

## **Chronic kidney disease in Asia – Protocol for a collaborative overview**

Asian Renal Collaboration (ARC)

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## ABSTRACT

### **Background**

The burden of chronic kidney disease (CKD) is growing rapidly around the world. However, there is limited information on the overall regional prevalence of CKD, as well as the prognostic implications and treatment patterns in Asian region. We have established the Asian Renal Collaboration (ARC) with the goal of consolidating region-wide data regarding CKD.

### **Design and Methods**

This collaborative project will synthesize data and perform meta-analyses of observational studies conducted in Asia. Studies will be identified through a systematic literature search including abstracts, proceedings of meetings, electronic databases such as MEDLINE and EMBASE. Personal enquiry among collaborators and experts in the region will identify additional studies, or other data sources such as registries. Both cross-sectional and longitudinal studies that describe the prevalence of CKD and its complications will be included, as will longitudinal studies that describe important clinical outcomes for people with CKD. Individual participant data will be sought, where possible, from each of the studies included in the collaboration for baseline parameters and subsequent outcomes, in order to maximize flexibility and consistency of data analyses.

### **Conclusions**

This study is an initiative offering a unique opportunity to obtain information about the prevalence and manifestations of CKD in Asia, as well as its risk factors. The ARC will also provide insights into important outcomes including progression of CKD, CKD complications, cardiovascular disease and death. These findings will improve our understanding of kidney

disease in Asia, and thus help inform service provision, preventive care and further research across the region.

**Keywords**

Asia, Cardiovascular disease, chronic kidney diseases, cohort study, prognosis, risk factors

## **BACKGROUND**

Chronic kidney disease (CKD) is an important cause of morbidity and mortality around the world. It has been suggested that the incidence and prevalence of CKD and end stage kidney disease (ESKD) will rise sharply in the coming decades, predominately in Asia (1-4). Individuals with CKD have a reduced life expectancy, and those who progress to end-stage kidney disease (ESKD) have 20-fold higher mortality rates compared with age- and sex-matched individuals with normal kidney function (5). The rising number of patients initiating renal replacement therapy in most Asian countries (1, 4, 6) is placing a substantial burden on healthcare systems.

During the past few decades, epidemiological studies have provided much valuable information about CKD, its progression to ESKD and its associations with complications such as anaemia, cardiovascular disease and mortality. Cross-sectional data indicate that the prevalence of CKD in the general population varies between 6 and 20% (1, 7-11). However, most of the evidence has been generated from studies conducted in European and North America and less evidence has been derived from Asian populations. Disease patterns and distribution of risk factors differ markedly in many Asian compared to non-Asian populations, as well as varying substantially within the region itself (for example, regional variations in the incidence of IgA nephropathy, CKD secondary to herbal therapy and of undetermined aetiology, lower blood cholesterol and body mass index, younger age of onset, amongst others) (12-16). Even less is known about the factors that determine progression and development of complications amongst subjects with CKD in the region. Therefore, it is imperative that information specific to Asian populations is collected and analyzed to improve our understanding of the challenges, in order to more effectively manage this complex condition in the region.

Collaborative overviews (with meta-analysis where appropriate), in which data from a number of observational studies are combined (17-21), provide useful information which is additional to that provided by the studies individually. The large number of participants will also facilitate discernment of important differences in the magnitude of associations between disease stages, geographical regions, and between patient subgroups.

The Asian Renal Collaboration (ARC) has been set up to enable these analyses using (where possible) individual participant data from observational studies or other sources, such as registries, in Asia on a broad range of risk factors and clinical outcomes. The main objectives of this project are to obtain information from a large number of subjects about the prevalence, manifestations and risk factors of CKD in Asia. Additionally, this study aims to provide insight into important clinical endpoints including progression of CKD, CKD complications such as anaemia, cardiovascular disease, mineral and bone disorder and mortality. It may be possible to produce estimates of the likely effects on CKD of exposure levels of risk factors. Furthermore, we may be able to estimate the impact of initiatives aiming to prevent CKD and/or its complications on disease progression or other outcomes such as cardiovascular disease. This report describes the protocol for the ARC project.

