What determines adherence to treatment in cardiovascular disease prevention? Protocol for a mixed methods preference study

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ARTICLE SUMMARY

Article focus
- To assess patient choices with regard to adherence to long-term therapy for the prevention of cardiovascular disease in indigenous and non-indigenous populations.
- To understand, from the perspective of patients and providers, the factors that influence how well guidelines-recommended therapy for cardiovascular disease in indigenous and non-indigenous populations are implemented.

Key messages
- This is an innovative study using a mixed methods approach to assess patient medications adherence that combines data on patients’ stated preferences and their observed behaviour.
- The study will examine underlying reasons why adherence outcomes were (or were not) achieved within the context of a clinical trial of a cardiovascular polypill-based strategy and, as such, serves as a process evaluation.
- The findings will extrapolate the level of adherence observed in the trial to different ‘real-world’ settings.

Strengths and limitations of this study
- The strengths of the study are that it involves the innovative application of a preference study alongside a clinical trial, provides insights into how patients may respond to factors that influence adherence but not necessarily during a clinical trial setting and addresses an important public-health issue—namely treatment gaps in relation to cardiovascular-disease prevention.
- The limitation is that it is a conducted in one country, Australia, and thus its generalisability may be limited by prevailing institutional arrangements.

BACKGROUND
Current gap between guidelines and practice
Despite the strong evidence base for therapies effective at reducing cardiovascular disease (CVD) morbidity and mortality, and incorporation of this evidence in therapeutic guidelines, a substantial gap between recommended treatment and clinical practice exists.

ABSTRACT
Background: Significant gaps exist between guidelines-recommended therapies for cardiovascular disease prevention and current practice. Fixed-dose combination pills (‘polypills’) potentially improve adherence to therapy. This study is a preference study undertaken in conjunction with a clinical trial of a polypill and seeks to examine the underlying reasons for variations in treatment adherence to recommended therapy.

Methods/design: A preference study comprising: (1) Discrete Choice Experiment for patients; and (2) qualitative study of patients and providers. Both components will be conducted on participants in the trial. A joint model combining the observed adherence in the clinical trial (revealed preference) and the Discrete Choice Experiment data (stated preference) will be estimated. Estimates will be made of the marginal effect (importance) of each attribute on overall choice, the extent to which respondents are prepared to trade-off one attribute for another and predicted values of the level of adherence given a fixed set of attributes, and contextual and socio-demographic characteristics. For the qualitative study, a thematic analysis will be used as a means of exploring in depth the preferences and ultimately provide important narratives on the experiences and perspectives of individuals with regard to adherence behaviour.

Ethics and dissemination: Primary ethics approval was received from Sydney South West Area Health Service Human Research Ethics Committee (Royal Prince Alfred Hospital zone). In addition to usual scientific forums, the findings will be reported back to the communities involved in the studies through site-specific reports and oral presentations.

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The reasons for the current treatment gaps are complex, but in addition to poor dissemination and uptake of guidelines, other factors include: low continuation rates by patients, inequities in health services, and resistance (by both doctors and patients) to the cost, complexity and stigmatisation of prescribing four or more cardiovascular medications. Low medication adherence rates are a well-documented, highly prevalent obstacle to successful ongoing prevention and treatment of chronic diseases such as cardiovascular disease.1–5 Barriers to adopting guideline recommendations by doctors may include lack of time, multiplicity and lack of awareness of guidelines, and insufficient resources to implement recommendations. From a patient perspective, non-adherence is associated with taking multiple medicines and complex dosing regimens.1–5 Cost can be an important contributory factor, and patients can delay or omit doses and not fill prescriptions as strategies for cost reduction.4–7

Existing study: a randomised controlled trial of a polypill-based strategy to improve implementation of guidelines for CVD prevention

The use of fixed-dose combination therapy to prevent CVD has generated debate since Wald and Law advocated the widespread use of a ‘polypill’ containing aspirin, a statin, three low-dose blood pressure-lowering drugs and folic acid for the prevention of CVD events.5 It has been proposed that fixed-dose combination pills may improve adherence by reducing the number and complexity of dosing regimens for doctors and patients, and improving access to treatment by reducing costs. The Kanyini GAP (Guidelines Adherence with the Polypill) trial, which commenced patient recruitment in the last quarter of 2009, is a prospective, open, randomised controlled clinical trial (n=1000) of a polypill-based strategy compared with usual care among individuals at high risk of cardiovascular events. Six hundred indigenous participants are being mainly recruited from around 10 Aboriginal Medical Service partners within the Kanyini Vascular Collaboration, while the 400 non-indigenous participants are being recruited from general practice sites in New South Wales, Victoria and Queensland.

