Translational Research for Improving the Care of FH: The Ten Countries Study

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Abstract
Familial hypercholesterolemia (FH) is the most common and serious form of inherited hyperlipidaemia. Dominantly inherited with a high penetrance, untreated FH leads to premature death from coronary artery disease due to accelerated atherosclerosis from birth. Screening enables early evidence-based and cost-effective interventions, such as diet and lifestyle measures and cholesterol-lowering medications which decrease the risk of heart disease. Despite the medical importance of FH, there is still a major shortfall in awareness, detection and treatment of FH worldwide. Internationally recognised models of care of FH have recently been published, but their implementation requires essential knowledge that is lacking about FH. This project aims to investigate selected diagnostic, epidemiological and service aspects, as well as primary care physician awareness and patient perceptions, of FH across several countries in the Asia-Pacific Region and the Southern Hemisphere. The value and significance of the data garnered is to inform best practice in the care of FH and to develop local and regional models of care. Five observational studies will be undertaken that will investigate phenotypic predictors of low-density lipoprotein receptor mutations, the point prevalence of FH in unselected community populations, knowledge and practices of primary care physicians concerning FH, availability and utilization of services and facilities for the care of FH, and patient perceptions and personal experiences of FH. A related objective is to close gaps in knowledge and awareness of FH through an educational program that will be provided under the aegis of country-specific societies that are members of the International Atherosclerosis Society.

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Mission, Aim and Objectives

Mission: To improve the care of patients and families with familial hypercholesterolaemia (FH).
Aim: To investigate diagnostic, epidemiological and service aspects, as well as primary care physician (PCP) awareness and patient perceptions, of FH in order to inform best practice in the care of the condition.
Objectives: To undertake the following studies:

1. The phenotypic predictors of LDL-receptor mutations.
2. The point prevalence of FH in unselected community populations.
3. Knowledge and practices of primary care physicians concerning FH.
4. Availability and utilization of services and facilities for the care of FH**.**
5. Assessment of patient perceptions and personal experiences of FH.

A related objective is to close gaps in knowledge and awareness of FH through an educational program that will be provided under a separate arrangement from the present application.

Context

Familial hypercholesterolemia (FH) is the most common and serious form of inherited hyperlipidaemia [1]. It is dominantly inherited with a high penetrance. If untreated, FH leads to premature death from heart disease in many families [2]. FH accelerates atherosclerotic cardiovascular disease (ACVD), particularly coronary artery disease. Screening enables early evidence-based interventions, such as lifestyle measures and cholesterol-lowering medications which decrease the risk of ACVD, improves the health of families, and saves lives and health expenditure [3, 4]. The effectiveness of the detection and treatment of FH is abundantly supported by the outcome of several international cohort studies [5-8]. Despite this, there are several gaps in knowledge concerning FH in respect of the phenotypic predictors of mutations, the community prevalence, primary care physician awareness, patients' perceptions and the availability and utilization of health service resources [3, 9].

Studies

Study 1: Plasma LDL-Cholesterol as a Predictor of FH Mutations

Specific Background: FH specifically elevates plasma low-density lipoprotein-cholesterol (LDL-C) concentration due to decreased receptor-mediated uptake of LDL-apoB by the liver. The accurate diagnosis of FH relies on identifying a causative mutation [1, 3, 9]. Most mutations causing FH occur in the LDL receptor and fewer in apoB and proprotein convertase subtilising/kexin type 9 (PCSK9) [1, 10, 11]. DNA testing is expensive and not commonly available, particularly in primary care. The diagnostic thresholds for untreated LDL-C for use in clinical practice have not been defined in relation to their ability to predict a pathogenic FH mutation. Phenotypic criteria also require detailed family history and detection of subtle physical signs, such as arcus cornealis or xanthomata, that are not frequently detected and are age-dependent, making them insensitive for the routine detection of FH [3, 9, 12].

Hypothesis: Plasma LDL-C concentration provides an accurate predictor of the presence of a pathogenic mutation causative of FH. The plasma concentration range that most accurately predicts a mutation is 4-7mmol/L in Australasian clinic populations. The LDL-cholesterol concentration predictive of a mutation will be lower in Chinese population.

Aims: We will carry out a cross-sectional study of the association between LDL-C and the presence of a mutation causative of FH, aiming to select a level of plasma LDL-C that has the highest sensitivity and specificity in predicting a mutation. We will investigate these associations primarily in paediatric and adult groups derived from clinics in Australia and New Zealand, but will also investigate clinic populations in China and Brazil.

Methods: 1500 people with a clinical probability of FH (index cases and family members) have been screened for this condition using both phenotypic information and DNA testing in three large centres in Australasia: Perth (Royal Perth Hospital), Sydney (Royal Prince Alfred Hospital) and Christchurch (Christchurch Hospital, NZ). Complete clinical and demographic details have been recorded, sufficient to assess the standard phenotypic criteria for FH. A full lipid and lipoprotein profile has been measured in the fasting state, with details of prescribed lipid-regulating drugs. Mutational analyses for defects in the *LDLR, ApoB* and *PCSK9* genes and assessment of pathogenicity have been uniformly carried out as described elsewhere [11, 13-15]. Collection and storage of DNA has been approved by local ethics committees, all subjects providing informed written consent. Information from the three centres will be centralised in de-identified form in a secure database for analyses.

Clinical and laboratory services for FH in Hong Kong (Chinese University of Hong Kong), Beijing (Beijing Institute of Heart Lunch and Blood Vessel Disease) and Sao Paulo (Incor, University of Sao Paulo) have collected similar information in patients screened for FH and these databases will also be explored using similar methods.

