Study Protocol

Understanding clinicians' decisions to offer intravenous thrombolytic treatment to patients with acute ischaemic stroke: a discrete choice experiment

Principal Investigator
Richard G Thomson, Professor of Epidemiology and Public Health
Institute of Health and Society (Decision Making and Organisation of Care Group), Newcastle University, Baddiley-Clark Building, Richardson Road, Newcastle upon Tyne, NE2 4AX, UK
Tel: +44 (0)191 2228760; email: richard.thomson@ncl.ac.uk

Co-applicants
Dr Emily Lancsar, Associate Professor
Centre for Health Economics, Faculty of Business and Economics, Monash University, Clayton, Victoria, Australia 3800
Tel: +61 (0)3 99050759; email: Emily.Lancsar@monash.edu

Dr Darren Flynn $_{C.Psychol}$, Senior Research Associate
Institute of Health and Society (Decision Making and Organisation of Care Group), Newcastle University, Baddiley-Clark Building, Richardson Road, Newcastle upon Tyne, NE2 4AX, UK
Tel: +44 (0)191 2225415; email: darren.flynn@ncl.ac.uk

Dr Laura Ternent, Lecturer in Health Economics
Institute of Health and Society, Newcastle University, Baddiley-Clark Building, Richardson Road, Newcastle upon Tyne, NE2 4AX, UK
Tel: +44 (0)191 2227083; email: laura.ternent@ncl.ac.uk

Helen Rodgers, Clinical Professor of Stroke Care
Institute for Ageing and Health (Stroke Research Group), Newcastle University, The Medical School, 3-4 Claremont Terrace, Newcastle Upon Tyne, NE2 4AE, UK
Tel: +44 (0)191 2228025; email: helen.rodgers@ncl.ac.uk

Dr Christopher Price, Clinical Senior Lecturer and Consultant Stroke Physician
Wansbeck General Hospital, Northumbria Healthcare NHS Foundation Trust, Ashington, Northumberland, NE63 9JJ, UK
Tel: +44 (0)1670 529442; email: christopher.price@nhct.nhs.uk

Gary A Ford, Jacobson Chair of Clinical Pharmacology
Institute for Ageing and Health (Stroke Research Group), Newcastle University, 6th Level Leazes Wing, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP, UK
Tel: +44 (0)191 2227744; email: gary.ford@ncl.ac.uk

List of Abbreviations

BASP - British Association of Stroke Physicians
CT/MRI – Computed (Axial) Tomography / Magnetic Resonance Imaging
DASH - Development and Assessment of Services for Hyperacute stroke
DCE - Discrete choice experiment
NICE - National Institute for Health and Clinical Excellence
QALYs - Quality Adjusted Life Years
rtPA - recombinant tissue plasminogen activator
NHS – National Health Service
NIHR – National Institute for Health Research
NIHSS – National Institutes of Health Stroke Scale
SINAP - Stroke Improvement National Audit Programme
SSNAP - Sentinel Stroke National Audit Programme
SITS-UK - Safe Implementation of Thrombolysis in Stroke UK
SITS-MOST - Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy
UK – United Kingdom

Table of Contents

Executive Summary

Background: Intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA/alteplase) is the most effective emergency treatment for acute ischaemic stroke and has been recommended by the National Institute for Health and Clinical Excellence (NICE) since 2007[1]. As with any treatment, there are risks as well as benefits, and these need to be taken into consideration when offering thrombolysis to individual patients. However, despite considerable evidence for the effectiveness in well-defined patient groups[2, 3], there is geographical variation in treatment rates in the UK[4, 5]. Although availability of services (such as access to urgent CT scanning) initially accounted for much of the variation in thrombolytic treatment rates between centres, with the wide implementation of 24 hours a day, 7 days a week, hyperacute stroke services, this has changed. Continuing variation is likely to increasingly reflect variations in clinical decision making on who should be offered thrombolysis. Contributors to this remaining variation are likely to include uncertainty surrounding benefit for individual patients within the *'grey zone'* (i.e. the upper and lower extremes of relative contraindications for treatment), as well as the impact of patient and clinician factors that go beyond those incorporated within licencing criteria and clinical guidelines[6]. Thus, clinicians' decisions are now a greater influence on who is offered treatment than service variations[7]. Factors that might explain variation in this context include the perceived balance between the benefits of treatment and the risks of intracranial haemorrhage[8], but it is unclear what are the important patient and/or clinician factors that influence offer of thrombolysis to patients, and especially their relative contributions.

Aim: To identify what factors contribute to variation in, and influence, clinicians' decision making about intravenous thrombolysis for acute ischaemic stroke, given what is already known about the most effective and safe use of the treatment, in order to inform programmes that seek to influence clinical behaviour and decision-making.