The randomised controlled trial (RCT) aims to assess whether provision of a polypill (containing low-dose aspirin, a statin and two blood-pressure-lowering medicines) compared with usual cardiovascular medications improves adherence to indicated therapies and clinical outcomes among high-risk patients. Participants are being followed up for an average of 18 months. The main outcome of interest is adherence to indicated therapies defined as self-reported current use of anti-platelet, statin and combination (≥2) blood-pressure-lowering therapy. However, as there are substantial challenges in reliably measuring adherence, the study is powered to detect meaningful differences in the biological proxies of blood pressure and total cholesterol levels. Details on the study protocol are contained in the Australian and New Zealand Clinical Trials Registry (ACTRN1260800583347).9

Analytical framework: Discrete Choice Experiment as a tool for assessing therapeutic adherence within a process evaluation

The polypill strategy is not simply a pharmacological intervention—patients’ adherence is likely to be influenced by their preferences and beliefs, the tangible and intangible costs incurred and the behaviour of providers. In this respect it can be defined as a complex intervention in which there are ‘several interacting components’ and in which providers and those receiving the intervention are expected to comply with behaviours that entail a significant degree of difficulty.10

The inclusion of a process evaluation alongside a trial or outcome evaluation of a complex intervention has been posited as a means of understanding how and why an intervention might or might not have been effective.10–13 Such evaluations utilise qualitative and quantitative methods and address specific issues about an intervention including how it is viewed by participants; how it was implemented; the distinction between its various components; the contextual factors that influence its effectiveness; its reach in terms of individuals/sites; and variation in effects across subgroups.11

The ongoing prescription and consumption of the polypill in the real-world setting relies on patient and physician choices which in turn are influenced by the interplay of physician, patient, therapy, disease, and health-system characteristics.14 In this context, a process evaluation is needed to provide some indication of the generalisability of the results of the trial to other settings. The findings will assist in translating the results into policy and practice.

We propose to undertake a discrete choice experiment, along with a series of qualitative interviews with patients, GPs and pharmacists, as a technique to address these issues. Discrete Choice Experiment (DCE) is based on the notion, drawn from economic consumer theory, that individuals’ demand for goods can be decomposed into preferences for specific attributes.15 For example, an individual’s demand for a particular drug will be determined by attributes such as its known efficacy, side effects, cost and convenience of dosing. However, what we can observe in practice is choices between particular goods—or bundles of such attributes. Accordingly, DCEs involve the use of surveys in which respondents choose between alternative goods which vary in the level of their attributes. For instance, respondents are asked to choose between Drug Regimen A and Drug Regimen B based on the description of their attributes provided, assuming all else to be equal between the options (see table 1). In this simplified example, the choice between Regimen A and Regimen B involves variation across four attributes: efficacy, side effects, cost and dosing. For a particular option (Regimen A or B) each of these attributes is set at certain
‘levels’—here, the level of efficacy for both options is equal between A and B for the attributes efficacy and dosing. The choice is reduced simply to one of cost versus of side effects (eg, a choice of B over A would imply that the respondent is willing to pay an extra $75 per month to avoid the side effect of nausea). In practice, a DCE survey would involve a series of such choices in which the level of each of the attributes is varied (Table 1).

| Drug regimen A | Drug regimen B |
|---------------|---------------|
| Efficacy 50%  | 50%           |
| Side effects  | Nausea Nil    |
| Cost $25 per month | $100 per month |
| Dosing 1 per day | 1 per day     |

In designing a DCE, the initial selection of attributes and their levels can be informed by a literature review or qualitative study. Typically, DCE surveys conducted in health have involved choice sets containing four to eight attributes. Given sufficient variation across all attributes through the appropriate design, the approach enables, using multivariate models, estimates of a utility function in which each attribute and background characteristic of respondents represents separate parameters. Ultimately, through the estimation of a utility function, the approach enables:

► estimates of the individual effect of attributes of the products being compared (such as efficacy and cost of different drug regimens) and the background characteristics of the respondents (such as age, sex and risk factors) on consumers/or patients’ choice of product (eg, drug regimen A vs B);
► estimates of the degree to which individuals are willing to trade-off one attribute for another—for example, how much individuals are willing to pay for reduction in side-effects from drug therapy;
► the forecasting of patient choices based on given attributes and respondent characteristics—for example, for a given cost and demographic profile, what level of demand we can expect for a specific product.