Statistics: The ability of plasma LDL-C concentration to predict a genetic variant will be investigated using a Bayesian approach and by Receiver Operator Characteristic Curve analysis based on Area-Under-Curve (AUC) in both adult and paediatric populations. The best value of LDL-C for predicting a mutation will be defined as a having a sensitivity > 90% with the highest corresponding level of specificity. The effect of other variables [family/personal history of hypercholesterolaemia or coronary heart disease (CHD); physical signs; ethnicity; non-HDL-C and apoB] on the strength of association between LDL-C and a gene variant will also be tested by multiple logistic regression analysis. An AUC of 0.80 will be used to define good discriminatory ability of LDL-C in predicting an FH mutation. Assuming a 50% prevalence of FH in the combined population, a sample size of 1500 will have 80% power in detecting an AUC of 0.835 as being significantly different from 0.80. In the adult population we will compare the Dutch Lipid Clinic Network criteria and plasma LDL-C concentration alone in predicting an FH mutation by analysis of the corresponding AUCs; concordance and discordance rates for these phenotypic diagnostic tests will also be compared by kappa statistics.

Value and Significance: The data will inform a simple screening test for FH, based on LDL-C measurement, for use in primary care. Similar value and significance is anticipated for data derived from the Chinese and Brazilian clinics. Such analyses have not yet been undertaken in any of these populations.

Study 2: Prevalence of FH in Community Populations

Specific Background: Excluding rare populations subject to a gene founder effect (in whom FH is particularly common), the community prevalence of FH is estimated to be 1 in 500. Reports vary, however, from 1 in 200 to 1 in 2000 [2]. Extant prevalence data may be inaccurate, since they are based on hospital patients, registry samples, or calculations employing the Hardy-Weinberg equation and the estimated frequency of homozygous FH. Data from a large community study in Denmark suggest that the prevalence of FH may be as high as 1 in 137 [16]. The prevalence of FH has not been investigated in community based populations (excluding those with gene founder effects eg. Christian Lebanese in Sydney) in Australia.

Hypothesis: The prevalence of FH in an Australian population exceeds 1 per 500, and may be as high as 1 per 200.

Aims: To assess the prevalence of FH in adult and childhood populations in Australia using the plasma LDL-C concentration found to best predict a genetic mutation causative of FH in Study 1.

Methods: The point prevalence of FH will be estimated using plasma LDL-C concentrations as measured in populations derived from the Raine Study (Collaborating Investigator: Professor Trevor Mori, University of Western Australia), and the Australian Diabetes, Obesity and Lifestyle (AusDiab) Studies (Collaborating Investigator: Professor Jonathan Shaw, Baker-IDI, Monash University). The AusDiab study is the largest Australian longitudinal population-based study examining the natural history of diabetes, pre-diabetes, heart disease and kidney disease. The project began with a baseline study of 11,247 Australians conducted throughout 1999 and 2000, with a follow-up of at least 10 years, that provides benchmark national data on the prevalence of diabetes, obesity, hypertension and kidney disease. Further details of the survey methods and sample collection have been previously described in detail [17]. The WA Pregnancy Birth Cohort (Raine) Study is an ongoing longitudinal study following 2,900 children, which began in 1989 as a pregnancy cohort of women enrolled at or before the 18th week of gestation from the public antenatal clinic at the principal obstetric hospital in Perth, WA, or nearby private practices. Since 1989, data has been collected from the participants (both the mother and her child) at regular intervals including when the child turned 1, 2, 3, 5, 8, 10, 14 and 17 years old. A large range of information, including health and well-being indicators for the child and their family was collected at each follow-up (http://www.rainestudy.org.au). The Raine data will be employed as representative of a childhood population in Australia. The AusDiab data will be used as representative of the general Australian population. Subjects with plasma triglyceride concentrations > 4 mmol/L will be excluded for the estimation of LDL-C, since above this threshold the Friedewald formula is inaccurate. LDL-C will be adjusted in people taking lipid-regulating drug therapy using published data. The effects of additional personal and family clinical information, as defined in the DLCN standard diagnostic criteria for FH, on the prevalence of FH will also be assessed. All data will be analysed in de-identified form in collaboration with the respective principal investigators of the above population studies, and appropriate ethics and study board clearance will be obtained. A similar approach will be adopted for two community populations from China (Dr Zumin Shi, Adelaide University;

Professor Dong Zhao, Capital Medical University, Beijing) and Brazil (Professor Raul Santos, University of Sao Paulo Medical School Hospital).

Statistics: The point prevalence of FH, based on plasma LDL-C concentration, will be estimated separately for children and adults using a proportion with 95% confidence limits. LDL-C levels will be adjusted for use of statins. The prevalence of FH in adults will also be assessed using modifications of the Dutch Lipid Clinic Network criteria. The effect of phenotypic variables of the prevalence of FH based in LDL-C alone will be tested by multiple logistic regression analysis. For an FH prevalence of 1 in 200, the 95% confidence intervals will be as follows: AusDiab Study (*n* = 11,000) 0.004 to 0.007; Raine Study (*n* = 1,500) 0.002-0.010. For an FH prevalence of 1 in 500, confidence intervals will be as follows: AusDiab Study (*n* = 11,000) 0.001 to 0.003; Raine Study (*n* = 1,500) 0.001-0.006. The proportion of FH patients receiving statins will be compared with those without FH on statins by chi-square tests. The association between having FH and the likelihood of CHD will be assessed by logistic regression analysis. Similar statistical methods will be applied to the Chinese and Brazilian populations.