## **OBJECTIVES**

We aim to understand the epidemiology and to estimate the impact of CKD in Asia by pooling already existing individual participant data (where available), or summary level data. Therefore, this project has the following main aims: firstly, to estimate the prevalence of CKD in Asian populations, both overall and country-specific; secondly to evaluate the prevalence of risk factors, complications and patterns of treatment in CKD patients in Asia, and thirdly to investigate clinical outcomes in CKD patients in Asia.



## **DESIGN AND METHODS**

### **Study eligibility**

Studies are potentially eligible for inclusion in this project if they include a population from the Asia-Pacific region (defined as South Asia, Southeast Asia and East Asia according to the United Nations), involve at least 500 adult (18 years or older) participants recorded or planned and have one of the following study designs:

- a) Cross-sectional study (or baseline data from longitudinal studies) that describe the prevalence of CKD in a community-based population and/or the prevalence of risk factors, complications and the patterns of treatment in people with CKD
- b) Longitudinal studies that describe clinical outcomes of interest in people with CKD

Given the relative paucity of data, we will include all available studies without a time limit.

### **Identification of studies**

Studies have been identified through a systematic search of the literature including abstracts and proceedings of meetings, as well as electronic databases such as MEDLINE and EMBASE. In addition, personal enquiry among collaborators and experts in the region has identified studies that have not yet been reported. Individual participant data will be sought from each collaborating study (see Appendix 1). Eligible studies identified subsequent to the preparation of this protocol will be invited to participate in the collaboration and to contribute data to the overviews.

### **Principal risk factors**

The data requested for each participant include: date of baseline survey, date of birth or age at baseline, gender, ethnicity, occupation, education, history of stroke and coronary heart



disease. The principal risk factors about which data will be sought are as follows: systolic and diastolic blood pressure, diabetes, serum total cholesterol, HDL and LDL cholesterol, triglycerides, obesity (assessed from height and weight), electrocardiogram abnormality, smoking status, alcohol consumption, exercise, serum creatinine, estimated glomerular filtration rate (eGFR), presence of albuminuria or proteinuria, haemoglobin, iron status, calcium, phosphate, parathyroid hormone and Vitamin D levels. For the risk factors measured on multiple occasions, data on all recorded measurements will be sought. Erythropoietin stimulating agent use, iron therapy, anti-hypertensive medications, antithrombotic medications, cholesterol lowering drugs, phosphate binders, calcium, vitamin D, and calcimimetic use will be collected as the information on treatment.

### **Principal outcomes**

Data will be sought from each study on the date of occurrence of each of the outcomes listed in table 1. CKD stage will be defined according to KDIGO guidelines. ESKD will be defined as receiving maintenance dialysis or having a functioning renal transplant whereas anaemia will be defined as haemoglobin (Hb) <100 g/l or on ESA therapy. Precise details of the diagnostic criteria used for defining the outcomes (eg. major cardiovascular events), and data on the completeness of follow-up will also be collected for individual studies. It is anticipated that definitions for outcomes may vary across included studies, but will be standardized whenever possible. All analyses will be based on events classified according to the tenth revision of the International Classification of Diseases (ICD-10) or similar. Quality assessment of outcome ascertainment will be conducted and subgroup analyses will take place in order to assess for potential bias. For any study that did not use this classification system, events are re-coded by the project secretariat using all available information.

### **Data transfer and checking**

A standardised central data request form has been developed to collect the relevant data from each of the involved studies. Data may be provided to the coordinating centre in any format convenient to the collaborator. A unique, anonymous identifier will be sought for each individual in submitted data sets, so as to allow further data linkage should this be necessary in the future. All data provided to the coordinating centre will be carefully checked for completeness and consistency. Computer-generated reports from the data will be referred back to the principal investigator of each study for review and confirmation in order to ensure that the individual study results are incorporated correctly into the overview. All data queries will be discussed and resolved with the responsible collaborating investigator. Where individual participant data are not able to be shared, tabular data will be sought using consistent definitions and statistical code wherever possible.

The data provided for inclusion in the ARC will be held in strict confidence by the coordinating centre. The data manager in the coordinating centre will store all data securely. The data from each study will remain the sole property of the principal investigators of that study and will not be used for any presentation or publication without the consent of the collaborating investigators from that study.