Although initially developed in the marketing field, DCEs have been used extensively in healthcare. Given the potential cross-cultural barriers that may exist with its deployment in the Kanyini GAP study population, extensive piloting will be needed in this study.16

The rationale for the use of DCEs within this process evaluation is the view that adherence is in essence a ‘rational choice’—such choice entails patients balancing a range of factors such as perceived efficacy, cost and side effects.17 This economic perspective, where patients are viewed as active agents in decisions regarding their care and that there may ultimately be good reasons for non-adherence, potentially provides alternative insights to often posited ‘medical’ perspectives where non-adherence is viewed as deviance.18

We are not aware of the use of DCEs as part of a process evaluation, despite the increasing recognition of their value in assessing patient and consumer preferences in the health-services research literature. Their role in process evaluation would be based on their capacity to explain the motivation and behaviour of agents in the course of an intervention—complex or otherwise. Furthermore, the use of DCE in conjunction with a clinical trial provides an opportunity for combining two sources of data. This represents an important methodological development, as although the outcomes of a clinical trial reflect the actual behaviour of participants (revealed preference), such behaviour is constrained by the parameters in which the study takes place. These constraints on behaviour and the attributes that may influence such behaviour that are imposed by the research design limit the ability to extrapolate to circumstances which may differ from those existing within the study. Thus, while clinical trial data involve a comparison of two fixed options, ‘stated preference’ methods such as DCE have the flexibility to allow for the construction and testing of hypothetical scenarios. With appropriate scaling, the data from such studies can be combined to provide more robust model estimates and furthermore allow consideration of a wider range of factors that modify adherence behaviour than stated or revealed preference data alone.19 20

The aims of this study are:

1. to assess patient choices with regard to adherence to long-term therapy for the prevention of cardiovascular disease in indigenous and non-indigenous populations;
2. to understand, from the perspective of patients and providers, the factors that influence how well guideline-recommended therapy for cardiovascular disease in indigenous and non-indigenous populations is implemented.

METHODS/DESIGN

This study comprises two inter-related components: (1) a DCE of patients to determine the factors that influence adherence to therapy; and (2) a qualitative study of patients, general practitioners and pharmacists.

DCE

The DCE will be carried out by interview-administered survey by a study nurse at the end of each final follow-up visit in the Kanyini GAP trial. This allows us to conduct the survey as a face-to-face interview (as opposed to the usual postal self-administered or telephone method). The advantages of this strategy are that it allows the interviewer to better explain the tasks involved in the survey, and it capitalises on access to the participant afforded by the trial, thereby minimising both the risk of non-response and the costs associated with administration. The questionnaire will undergo extensive piloting.
across the study sites on patients not involved in the trial—this will inform its design, wording and formatting.

Establishing relevant attributes and levels
An initial set of attributes will be established through a review of the literature on therapeutic adherence and cardiovascular disease. The aim of this review is to capture, for potential inclusion as attributes in the DCE survey, the most important factors likely to influence individuals’ adherence behaviour. Specifically, the task here will be to: (1) establish a feasible set of attributes for inclusion in the survey (usually up to eight) and; (2) establish the levels at which these attributes are set (eg, the range of cost to the patient might be set from zero to $100 per month) based on their feasibility in practice.

Questionnaire design
The appropriate combination of attributes and levels to be posed in the DCE survey will be based on consideration of both the statistical properties of Efficient Choice (EC) design and pragmatic judgements about the plausibility of the choice sets offered. CI Rose is a recognised leader in research into such design principles and will lead this aspect of the study.

It is rarely feasible or efficient to test every combination of attribute and attribute levels through a ‘full factorial design,’ and thus an EC approach can be deployed to establish a ‘fractional factorial design’ that links statistical efficiency to the likely econometric model, that is, to be estimated from discrete choice data. Design software package NGene 1.0 will be deployed to generate such a design. The principle used is the minimisation of the correlation in the data for estimation purposes so that standard errors on parameter estimates are ultimately minimised.21 22 Such a design makes use of prior information about such estimates which can be derived in this study from data obtained from the initial piloting as described above.

In addition, the characteristics of the choices posed will also be influenced by judgement about the real-life feasibility of the specific combinations—for example, if the number of pills taken per day and co-payment are posed as attributes, then for any choice, it is highly unrealistic that the co-payment level will be set higher when the number of pills per day is lower. Thus, the design will be restricted from allowing such combinations.