Value and Significance: The data will emphasize the public health problem presented FH, including the shortfalls in detection and treatment. This will inform screening programs for FH in the community.

Study 3: Knowledge and Practices of Primary Care Physicians (PCP) concerning FH

Specific Background: FH is the most common monogenic lipid disorder causing premature CHD. However, the majority of people with FH are undiagnosed and undertreated [3, 9]. Most people in the community will have contact with their primary care physician (PCP) or family doctor. Models of care for FH should be multidisciplinary [3]. PCPs can perform absolute cardiovascular risk assessments and are well placed to opportunistically detect FH [18, 19]. Well controlled and low complexity patients could be transitioned to primary care for long-term management or for shared care, while high complexity patients should be followed-up by a specialist service [3]. Cascade screening should, however, be co-ordinated centrally within a framework that integrates specialist and primary care. Education and training of primary care providers in lipid management is important for improving and maintaining the total quality of care. A structured review should be offered at least annually to all patients [3, 20], especially low complexity patients who may be more at risk of loss to follow-up. The majority of people with FH who are detected early on may be managed in primary care. The role of primary care in the care of FH has not been adequately defined and our preliminary data suggest a significant shortfall in awareness, knowledge and practices among family doctors [21].

Hypothesis: PCPs' awareness, knowledge and practices concerning the care of FH is suboptimal.

Aims: To determine PCP's awareness, knowledge and practices regarding FH.

Methods: A formal questionnaire will be offered to PCPs attending education sessions on the assessment and management of cardiovascular risk before the session commences in

the countries shown in Appendix B. The survey will be voluntary, anonymous and completed without discussion with either the specialist leading the education session, or other GPs attending the session. The *Questionnaire*, shown in Appendix F, employed will make enquiries regarding [21]: general familiarity with FH; awareness of national and international guidelines for FH;, the clinical description of FH; identification of the typical lipid profile; prevalence and inheritance of FH; extent of elevation in risk of CVD, definition of premature CVD and physical features in FH; whether the diagnosis requires genetic confirmation; methods for alerting PCPs about the possibility of FH; type of health professional best placed to detect FH; number of patients with FH currently being treated; specific treatments; knowledge and practices concerning family screening; treatment and referral practices regarding patients with severely elevated cholesterol. PCPs will be asked to select one correct answer to questions from a list of options provided; there will be no open questions. The sample questionnaire is shown in Appendix F. De-identified demographic data were sought from the participants including, gender, qualifications and training status, years of practice, number of patients seen in clinic per month and location of practice as metropolitan, rural or other.

Statistics: Based on preliminary data, a sample size of 500 PCPs is considered sufficient to test the hypothesis and to identify potential regional differences in knowledge and practices [21]. Data will be collated in de-identified format and analyses performed using Microsoft Excel 2003 and analysed using SPSS. Data will be described using both parametric and non-parametric methods. Chi-square and Fishers exact tests will be used to explore differences in FH awareness, knowledge, practices and opinions regarding FH. The impact of PCP gender, age, training, qualifications and metropolitan or rural practice as predictors of selected responses will be analysed by logistic regression methods.

Significance and Value: Defining the role of PCPs in the care of FH is essential for developing multidiscplinary and integrated total quality management. Assessing current knowledge and practices is the starting point. The information also will be imployed to design effective teaching and training modules for PCPs in the detection and management of FH. It will also form the basis for an internationally agreed model of care for FH centred on primary care.

Study 4: Comparison of Services and Facilities for the care of FH

Specific Background: In spite of the increasing recognition of the importance of FH, the care of patients and families remains suboptimal [3, 9]. Services need improvement and standardisation at several levels [13, 22]. Close collaboration between healthcare systems, patient support groups and non-government organizations is essential [3]. Clinical pathways that seamlessly integrate primary and specialist care are required. Models of care for FH should be multidisciplinary. Services should be managed by personnel accredited in cardiovascular prevention. Severe FH requires careful lifetime follow-up by specialist services. Primary care providers have an important role in detecting index cases [13, 18], but cascade screening should be co-ordinated centrally. Telehealth services are needed for remote care. Children need a specialist paediatric service. Nurses have a role in co-ordinating screening and are central to multidisciplinary care, that ideally should involve dieticians, clinical geneticists, psychologists, exercise physiologists and pharmacists. FH services should also have close links with laboratory medicine and a DNA testing service.

Comprehensive patient assessment requires access to cardiac and imaging facilities, as well as close links with cardiology. Collaboration with a transfusion medicine centre is important for managing apheresis. A database for storing clinical data and information technology support systems are essential for effective provision of services [3, 22]. A clinical registry provides invaluable information for research and audit, as well as for improving the quality of care, especially in coordinating cascade screening at several levels [23]. All models of care must address the perspectives and requirements of patients and families [3, 22]. Hence, an active association for supporting patients and families with FH is essential. There are no published worldwide data describing nor comparing healthcare resources for the detection and management of FH across different countries with diverse healthcare systems.

Hypothesis: Health services and facilities for FH are universally suboptimal, especially so in less developed countries.

Aims: To describe and compare existing health services, facilities and resources for the care (screening, diagnosis, treatment, family support) of FH in countries in the Asia-Pacific region, South Africa and Brazil. Comparison will also be made with the Netherlands, a country that has the most highly developed healthcare system for FH [5, 24-29].

