older than age 75 years who met two or more of the following statistically significant very poor prognosis criteria: 1) clinician response of "No" to the 'surprise' question, 2) high comorbidity score, 3) significantly impaired functional status (e.g., Karnofsky score less than 40), 4) severe chronic malnutrition (e.g., serum albumin < 2.5 g/dl).

Forgo dialysis if initiating or continuing dialysis is deemed to be harmful, of no benefit, or merely prolongs a child's dying process. The decision to forgo dialysis must be made in consultation with the child's parents. Give children and adolescents the opportunity to participate in the decision to forgo dialysis to the extent that their developmental abilities and health status allow.

Consider forgoing dialysis in a patient with a terminal illness whose long term prognosis is poor if the patient and the family are in agreement with the physician that dialysis would not be of benefit or the burdens would outweigh the benefit.

Develop a palliative care plan for all pediatric patients with ESRD from the time of diagnosis and for children with AKI who forgo dialysis. The development of a palliative care plan is a continuation of the process of advance care planning and should be family-centered.

AKI, acute kidney injury; CKD, chronic kidney disease; ESRD, end-stage renal disease.

Table S9. Key goals and activities identified by the Clinical Trials Group at the Vancouver Kidney Health Summit

Goals	Activities
Encourage and promote the conduct of clinical trials in people with CKD	Develop value proposition for trials in kidney disease
	Promote trials in areas of unmet need and orphan diseases
	Engage activated patient groups, payers and other stakeholders, aiming to substantially increase the number of clinical trials in CKD
	Promote models for early conditional approval of new therapies to encourage investment
	Work to increase the number of people with CKD who are included in CV, diabetes, and oncology trials, aiming to reflect the prevalence of CKD in such patient populations
	Develop a regular stand-alone meeting to review ongoing and planned clinical trials with CKD patients
Optimize the design of clinical trials in people with CKD	Develop and refine appropriate endpoints for CKD trials and promote their uptake and dissemination
	Assess factors that lead to "success" or "failure" of clinical trials in CKD trials
	Facilitate strategies to pre-select patients for clinical trials according to their risk for progression or likelihood to respond to an intervention
	Develop innovative trial designs to enhance feasibility and success of CKD trials
	Implement priority setting exercises for interventions to be tested in clinical trials globally and by region
	Establish recommendations for clinical trials in people with CKD for use by ethical and regulatory boards, including opportunities for sample collection for future analyses
Grow capacity in conducting clinical trials in people with CKD	Develop networks of kidney clinical trialists including community physicians, and other specialties, etc.
	Catalogue sites/centers capable of participating in kidney trials
	Develop and implement professional training in trial design and conduct, involving nephrology and related specialties

CKD, chronic kidney disease; CV, cardiovascular Reproduced with permission from Levin A *et al*. (2017)[S24]