Design and rationale: To understand the factors that influence decision making when considering thrombolysis, we need to understand the thought processes of clinicians who are making these decisions in a way that reflects decision making in practice. We also need to understand the relative importance of the range of possible factors which influence decision making by quantifying the trade-offs that are made. A discrete choice experiment (DCE) will be conducted to understand which factors are important to the deliberations that clinicians make when considering offering thrombolysis to patients. DCEs are the method of choice to explore the relative importance of different (and sometimes implicit) factors within a decision making process, that are not easily captured using more traditional approaches such as questionnaire survey methods or observation. We have already developed understanding of the likely factors influencing clinical decisions from literature review and interviews with clinicians undertaken in a previous NIHR programme grant, which will inform the attributes to include in the DCE. We will undertake further semi-structured interviews with clinicians to develop the attribute content of an online DCE survey, following which stroke physicians and neurologists will be asked to state whether they would offer thrombolysis when given hypothetical patient vignettes, which vary in terms of their characteristics (attributes, e.g. age) and the magnitude of these characteristics (levels, e.g. patient age 60 or 75 years)[9]. The relative importance of different attributes (and levels) to the decision can then be quantified and the estimated choice model used to predict the probability of offering thrombolysis given certain characteristics of the patient and the clinician[9, 10]. This will enable us to understand which patient factors and clinical characteristics are influencing the offer of thrombolysis, and determine which of these are more or less appropriate.

By understanding how different clinicians currently negotiate the (often difficult) trade-offs between risks and benefits in different patients, we can use such data to optimise appropriate use of thrombolysis and better support risk communication, consent and decision-making with patients. Thus, the study findings will be used to inform strategies to reduce unwarranted variation in thrombolysis rates, with tangible benefits in terms of improved stroke patient care and likely costs savings associated with optimal use. To this end, we will mobilise our learning to inform practice by: i) feeding the study findings into regional professional development opportunities provided through the NHS Stroke Improvement Programme[11] and nationally through the British

Association of Stroke Physicians[12] and Stroke Medicine trainees' curricula[13, 14]; (ii) supporting implementation of a decision support tool we have recently developed to inform clinician decision-making and risk communication in thrombolysis[15]; and (iii) informing content and interpretation of clinical audit and evaluation programmes (e.g. the newly formed Sentinel Stroke National Audit Programme (SSNAP)[16]).

To understand the factors that influence decision making about thrombolysis we need a method that allows us to understand the preferences of clinicians who are making these decisions in a way that reflects decision making in practice[17]. The DCE approach allows delineation of complex decision making pathways by characterising which factors drive the decision, the trade-offs decision makers apply across these factors and how these vary between decision makers[9]. In short, DCEs offer a route into the 'decision-making behind the decision', thereby capturing the most and least important influences in the decision pathway which other methods would fail to uncover.

Plan of investigation:

(i) Establish factors influencing decision making (determine attributes/characteristics and levels/the magnitude of these characteristics, months 1-2): we will draw upon the findings from our previous NIHR programme grant, in particular existing qualitative data from interviews with stroke clinicians[18], as well as literature review, which we will then enhance with additional semi-structured interviews focused upon early career clinicians (up to ten), to characterise a comprehensive range of likely factors influencing decision making about thrombolysis.

(ii) Create clinical scenarios and development of questionnaire (experimental design, months 3-6): A fractional factorial experimental design will combine these factors (attributes) and levels to construct a variety of hypothetical patient vignettes that will form the materials for the DCE. Clinical vignettes have been chosen to reduce cognitive burden; this narrative approach is more familiar for clinicians and therefore more engaging. The vignettes will be incorporated into a questionnaire, asking clinicians to state whether they would offer thrombolysis or not. We will also include questions on possible clinician variables (covariates) such as age, experience of thrombolysis, experience of patient intracranial haemorrhage, personality type/risk aversion[19] etc.

(iii) Online survey development (months 7-8): The DCE will be programmed into an online survey to enhance ease and speed of survey dissemination.

(iv) Pilot DCE (months 9-10): The online DCE survey will be pretested with a convenience sample of 8-10 clinicians to further test the credibility of the vignettes, examine participants' understanding of the task and to check how long it takes to complete. Pretesting will include a think aloud approach, using a subset of vignettes, to facilitate adaptation of the survey instrument.

(v) Data collection (months 11-16): Stroke physicians and emergency medicine specialists will be recruited from across the UK via the British Association of Stroke Physicians, the NHS Stroke Improvement Programme and the Society for Acute Medicine. The online survey will be administered with follow up reminders at two and four months

(vi) Analysis (months 16-19): Data will be analysed using a random utility model framework and appropriate logistic regression techniques to investigate which attributes act as barriers to, or facilitators of, the decision to offer thrombolysis and how such decisions relate to characteristics of the clinicians making those decisions.