Methods: A questionnaire, shown in Appendix G, that specifically investigates the key elements of a desirable model of care [3, 20, 30] will be completed by the leading experts in FH shown in Appendix A in all countries shown in Appendix B. All countries included in this application will participate in this study. Respondents will also participate in group focus workshops convened at international meetings. A sample of the questionnaire is shown in Appendix G and will include questions relating to: national guidelines and protocols, principal medical specialty involved in care, role of primary care, screening, diagnostic and assessment protocols, DNA testing facilities, paediatric services, therapeutic strategies, apheresis and liver transplantation; clinic support (nurses, dieticians, counsellors, information technology and registry), biochemistry laboratory services, cardiology services, funding (public, private, health insurance), drug re-imbursement, education and training programmes, research programmes, links with and support from government and non-government organisations, availability of a family support group [3, 22, 30].

Statistics: Data will be described parametrically and non-parametrically. Comparisons will be made using chi-square and t-tests were applicable. Logistic regression will also be employed to assess which healthcare system is the best predictor of the full range of services. Qualitative analysis will be performed and interpreted in the light of ancillary information relating to health economics.

Significance and Value: The study will provide international benchmarking of performance in health care for FH. It will identify and promote successful strategies within a context that takes into account cultural, economic and logistic differences and create opportunities for implementing country-specific or region-specific models of care for FH. It will promote regional and international collaboration and avoid duplication of effort with respect to, for example, DNA testing.

Study 5: Patient Perceptions and Personal Experiences of FH

Specific Background: Successful management of FH is dependent on patients receiving the correct treatment, including maintaining adherence to therapy. Treatment includes the use of medication (statins) to control cholesterol levels. However, management of lifestyle behaviours such as taking regular physical activity and eating a diet low in saturated fat are also important due to the much higher risk presented by chronic conditions like diabetes, hypertension, and obesity among FH patients. Numerous psychological factors have been found to be associated with salient adaptive outcomes and successful management of FH [31]. Studies have focused on FH patients' knowledge, perceptions of risk, and attitudes and beliefs toward the condition and how they relate to behavioural, psychological, and clinical outcomes [32, 33]. Overall, the current research suggests that attitudes and beliefs about the severity of FH have been associated with intentions and motivation to engage in treatment [33]. However, much of the research has been conducted in relatively small samples and using qualitative methods [34]. There is a need for large scale research adopting quantitative methods to examine relations between FH patients' attitudes and beliefs with respect to FH. Furthermore, a number of additional psychological factors that may be related to important outcomes related to management of illness should be investigated in FH patients. These include facilitating factors and barriers to compliance with behavioural therapy and lifestyle change (e.g., increasing physical activity, improving diet), particularly among those who do not have any clinical manifestation of the illness (e.g., cardiovascular disease) and are asymptomatic [35]. It would also be important to investigate the perceived support provided by family members and loved ones , and by the clinic or health professionals administering treatment, of FH patients. In addition, factors that may affect treatment compliance including beliefs about the controllability of the illness and efficacy of medication should be identified and investigated. Finally, we will control for demographic and dispositional factors that may affect the behavioural outcomes including age, gender, duration of FH, and health literacy [31, 33].

Hypotheses: Illness beliefs and attitudes toward FH, beliefs in treatment and medication efficacy, perceived support from family members, loved ones and health professionals, and facilitating factors and barriers will be statistically significantly related to behavioural (e.g., lifestyle change, drug adherence, dietary change, physical activity uptake), psychological (e.g., psychological well-being, quality of life, emotional distress), and clinical (e.g., blood lipid profile, clinic attendance) outcomes in FH patients across the clinics.

Aims: (1) To investigate the association between patients' psychological factors and key behavioural, psychological, and clinical outcome variables salient to the management of FH. (2) The research will also enable a comparison of the levels of psychological factors across samples collected in different groups of patients with FH in Australia, Brazil, Hong Kong, Japan, and New Zealand and the strength of the effects between the factors and outcome variables.

Methods: Participants will be recruited from clinics managing FH detection and treatment in five of the participating national teams (Australia, Brazil, Hong Kong, Japan, and New Zealand). Participants will be recruited via clinic staff who will offer patients the opportunity to participate via an invitation letter. Invitation letters will be sent to patients meeting study inclusion criteria: aged over 18 years and had received a genetic diagnosis for FH. The study will adopt a correlational, quantitative design with psychometric measures of psychological variables and

psychological and behavioural outcomes administered to samples of FH patients in the clinics of the collaborating investigators. Key clinical (e.g., blood lipid profile) and behavioural (e.g., medication compliance) outcomes will also be collected from patient records in the collaborating clinics. The development and identification of measures to be included in the final survey is based on an initial qualitative focus-group pilot study conducted in a small clinic population of FH patients by members of the current investigator team. Measures will include measures of attitudes toward FH (Theory of Planned Behaviour Questionnaire), illness perceptions (Illness Perception Questionnaire), medication beliefs (Beliefs about Medication Questionnaire), health literacy (Short Test of Functional Health Literacy in Adults), facilitating factors and barriers (Self-Efficacy Questionnaire), psychological wellbeing and functioning (Medical Outcomes Survey – Short Form), health-related quality of life (WHO-Quality of Life Questionnaire), validated self-reports of medication compliance, diet and physical activity, and patient intention to refer/encourage relatives to attend FH screening. All measures are standardized measures previously validated with good psychometric properties in previous studies. Patient records for key clinical (e.g., blood lipid profile) and behavioural (e.g., medication compliance, clinic attendance, consent to contact relatives) outcomes will be accessed with the consent of the patient. A research associate will coordinate the collection, collation, and analysis of the data and day-to-day management of the project. Questionnaires will be administered by clinic staff and sent to the research associate. Language-specific versions of the questionnaire will be developed from the English-language version using standardized back-translation techniques with the aid of bilingual translators. An outline of the quantitative tool is provided in Appendix H.