### **Statistical analysis**

We use cross sectional data. With IPD we obtain prevalence as the relative frequency and compute at least nation specific results. Relevant information will be extracted from published data including by contacting authors if necessary. If we have enough values from published data we will also compute age and sex specific results from the IPD. Prevalence data will be collected from nationally representative studies where these are available, but non-representative national and regional data will also be collected where these are not available. Summary pooled estimates will be calculated, and associations with risk factors

estimated. Models will be developed in an effort to estimate CKD prevalence where data are not available. In the first instance, the principal analyses of the associations of risk factors with disease for each study will be performed using Cox proportional hazards models (Cox 1972). We shall pool results using random effects meta-analysis, weighting by inverse variance (22). If appropriate, we will adjust for the effects of regression dilution bias using repeat risk factor measurement data (ESCHDC group 1998). Analyses will also be adjusted for potential confounding factors and stratified by potential effect modifiers. Analyses will be conducted to assess the separate associations in men and women, in different regions and ethnic groups, in different age groups (at baseline and at death), and in different periods of follow-up. Analyses will be conducted to determine whether any subgroup differences are due to confounding (eg. different age distributions in the cohorts), effect modification (eg. different predictor-risk relationship across regions) or different diagnostic practices between countries, using random effects meta-regression(22). In addition to exploring heterogeneity of the associations between these subgroups, we will explore heterogeneity between individual studies (adjusting for major confounders) using i-squared statistics and chi-square tests(22). Sensitivity analyses taking account of factors including completeness of follow-up, methods of outcome assessment, availability of repeat risk factor measurements and imputation of missing values(22) will be performed to determine the robustness of the findings. This analysis plan will be continuously evaluated and a more detailed analysis plan will be developed, depending on available data.

### **Time frame and publication policy**

Initial data collation is expected to be completed by the end of December 2015. Statistical analysis will begin in 2015 with reports prepared for publication from 2015 onwards. The results of the study will be disseminated by manuscripts in peer-reviewed publications and by presentations at international meetings. All reports from this project will be sent to all

collaborating investigators for prior comments and approval. All such reports will be published in the name of the Asian Renal Collaboration. **Ethical approval and subject consent**

Individual studies will have obtained ethical approval and subject consent from their relevant institutions prior to participation in the collaboration. Thus, no further ethical approval or subject consent will be sought from individual participants. For the process of central data collection and analysis, a separate ethics approval has been granted by the University of Sydney, Australia (ARC project ID: 2015/217).

## **ORGANISATION**

The ARC is a collaborative project between the principal investigators of contributing observational studies. The project secretariat is based at the George Institute for Global Health, Sydney, Australia. The Executive Committee and the Secretariat, both of which are responsible to the collaborating individual study investigators, manage the central coordination of the overall project. External researchers will be able to propose research projects to ARC. The Steering Committee comprises regional representatives (from China, Japan, South Korea, India, Taiwan, Thailand and Malaysia) and representatives from the project secretariat (appendix 2, figure 1) and has overall responsibility for the design, conduct, progress, data collection, data analysis and publication of study results.

More than 20 studies from 7 countries are participating to date, representing more than 2.1 million study participants. This project has been funded by a grant from GlaxoSmithKline limited (table 2, figure 2).

## **CONCLUSION**

The ARC will aim to define the burden of CKD in Asia, and identify associated patterns of risk factors and outcomes. It will highlight differences and similarities between CKD in Asia and other regions, and provide important information that will inform future research directions in the region, as well as health service planning.