From such principles, a survey will be designed in which a series of choices will be posed between two unlabelled options representing alternative treatment regimens. These will vary by attributes that potentially influence patient adherence to treatment such as cost, dosing, whether administered as a polypill or not, side effects and perceived effectiveness.

DCE survey
The sites for the DCE will be those involved in the Kanyini GAP RCT. Aboriginal participants are being mainly recruited from health-service partners comprising Aboriginal-community-controlled health services across Australia. The surveys of Aboriginal participants will be carried out specifically by an Aboriginal project officer. Non-Aboriginal participants will be recruited predominantly from general practices in NSW, Victoria and Queensland.9

Centres have been selected on the basis of interest in participating in the study, practice size and location, and clinical research experience. Sixty per cent of individual participants will be indigenous. We anticipate that taking into account attrition of 10% from loss to follow-up and death, 900 of the original 1000 participants will be eligible to participate in the survey at final follow-up. One significant advantage of conducting the DCE within the clinical trial is in the potential to access large numbers of well-motivated respondents. As such, we anticipate that the response rate to the survey will be higher than those conventionally encountered in DCE studies which are generally conducted in a general population setting—previous studies conducted in clinical settings have yielded response rates of 90–100%.23

Assuming a refusal rate of 10%, we would expect 810 respondents. Because each respondent yields multiple observations based on the number of discrete choice questions they answer and that most DCE studies in healthcare have contained nine to 16 choices,23 we would thus expect to obtain 7290–12 960 observations. In our experience, previous comparable surveys in healthcare have been successfully carried out with the number of participants generally well below 800.

Analysis and interpretation
A post-hoc analysis of the Kanyini GAP RCT will be undertaken to provide an initial assessment of the factors influencing adherence to treatment. As we are interested in the role not simply of the intervention but potentially a broader set of covariates in influencing this outcome—and because randomisation controls for such covariates—the analysis will be carried out on a pooled dataset of subjects in both arms of the trial. The modelling strategy will entail a multivariate logistic analysis in which adherence will be assessed as a function of individuals’ background characteristics (such as age, sex, disease history, Aboriginality), attributes of intervention (eg, copayment and dosing), contextual variables (eg, urban/rural) and the treatment group to which the individual was allocated. Adherence as a primary outcome is assessed in the trial in terms of self-reported current use of antplatelet, statin and combination (≥2) blood-pressure-lowering therapy at the end of follow-up. For modelling purposes, it will be measured as a dichotomous variable (adherent vs non-adherent) in which adherence is defined by an individual who reports ≥80% compliance with prescribed dosing. This threshold is based on the minimum required for therapeutic response and is consistent with the literature.24 25

The analysis of the DCE will entail the use of a mixed multinomial (random parameters) logit (MMNL) model using a panel size specification. A panel specification of the model allows for multiple and potentially correlated
An indication of the predicted values or ‘market shares’ associated with different parameter levels within the estimated utility functions. This allows forecasting of, for instance, the level of adherence that could be expected given a fixed set of attributes (eg, cost, effectiveness and side-effects) and contextual and socio-demographic characteristics. This forecast can be used to inform policy directed at altering attribute levels to enhance adherence and be estimated separately across different contexts and population subgroups.

Qualitative study
A series of interviews with patients and providers involved in the Kanyini GAP RCT will be carried out to provide in-depth understanding of the reasons for adherence/non-adherence to therapy for cardiovascular disease prevention—as observed within the trial and in practice, as would be the case beyond the trial setting. Recruitment of both providers and patients for interview will be purposive, to maximise variation on criteria such as location, practice size and degree of participation (for providers) and location, gender, age and outcomes (for patients). Background and adherence data obtained from the trial and DCE will be used to inform this recruitment. Sampling will continue until no new themes or categories emerge from the data (so-called ‘thematic saturation’). We anticipate from previous experience the need to conduct around 20 GP interviews, 10 pharmacist interviews and 40 patient interviews (20 indigenous and 20 non-indigenous)—and this is reflected in our budget estimates. Interviews will be scheduled to take place after the DCE. The interviews will be conducted face to face by a project officer, with an Aboriginal project officer responsible for conducting the interviews with Aboriginal participants.