Statistics: To test H_1 a series of separate multiple regression analyses with each of the behavioural, psychological, and clinical outcomes as dependent variables and the psychological variables as independent predictors will be conducted. Where the dependent variable is continuous (e.g., physical activity, quality of life, blood lipid levels, intention to contact relatives), the analysis will be linear, and where the dependent variable is discrete or dichotomous (e.g., medication compliance, clinic attendance, patient consent for screening), logistic regression will be used. Statistical power analysis conducted using G*Power with alpha set at 0.05 and power set at 0.90, assuming medium effect sizes, and a minimum of 10 predictors resulted in a projected sample size of 147. The sample size is entirely feasible given the network of collaborators have access to over 150 patients per clinic.

Significance and Value: It will identify the key psychological factors associated with compliance and patient decisions to consent to refer relatives for screening. The factors can then be used as a basis for behavioural interventions to promote better treatment compliance and patient decisions to refer relatives for generic testing for FH in clinics adopting cascade screening.

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APPENDICES

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Appendix A: Countries, Societies and Investigators participating in the project

Country	Societies	Name	Title	Speciality	Institution
Australia	AAS/APSAVD/IFHF	Gerald F Watts	Prof	Cardiometabolic Medicine	Royal Perth Hospital/University of Western Australia,
	AAS/APSAVD	David R Sullivan	A/Prof	Lipidology	Royal Prince Alfred Hospital/University of Sydney
	AAS	Stephen Nicholls	Prof	Cardiology	South Australia Heart Research Institute/University of Adelaide
	AAS	Martin Hagger	Prof	Health Psychology	Curtin University, Western Australia
New Zealand	AAS/APSAVD	Peter George	Prof	Biochemistry, Genetics	Canterbury Health Laboratories/University of Otago, Christchurch
Brazil	SBC	Raul Santos	A/Prof	Lipidology	Lipid Clinic Heart Institute (InCor)/University of Sal Paulo
Japan	JAS/APSAVD	Shizuya Yamashita	Prof	Cardiovascular Medicine	Osaka University Graduate School of Medicine
	JAS	Tamio Teramoto	Prof	Internal Medicine	Teikyo University
China, Hong Kong	APSAVD	Brian Tomlinson	Prof	Biochemisty, Lipidology	Prince of Wales Hospital & Chinese University of Hong Kong
China, Beijing	APSAVD	Dong Zhao	Prof	Epidemiology	Beijing Institute of Heart Lung and Blood Vessel Disease/Capital Medical University
		Jie Lin	Prof	Genetics	
Philippines	APSAVD	Lourdes Santos	Dr	Cardiology	Philippines General Hospital/University of Philippines
Taiwan	APSAVD	Phillip Ding	Prof	Cardiology	Western Garden Teaching Hospital
South Korea	KSLA/APSAVD	Jeong Euy Park	Prof	Cardiology	Samsung Medical Center/Sungkyunkwan University
	KSLA	Ki Hoon Han	Prof	Cardiology	Asan Medical Center/University of Ulsan
Malaysia	MHF/APSAVD	Kah Lin Khoo	Prof	Cardiology	Pantai Medical Centre
South Africa	LASSA	A David Marais	Prof	Chemical Pathology, Lipidology	University of Cape Town/National Health Laboratory Service
Netherlands	EAS	Eric Sijbrands	Prof	Pharmacology, Genetics	Erasmus University Medical Centre
United Kingdom	IFHF	Michael Livingston	Dr	Director of Foundation	International Familial Hypercholesterolaemia Foundation