(vii) Dissemination of findings and translation into practice (months 19-24): The findings will be used to influence clinicians' behaviour by: i) translating learning into regional professional development opportunities provided through the NHS Stroke Improvement Programme[11] and nationally through the British Association of Stroke Physicians[12] and Stroke Medicine trainees' curricula[13, 14]); (ii) supporting implementation of a recently developed decision support tool designed to inform clinical decision making and risk communication[20]; and (iii) informing the content and interpretation of clinical audit and evaluation programmes (e.g. the newly formed Sentinel Stroke National Audit Programme (SSNAP)[16]).

1.0 Background

Thrombolysis is a cost-effective treatment for acute ischaemic stroke[2, 3], but geographical variation exists in treatment rates in the UK[4] despite evidence-based guidelines[1] and licensing criteria[21]. Under current licensing criteria, clinicians have to (i) make a rapid decision about patient eligibility (treatment must be given as soon as possible within four and a half hours of symptom onset)[22] and (ii) consent the patient to treatment involving trade-off between immediate bleeding risk (intracranial haemorrhage leading to death or severe disability) and improvement in early and long-term outcome.[8]

According to the National Sentinel Stroke Audit (2011), approximately 14% of patients were eligible to receive thrombolysis with rtPA in 2010 but only 5% received it, with wide variation, even between neighbouring services [4]. Similar levels of geographical variation are seen in the most recent data in *Stroke Improvement National Audit Programme (*SINAP, January-March 2012)[5]. There is already literature which addresses reasons for the failure of clinicians to adhere to clinical practice guidelines [23-25]. Possible barriers to guideline adherence exist at different levels, from the individual and team to the system level[23], and include lack of awareness, familiarity or agreement with guidelines; sense of competence/self-efficacy; inability to overcome the inertia of previous practice; and external barriers to perform recommendations[23, 24]. Specifically in terms of thrombolysis, barriers are both structural (access to services)[4] and individual (clinician and patient-related). Because structural barriers have recently substantially reduced[4], with the roll out of 24 hours a day, seven days a week, hyperacute stroke services, there is a need to better understand the latter, that is the trade-offs that are made between different patient factors that contribute to variation in treatment decision making, and how and why decision making varies between clinicians. Factors (other than eligible patients presenting too late to secondary care) that may have a negative impact on thrombolytic treatment rates include physicians' over-estimation of rates of adverse effects and uncertainty about effectiveness[7, 26]. Unwarranted practice variation[27] is also likely to reflect ambiguous or 'grey' areas within the guidelines, licensing criteria and underpinning research evidence.

An international Delphi study of specialists, which sought to establish consensus on the relative contraindications for offering intravenous thrombolysis in acute ischaemic stroke, failed to reach consensus on factors such as age, onset time to treatment, recent medical procedures, spontaneous improvement rate and blood pressure treatment[6]. Licensing criteria currently restrict treatment to patients aged 80 years or below, but many clinicians treat over 80 year olds on the basis of observational case control studies, more recently randomised trial evidence from IST-3[28] and perceptions of the distinction between chronological and physiological age. The European Cooperative Acute Stroke Study (ECASS 3) trial[29] supported extension of the time window for treatment to 4.5 hours and the European licence time window has recently been extended[21]. According to the Safe Implementation of Thrombolysis in Stroke-Monitoring (SITS-MOST) study, it is not unusual for patients outwith licensing criteria to be treated,[30] suggesting that different clinicians are satisfied with different levels of evidence and/or vary in their decision making process given the same evidence.

Potential physician-related factors that might influence consideration of thrombolysis have been posited, and include factors such as over-estimation of the rate of adverse effects (symptomatic intracranial haemorrhage) and uncertainty about the effectiveness of thrombolysis[7, 26]. The situation is further complicated by the absence of data on outcomes as a function of individual patient characteristics and lack of consensus on relative contraindications for thrombolysis[6, 31]. Whilst the licensing criteria provide broad eligibility guidance, they do not reflect variation within the criteria in terms of potential outcomes and adverse effects; although it is clear that these will vary from patient to patient (for example related to variations in blood pressure, age, stroke severity). As others have observed "*managing uncertainty is central to clinical practice and requires the linking of experience and evidence: this places specialists at an advantage*"[32](p.139). It is important, therefore, to understand how clinician factors such as level of expertise, age, seniority, practice setting, attitude to risk[19] etc. influence the decision to offer thrombolysis. Further, there is a paucity of available tools to support individualised decision making about thrombolysis and those tools that are currently widely available have limitations in terms of their risk communication

functionality[33]. For example, the great majority of currently available tools (with the exception of the tool we have recently developed) lack detail on important outcomes, present risk data without the necessary qualifiers such as time periods and denominators, and do little to acknowledge uncertainty and to minimise framing biases[33].