## **ACKNOWLEDGMENT**

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## **FIGURE LEGENDS**

**Figure 1:** Organisational Structure of the Asian Renal Collaboration

**Figure 2:** Studies included in the Asian Renal Collaboration (as at 31/11/2015)

**Table 1: Principal outcomes of interest and their ICD-10 codes (where available)**

Principal outcomes	ICD – 10 codes
<i>1. The prevalence of CKD in Asia</i>	
a) Reduced eGFR	N18
b) Presence of albuminuria/proteinuria	R80
c) CKD stages (defined by KDIGO)	N18
d) ESKD (defined by treated ESKD – dialysis, HD and PD and transplant)	N18.5
e) Renal transplant recipients	Z94
<i>2. Prevalence of risk factors, complications and treatment patterns among CKD patients in Asia</i>	
a) Clinical characteristics – Age, gender, cause of CKD, history of blood pressure, diabetes mellitus, BMI, smoking status, other co-morbidities	
b) Laboratory characteristics – Haemoglobin, iron stores, albumin, calcium, phosphate, PTH, Vitamin D, urine protein/creatinine ratio, urine albumin	
c) Treatment pattern– Iron, ESA, antihypertensive medication, Vitamin D, and other treatments	
d) Prevalence of anaemia defined by haemoglobin (Hb) <100 or on ESA therapy	
e) Quality of life	
<i>3. Clinical outcomes in CKD patients in Asia</i>	
<i>a) Kidney outcomes</i>	
1) Increase in CKD stage	
2) Progression to ESKD	
3) Doubling of serum creatinine	
<i>b) Cardiovascular outcomes</i>	
1) Major cardiovascular events (Coronary heart disease, stroke, or cardiovascular mortality)	
2) Coronary heart disease (Myocardial infarction or hospitalization from angina)	I20-25
3) Stroke	I60-69
4) Cardiovascular mortality	
5) Hospitalization from heart failure	I50
6) Any other atherosclerotic disease (e.g. peripheral arterial disease and aneurysm)	I70-73
7) Thromboembolic events (vascular access and non-vascular access related)	I74

c) *Mortality*

1) All-cause mortality

2) Cause-specific mortality

All cardiovascular disease	100-178
Coronary heart disease	120-125
Pulmonary circulatory disease	126-128
Sudden cardiac death	149-149
Heart failure	150
Stroke	160-169
Subarachnoid haemorrhage	160
Haemorrhagic stroke	161-162
Ischaemic stroke	163-166
All neoplasms	C00-C97
Oesophageal cancer	C00-C14
Stomach cancer	C10-C16
Colorectal cancer	C18-C21
Liver cancer	C22
Lung cancer	C33-C34
Breast cancer	C50
Liver disease	K70-K77
Kidney disease	N00-N19
Lung disease	J00-J99

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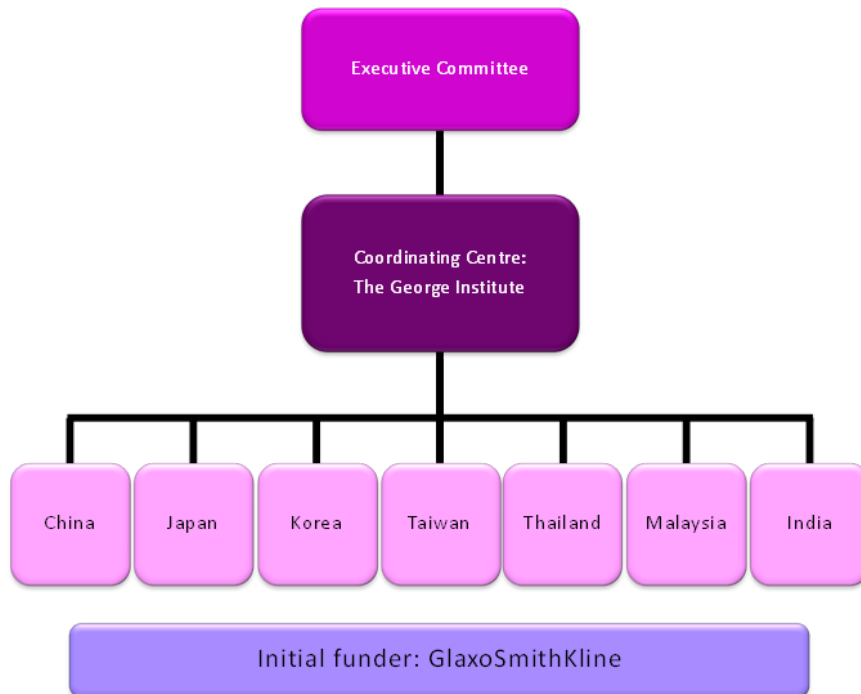
ICD – 10: Tenth version of the International Classification of Diseases