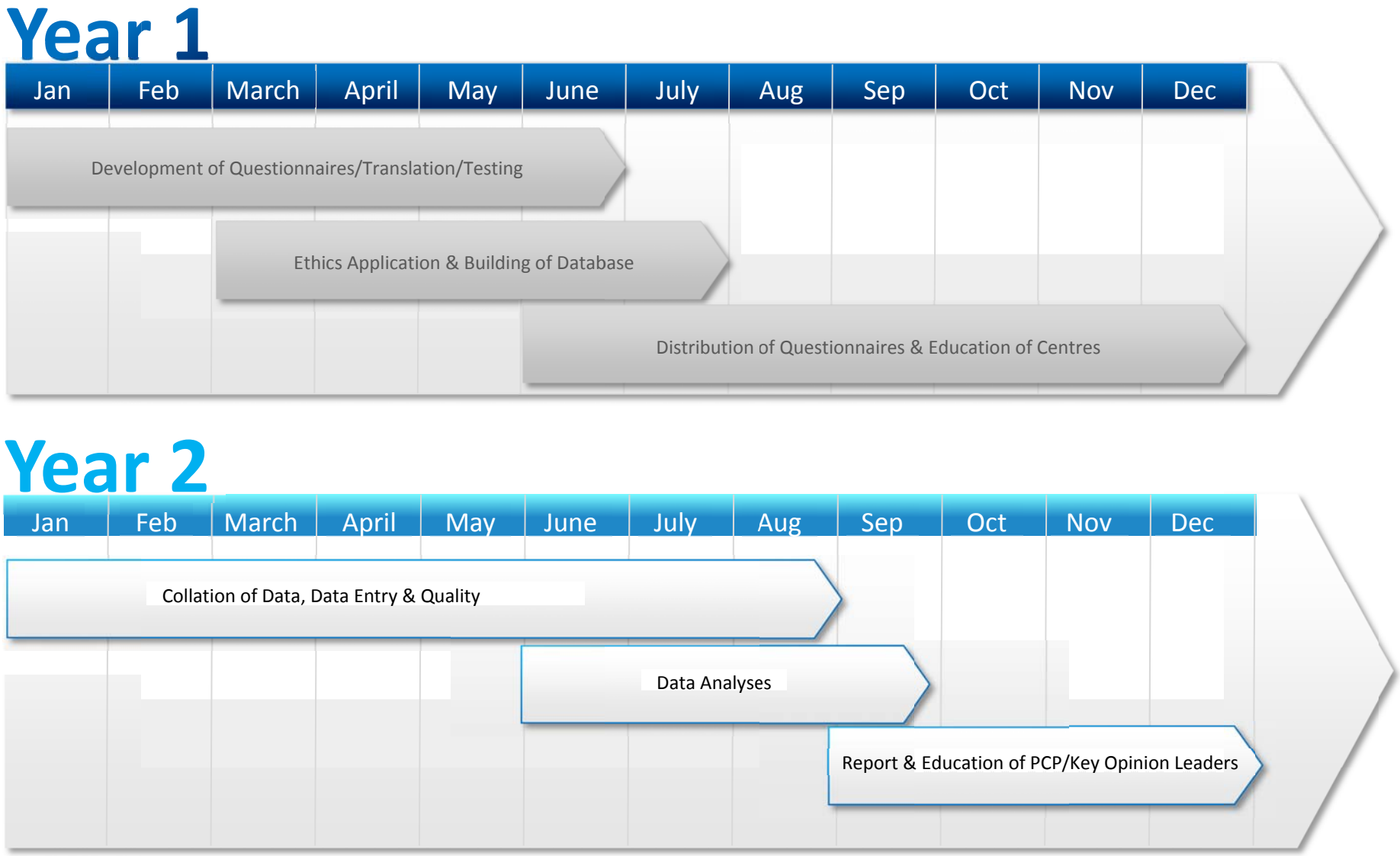
AAS = Australian Atherosclerosis Society
APSAVD = Asian-Pacific Society of Atherosclerosis and Vascular Diseases
IFHF = International Familial Hypercholesterolaemia Foundation
SBC = Brazilian Society of Cardiology
JAS = Japanese Atherosclerosis Society
KSLA = Korean Society of Lipidology and Atherosclerosis
MHF = Malaysian Heart Foundation
LASSA = Lipid and Atherosclerosis Society of Southern Africa
EAS = European Atherosclerosis Society

Appendix B: Countries participating in the studies

Country	Study 1	Study 2	Study 3	Study 4	Study 5
Australia	✓	✓	✓	✓	✓
New Zealand	✓	✓	✓	✓	✓
Brazil	✓	✓	✓	✓	✓
Japan			✓	✓	
China, Hong Kong	✓			✓	✓
China, Beijing	✓	✓		✓	
Philippines				✓	
Taiwan				✓	
South Korea				✓	
Malaysia				✓	
South Africa			✓	✓	✓
Netherlands			✓	✓	✓

Study 1: Plasma LDL-Cholesterol as a Predictor of FH Mutations
Study 2: Prevalence of FH in Community Populations
Study 3: Knowledge and Practices of Primary Care Physicians (PCP) concerning FH
Study 4: Comparison of Services and Facilities for the care of FH
Study 5: Patient Perceptions and Personal Experiences of FH

Appendix E: Study timelines



Appendix F: Familial Hypercholesterolaemia PCP Questionnaire

Q1. On a scale of 1 to 7; how familiar are you with familial hypercholesterolaemia?

	1 = Not at all familiar						7 = Extremely familiar
Please circle:	1	2	3	4	5	6	7

Q2. Which <u>one</u> description below <u>best</u> describes familial hypercholesterolaemia?

✓	*Please tick one*
	The presence of family members with diagnosed high cholesterol
	A genetic disorder that is characterized by very high cholesterol and a family history of premature heart disease
	The presence of multiple lipid abnormalities that may be genetic in nature
	An ultra-rare, potentially fatal condition caused by cholesterol levels that can be up to six times the normal level
	Other (please specify)
	Don't know

Q3. Which <u>one</u> of the following lipid profiles is most consistent with the diagnosis of familial hypercholesterolaemia?

	Reference intervals	**a**	**b**	**c**	**d**	**e**
Total cholesterol	< 5.5mmol/L	6.0	6.3	8.0	5.4	7.1
Triglyceride	< 1.7mmol/L	3.4	12.2	1.1	1.3	1.0
HDL – cholesterol	> 1.0mmol/L	0.8	1.0	1.0	1.7	3.5
LDL – Cholesterol	< 3.5mmol/L	3.8	-	6.5	3.1	3.2
	Please tick one					

Q4. Which of the following options could usefully assist you in detection of familial hypercholesterolaemia in your practice?

✓	*Please tick one.*
	Laboratory report on a lipid profile alerting possible familial hypercholesterolaemia
	Alert by the clinical software system in your practice
	Direct telephone call from the laboratory
	All of the above
	None of the above
	Other (please specify)
	Don't know

Q5. What is the prevalence of familial hypercholesterolaemia worldwide?

✓	*Please tick one*
	1 in 100 persons
	1 in 500 persons
	1 in 1,000 persons
	1 in 2,000 persons
	1 in 5,000 persons
	Don't know

Q6. Are you aware of any of the following criteria for the diagnosis of familial hypercholesterolaemia?