Provider interviews
Participating GPs and pharmacists will be administered an in-depth interview to explore:
- their views on the advantages, disadvantages, acceptability and applicability of the polypill strategy relative to current practices;
- what variations there were across patient groups in terms of experience and performance of the polypill strategy relative to current practices;
- particular incidents when prescription of the polypill proved helpful for themselves and/or the patient, and incidents when it was not advantageous;
- how their behaviour within the trial might be modified outside the study setting;
- what characteristics of the study setting mean that behaviour observed within it may not be reflective of provider behaviour in practice;
- broader questions about their perceptions regarding the factors that either hinder or facilitate patient adherence to either the polypill strategy or current prescribed treatments in practice;
- suggestions for interventions or policies to improve adherence.

Patient interviews
Patient interviews which will be conducted in patients in both treatment and control groups will be used to explore in greater depth:
- their views on the benefits, disadvantages and acceptability of their current treatment (polypill or usual care);
- reports on specific instances where changes occurred to their usual adherence behaviour and the circumstances surrounding these;
- the factors that hinder or facilitate their attitude towards adherence to therapy within the trial;
- the factors that in practice would modify patients’ adherence behaviour from that exhibited in the trial. Analysis of the interview data will be thematic, and NVivo 8 will be used to assist with the management of the data. Coding will be carried out inductively based on the themes that emerge from the interviews. The analysis
will be undertaken by members of the study team (TU, DP and PSPs 1 and 2) so that themes can be cross-checked. In accordance with normal qualitative research practice, analysis will occur concurrently with the interviews, and thus themes will be assessed continually in light of additional data. Such data will be used as a means of exploring in greater depth the preferences observed in both the trial and the DCE, and ultimately provide important narratives on the experiences and perspectives of individuals with regard to adherence behaviour. This will form the basis for a set of stand-alone research findings (Aim 2).

Consent
Participants in the trial will be provided an information sheet about the study and asked to sign and date a consent form. A copy will be given to the participant and the original retained at each site attached to the medical records of the participant.

Data management and handling
Data management will be carried out at the George Institute. The recordings and transcripts from the qualitative interviews and completed DCE surveys will be securely stored with data files password protected and accessible only to the study team. These records will be destroyed after 15 years.

Reporting
In addition to usual scientific forums, the findings will be reported back to the communities involved in the studies through site-specific reports and oral presentations.

Study organisation and ethics
The study will be administered by The George Institute, with the design and conduct overseen by a project management committee (authors). This committee has expertise in both large-scale clinical trials and qualitative research, economic analysis (particularly the use of DCEs), clinical CVD management, Aboriginal and Torres Strait Islander health research and health policy. This study will be subject to oversight from the Scientific Steering Committee for that study of the Kanyini-GAP trial. The study will adhere to National Health and Medical Research Council and Aboriginal Health & Medical Research Council ethical guidelines for human research. Ethics approval for Kanyini-GAP was first granted by Sydney South West Area Health Service Human Research Ethics Committee (HREC) (Royal Prince Alfred Hospital zone), and subsequently by relevant HRECs across the country, which are the Aboriginal Health & Medical Research Council HREC, Cairns and Hinterland Health Service District HREC, Central Australian HREC, Metro South Health Service District HREC and Monash University HREC.

DIsCUSSION
Non-adherence represents a major reason for the significant health inequalities that exist for chronic illnesses in Australia. CVD represents the single largest public health burden for Australia, and major challenges in providing preventive therapy of proven effectiveness remain. Currently a trial is under way assessing a fixed-dose combination therapy to improve adherence to therapy. This study will provide an opportunity to add value to this trial by examining the underlying reasons why providers and patients may or may not adhere to recommended guidelines, taking into account the role of providers, tangible and intangible costs and the preferences of patients. The findings of the trial will thus be extended and quantified using a DCE to model the impact of both patient and treatment attributes on adherence. Methodologically, this use of DCE will represent a significant development in RCT process evaluation that will generate deep insights into the preferences and behaviour of individuals and allow extrapolation to settings that differ from those in which the trial was conducted. The study will enable policy makers to model the cost and other attributes of treatment to achieve targeted levels of adherence, understand better the trade-offs in doing so and ultimately deliver more effectively proven long-term strategies for the prevention and management of cardiovascular disease and other chronic illnesses.

Correction notice The “To cite: …” information and running footer in this article have been updated with the correct volume number (volume 1).

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Competing interests None.

Patient consent Obtained.

Ethics approval Ethics approval was provided by the Sydney South West Area Health Service Human Research Ethics Committee (Royal Prince Alfred Hospital zone).

Contributors SJ, TU, AP, AC and DP conceived the original concept of this study. All authors contributed to the design of the study and are involved in the implementation of the project. SJ wrote the first draft of the protocol.

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