**Table 2: Individual study characteristics of studies included in the Asian Renal Collaboration (as at 31/11/2015)**

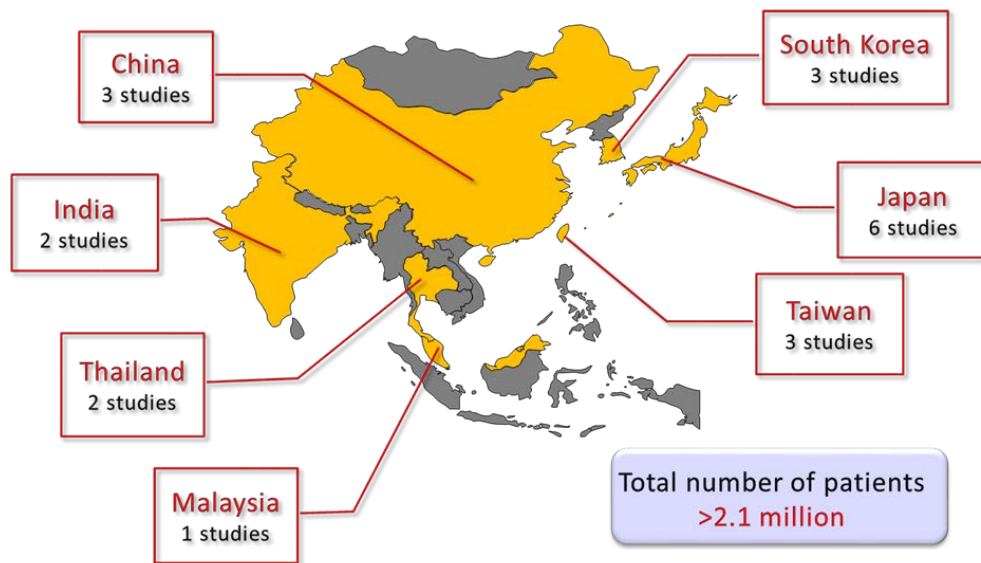
Dataset	Country	No. subjects	Funding	Current status
<b>Studies based on general population</b>				
National survey of CKD	China	50000		Tabulated data received
Okinawa cohort study	Japan	154265		IPD received
Korean general population study	South Korea	147312		IPD received
CKD epidemiology survey in southern Taiwan	Taiwan	3352		IPD received
Multicenter prospective cohort study	Thailand	3000		Awaited
<b>Studies based on CKD Patients</b>				
Chinese Cohort Study of CKD in China	China	3200		Awaited
The CKD-JAC Study	Japan	2977		Tabulated data received
Nagoya CKD Cohort	Japan	389		Tabulated data received
The Hisayama Study	Japan	3503		Tabulated data received
The Gonryo Study	Japan	2692		Tabulated data received
Korean CKD Cohort Study "KNOW-CKD".	South Korea	?		Awaited
CKD stage 3-5 Clinical Cohort —Kaohsiung Hospital	Taiwan	3334		Awaited
<b>Studies based on ESRD patients</b>				
<i>Registry data</i>				
Beijing ESRD Registry	China	12500		Awaited
Japan Society of Dialysis Therapy Registry	Japan	301538		Tabulated data received
Malaysian Dialysis and Transplant Registry	Malaysia	32159		Tabulated data received
Korean Society of Nephrology - ESRD Registry	South Korea	72867		IPD received
Taiwan ESRD Registry	Taiwan	75000		Awaited
Thailand Renal Replacement Registry	Thailand	52641		IPD received
<i>Other datasets</i>				
Indian Dialysis Cohort - 1	India	1653		IPD received
Indian Dialysis Cohort - 2	India	2926		IPD received
The Q-Cohort Study	Japan	3567		Tabulated data received
The (AICOPP) Study	Japan	1515		Tabulated data received

IPD: Individual patient level data

**Figure 1:** Organisational Structure of the Asian Renal Collaboration



**Figure 2:** Studies included in the Asian Renal Collaboration (as at 31/11/2015)



## **APPENDIX 1: Data Request Format**

### **1 Demographic factors**

- 1.1 Date of birth or age at baseline
- 1.2 Gender
- 1.3 Ethnicity
- 1.4 Occupation (for whole cohort or individually, if available)
- 1.5 Education level
- 1.6 Some unique (but anonymous) identifier in case queries arise

### **2 Baseline survey data (coded in whatever way the study has used)**

Details of the coding conventions, preferably accompanied by a copy of the questionnaire or data coding or data entry forms used in the study.