✓	*Please tick all that apply*
	Simon Broome diagnostic criteria
	Dutch Lipid Clinical Network criteria
	MED-PED criteria
	Other (please specify)
	Don't know

Q7. What is the likelihood that first-degree relatives (i.e. parents, siblings and children) of someone who has familial hypercholesterolaemia (index case) will also have the condition themselves?

✓	*Please tick one*
	0%
	25%
	50%
	75%
	100%
	Don't know

Q8. After diagnosing an index case, family cascade testing is:

✓	*Please tick one*
	Indicated only if the index case suffers from premature heart disease
	Recommended only if there is a family history of premature heart disease from both parents
	Recommended only if there is tendon xanthoma and/or genetic mutation in the index case
	Recommended by guidelines
	Don't know

Q9. Have you ever detected familial hypercholesterolaemia in the first-degree relative of a patient already diagnosed with familial hypercholesterolaemia?

✓	*Please tick one*
	Yes; how many?
	No
	Don't know

Q10. How much greater is the risk of premature coronary heart disease (CHD) in untreated familial hypercholesterolaemia patients compared to the general population?

✓	*Please tick one*
	2 times greater
	5 times greater
	10 times greater
	20 times greater
	50 times greater
	Don't know

Q11. When you are assessing a patient's family history, at what age for males and females do you consider heart disease to be "premature"?

	#		✓	
Premature heart disease in **males**:		years of age or younger		Don't know
Premature heart disease in **females**:		years of age or younger		Don't know

Q12. In patients with documented premature coronary artery disease which of the following do you routinely carry out?

✓	*Please tick all that apply.*
	Look for arcus cornealis
	Look for tendon xanthomata
	Take a detailed family history of coronary artery disease
	Screen close relatives for hypercholesterolaemia
	All of the above
	None of the above

Q13. Is the following statement true or false?

✓	*An accurate diagnosis of familial hypercholesterolaemia can only be made via genetic test.*
	True
	False
	Don't know

Q14. Do you have access to genetic testing for familial hypercholesterolaemia?

✓	*Please tick one*
	I have unrestricted access
	I have restricted access for selected cases
	I have no access
	Don't know

Q15. How many patients <u>currently</u> under your care, if any, have been formally diagnosed with familial hypercholesterolaemia?

#	*Enter "0" if appropriate*
	patients

✓	
	Don't know

Q16. Which of the following would improve the care of FH patients?

✓	*Please tick all that apply.*
	Better access to Lipid Clinic
	More education for primary care providers
	Patient forums
	Raise public awareness of FH
	None of the above; FH is sufficiently well care for
	Don't know
	Other (please specify)

Q17. If you have patients with familial hypercholesterolaemia under your care do you routinely screen close relatives for this condition with a lipid profile?

✓	*Please tick one*
	Yes, patient's children only
	Yes, patient's children and other close relatives
	No
	Not applicable

Q18. In your view, which healthcare providers would be most effective at early detection of familial hypercholesterolaemia and screening first-degree relatives?

✓	*Please tick up to two.*
	Lipid specialists
	General practitioners
	Cardiologists
	Nurses with experience in cardiac risk prevention
	Pediatricians
	Obstetricians/Gynecologists
	Endocrinologists
	Other (please specify)

Q19. At what age would you test young individuals for hypercholesterolaemia in a family with premature coronary heart disease?

✓	*Please tick one.*
	0 – 6 years
	7 – 12 years
	13 – 18 years
	None of the above
	Don't know

Q20. Are you aware of any specialist-clinical services for lipid disorders to whom you can refer patients?

✓	
	Yes
	No *(Go to question 17)*

Q21. If yes to question 15, have you referred patients with familial hypercholesterolaemia to this service?

✓	
	Yes
	No
	Don't know

Q22. Which drugs do you use to treat hypercholesterolaemia?

✓	*Please select all that apply*
	Exchange resins / bile acid sequestrants
	Ezetimibe
	Statins
	Fibrates
	Nicotinic acid
	Other (please specify)
	None of the above

Q23. Which drug combinations do you use to treat severe hypercholesterolaemia?

✓	*Please select all that apply*
	Statin + Exchange resins / bile acid sequestrants
	Statin + nicotinic acid
	Statin + ezetimibe
	Statin + ezetimibe + nicotinic acid
	Statin + ezetimibe + Exchange resins / bile acid sequestrants
	Other (please specify)
	None of the above

Q24. Which of the following new lipid modifying therapies in development may be useful for treatment of familial hypercholesterolaemia?

✓	*Please select all that apply*
	Antisense oligonucleotide inhibitors
	ApoA1 mimetics
	CETP inhibitors
	DGAT inhibitors
	MTP inhibitors
	PCSK9 inhibitors
	Other (please specify)
	None of the above

GP Demographics and Practice details

The following questions are for classification purposes only.

1. What is your gender?

✓	*Please tick one.*
	Male
	Female
	Prefer not to say

2. What is you location? (city/town, state/province, country)

_____

_____

3. How would you describe the area of your primary practice?

✓	*Please tick one.*
	Metropolitan
	Outer metropolitan
	Rural

4. Have you a qualification/certification that accredits you in your country to practice in primary care?

✓	*Please tick one.*
	Yes; how many years have you been in practice since completing your fellowship? #_____ years
	No
	Prefer not to say

5. Approximately how many patients do you see for <u>any condition</u> in an average month?

	patients/ month

6. Do you use electronic medical records?

✓	*Please tick one.*
	Yes; what software package do you employ? _____ _____
	No

Appendix G: Familial Hypercholesterolaemia Clinical Service Questionnaire

Please note that this is not the full and final questionnaire. The complete questionnaire will be developed as part of the proposed project. Below is the basic structure of the questionnaire and some sample questions.

General Information

What is the population of your country?

What is the estimated prevalence of FH for your population?

Is there a population with a 'gene founder' effect in your country?

☐ Yes ☐ No

Is there a network of lipid clinics in your country?

☐ Yes ☐ No

How many specialist centres are there in your country?

Does your country have a Heart Foundation or similar organization?

☐ Yes ☐ No

Are there guidelines for managing FH?

a) National ☐ Yes ☐ No
b) Local ☐ Yes ☐ No
c) Hospital ☐ Yes ☐ No
d) Clinic ☐ Yes ☐ No

Section 1: Clinical Set-up

1.1 What type of hospital?

☐ Teaching/University Hospital
☐ Public Hospital
☐ Private Hospital

1.2 Does your hospital provide outpatient services for the clinical management of:

a) Adults with FH? ☐ Yes ☐ No
b) Children/young people (under 16s) with FH? ☐ Yes ☐ No

Section 2: Clinical Time

2.1 In your service, how much clinical time is devoted to specialist lipid management/FH by your employed staff?

a) How many consultants are devoted to specialist lipid management?
#_____

b) How many consultants have formally trained in the care of lipid disorders?
#_____

c) On average, what proportion (%) of their time is estimated to be spent on the management of FH?
☐<10% ☐11-20% ☐21-40% ☐41-60% ☐61-80% ☐81-100%

d) How many lipid specialist nurses are there (whole time equivalents)?
#_____

e) On average, what proportion (%) of this is estimated to be spent on the management of FH?
☐<10% ☐11-20% ☐21-40% ☐41-60% ☐61-80% ☐81-100%

f) Do you have a telehealth service for FH?
☐ Yes ☐ No

Section 3: Assessment and Management of FH

3.1 Does your service formally classify patients according to the:

a) Simon Broome criteria	☐ Yes	☐ No
b) Dutch Lipid Clinical Network criteria	☐ Yes	☐ No
c) MED-PED	☐ Yes	☐ No
d) Other	☐ Yes	☐ No

Section 4: Screening and Cascade testing

4.1 Is screening for index cases of FH undertaken in your country?

☐ Yes ☐ No

4.2 Are there population age- and gender- specific LDL-cholesterol levels for your country?

☐ Yes ☐ No

Section 5: Service Components

5.1 Does your service have arrangements for DNA mutation testing for FH patients attending your clinical service?

- ☐ Yes - funded
- ☐ Yes – not funded
- ☐ Available only in special cases
- ☐ No

5.2 Does your service have a laboratory that is currently accredited for testing lipid measurements?

☐ Yes ☐ No

Section 6: Patient Information

6.1 Do you provide information leaflets to FH patients/carers?

☐ Yes ☐ No

Section 7: Service Improvement

7.1 Does the FH service have specific links to a patient/service user group?

☐ Yes ☐ No

Section 8: Research, Teaching and Training

8.1 Do you undertake research into FH?

☐ Yes ☐ No

8.2 Do you have an academic-service partnership focusing on FH?

☐ Yes ☐ No

Appendix H: Familial Hypercholesterolaemia Patient Questionnaire

Please note that this is not the full and final questionnaire. The complete questionnaire will be developed as part of the proposed project. Below is the basic structure of the questionnaire.

Patients will be required to complete a health literacy questionnaire (HLQ) prior to participation; patients with low health literacy (falling below threshold on the HLQ) will be excluded from the study.

Familial Hypercholesterolaemia (FH) Patient Questionnaire

Thank you for agreeing to participate in this important study. The aim is to study the views and opinions of people with FH about their condition, their health, their treatment, and their clinic attendance. The study is important as it will help us improve the service and care of FH patients.

We will ask you a number of question about your experiences with FH, your clinic attendance, your treatment and other activities related to FH. Some of the questions will be facts about you and your clinic treatment. Some of the questions will be asking you for your opinions, attitudes, and beliefs. For these questions, there are no right or wrong answers. So just give the answer that is right for your and best describes how you feel.

All answers are completely confidential, please be as **honest** and **accurate** as you can. If you have any questions, please feel free to contact the study team, their details are provided below.

First, please answer the following questions about the clinic you attend for FH.

Name and Address of the Clinic You Attend *(please write in the box below*)

Please Write the Name of the Consultant *(please write in the box below*)

How confident do you feel about filling out this questionnaire (by yourself)? (Circle one)

Not at all	**A little**	**Moderately**	**Mostly**	**Completely**

Part 1: About You and Your Condition

- Personal information
- Demographics
- FH Diagnosis
- Cardiovascular disease
- Risk factors for cardiovascular disease

Part 2: Your Thoughts FH

- Perception
- Knowledge
- Attitudes/beliefs
- Symptoms
- Example:
    - How long will FH last?
    - Efficacy of FH treatment
    - Control over FH
    - How often you have symptoms?
    - Understanding of FH
    - FH causing emotional distress
    - FH affects my life
    - What do you think caused your FH?

Part 3: How FH has Affected Your Life

- Rating of overall health

Part 4: Your Views About Medicine

- Personal views about medications in general

Part 5: Your Quality of Life

- Rating of overall quality of life

Part 6: Your Activity, Diet and Medication

- Physical activity
- Healthy eating
- Medication