- 2.1 Date or year of the baseline survey
- 2.2 History of stroke and coronary heart disease
- 2.3 Cause of kidney disease
- 2.4 Systolic and diastolic blood pressure
- 2.5 Diabetes
- 2.6 Lipid parameter (serum total, HDL- and LDL cholesterol and triglycerides)
- 2.7 Body parameters (Height, weight, body mass index)



- 2.8 Electrocardiogram abnormality (Left ventricular hypertrophy and atrial fibrillation)
- 2.9 Smoking status
- 2.10 Alcohol consumption
- 2.11 Exercise
- 2.12 Serum creatinine, eGFR
- 2.13 Urinary albumin-to-creatinin ratio or daily albumin excretion
- 2.14 Presence of proteinuria, urinary protein-to-creatinine ratio, or daily protein excretion
- 2.15 Haematology (Haemoglobin, white cell count and platelets)
- 2.16 Iron status (Serum iron, serum transferrin and serum ferritin)
- 2.17 Biochemistry (Urea, electrolytes, calcium and phosphate)
- 2.18 Parathyroid hormone and Vitamin D

### **3. Treatment**

- 3.1 Erythropoietin stimulating agent (yes/no, type, dose, mode of administration)
- 3.2 Iron therapy (Use or not, type, dose, mode of administration)
- 3.3 Anti-hypertensive medications (y/n, type, dose)
- 3.4 Antithrombotic medications (y/n, type, dose)
- 3.5 Cholesterol lowering drugs (y/n, type, dose)
- 3.6 Phosphate binders (y/n, type, dose)

3.7 Calcium and Vitamin D therapy (y/n, type, dose)

3.8 Calcimimetics (y/n, type, dose)

#### **4 Repeat survey(s) data**

Please provide data from any repeat survey(s) in a format as similar as conveniently possible to that for the baseline survey.

#### **5 Events**

5.1 Date last known to be alive (if not recorded as dead)

5.2 Date of event or, if date not available age at event, for all non-fatal events of these types:

a) Kidney outcomes

1) Increase in CKD stage

2) Progression to ESKD

3) Doubling serum creatinine

b) Cardiovascular outcomes

1) Major cardiovascular events

(Coronary heart disease, stroke, or cardiovascular mortality)

2) Coronary heart disease (Myocardial infarction or hospitalization from angina)

3) Stroke

4) Cardiovascular mortality

5) Hospitalization from Heart failure

6) Any other atherosclerotic disease (e.g. peripheral arterial disease and aneurysm)

5.3 Date of death (or, age at death, if date not available)

5.4 Underlying cause of death [preferably coded according to some specified version or other (e.g. 7th, 8th, 9th or 10th) of the 4-digit International Classification of Diseases, but if a 4-digit ICD code is not available then whatever code the study already uses]

5.5 Stroke investigated by CT/MRI (y/n)

5.6 Autopsy (y/n)

## **Appendix 2: Committee members and collaborators of the ARC**

Secretariat	Executive committee	Steering committee*
Helen Monaghan	Heide Stirnadel-Farrant	Atsushi Wada
Mark Woodward	Helen Monaghan	Daiki Inaguma
Thaminda Liyanage	Ho Jun Chin	Heide Stirnadel-Farrant
Toshiharu Ninomiya	Hong Zhang	Helen Monaghan
Vivekanand Jha	Kearkiat Praditpornsilpa	Ho Jun Chin
Vlado Perkovic	Kunitoshi Iseki	Hong Zhang
	Luxia Zhang	Hooi Lai Seong
	Mark Woodward	Ikuto Masakane
	Masafumi Fukagawa	Kamal Shah
	Shang-Jyh Hwang	Kazuhiko Tsuruya
	Takayuki Hamano	Kearkiat Praditpornsilpa
	Thaminda Liyanage	Kunihiro Matsushita
	Toshiharu Ninomiya	Kunitoshi Iseki
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		Thaminda Liyanage
		Toshi Ninomiya
		Vivek Jha
		Vlado Perkovic
		Yoshinari Yasuda
		Young-Hwan Hwang
		Zuo Li

\*Steering committee consists of executive committee members and other collaborators not included in executive committee