Work undertaken in our NIHR programme grant (RP-PG-0606-1241)[34] to develop a thrombolysis decision analytical model has identified the most important 'clinical' patient characteristics that explain variation in outcomes and hence could better guide decision making (age, gender, onset time to treatment, systolic blood pressure, blood glucose, stroke severity, recent infarction on CT/MRI scan, previous stroke, diabetes and aspirin monotherapy, aspirin plus clopidogrel, and history of hypertension), but even this detailed model does not incorporate the full range of factors that might influence clinical decisions within the real life context of acute stroke care[20]. Additional patient factors such as prior cognitive function, prior functional ability, comorbidity and availability of social support are likely to influence decision-making[35]. Clinician-related factors such as level of expertise, personality type, fear of adverse events, recent experience of patient intracranial haemorrhage related to thrombolysis and attitude to risk, in addition to cognitive biases[36], are likely to affect decision making. Little is known about the relative importance of these factors and indeed whether or not other factors are at play here. Furthermore, some of these factors are likely to be appropriate considerations (e.g. prior functional ability), but others are likely to be less so (e.g. clinical attitude to risk, cognitive biases).

To better understand how clinicians make decisions about whether or not to offer thrombolysis, and to capture the underpinning trade-offs made, we will use a discrete choice experiment (DCE). Based on the precepts of random utility theory[37], a DCE is designed to elicit participants' preferences and the relative importance of different factors within a decision-making model[9]. DCEs assume that there is more than one factor influencing decision-making and that all choices involve trade-offs[17]. Ryan et al. (p.15)[17] observe that, since "*researchers cannot get inside the heads of these individuals* [clinicians] *and observe all factors affecting preferences*", a DCE offers a means to explore and quantify the implicit trade-offs made between multiple competing factors within a decision making scenario. This method can be used to systematically assess preferences within any given decision making scenario and thereby can be used to access the underpinning thought processes which lead to a decision about the offer of thrombolysis. Participants will be asked whether they would offer thrombolysis when given hypothetical patient vignettes, which will vary in terms of patient characteristics (attributes e.g. age, and levels, e.g. ,75-79 years, 80-85 etc.)[9], whilst other components of the survey will capture relevant clinician characteristics.

The relative importance of different attributes to the decision can be quantified and the estimated choice model used to predict the probability of offering thrombolysis given both patient and clinician characteristics[9, 10]. We are interested in factors beyond those established in earlier work and also in the trade-offs that are made between new and previously identified factors. As well as patient factors, we will also use the DCE to establish how decision making varies by clinician characteristics. A study examining variation in diagnostic decision making in heart failure (a similarly complex decision - although diagnostic rather than therapeutic - characterised by high levels of uncertainty) found that clinician characteristics, such as grade or level of seniority, influence how evidence is weighted and used to inform a diagnostic decision [32]. Based on this understanding, the DCE will be used to explore how preferences and trade-offs differ depending on clinician characteristics (e.g. clinician age, grade, clinical background, overall experience, experience with thrombolysis, personality type/risk aversion etc.).

1.1 Rationale for the DCE approach

Decision making about thrombolysis is complex, due to the time limited window for treatment, the emergency context of the decision, difficulties in obtaining consent and the many clinical factors that might influence the balance between risk and benefit for individual patients. In order to optimise decision making about thrombolysis, we need to understand how clinicians are making these decisions by accessing their underlying preferences and the trade-offs that they make. We will use the DCE method to "get into the heads" of clinicians to unpack the thought pathways and trade-offs made in decision making about thrombolysis. The DCE approach offers a means though

which the nuances of decision making can be understood, by providing insights into the, sometimes implicit, trade-offs made, which are not easily accessed through other more traditional research methods.

The DCE method is specifically designed to examine the trade-offs in a particular decision making model making it ideally suited to address our question of interest. DCEs have a strong theoretical basis in consumer choice theory, are designed using experimental design theory and estimated in a random utility theory framework. Generation of the patient vignettes using an experimental design ensures particular desirable features are "designed into the data" such as the avoidance of multi-collinearity (i.e. when two or more predictor variables in a multiple regression model are highly correlated) of the data used to estimate the choice models, meaning that the effect of each attribute can be estimated independently of the effect of other attributes. The capacity to undertake sophisticated analyses of DCEs will be drawn upon. In particular, data collected in DCEs are used to display choice (in our case of whether or not to offer thrombolysis) as a function of the attributes of the alternatives between which respondents are asked to choose (in our case the characteristics of the patient vignettes) and the characteristics of the decisions makers (the clinicians' characteristics). This makes them ideally suited to investigate which attributes described in the vignettes are important to clinicians when deciding to offer thrombolysis; which of these attributes act as facilitators to, or have a positive impact on, the decision to offer thrombolysis; and which act as barriers to, or reduce the likelihood of offering, thrombolysis. Calculation of the marginal rates of substitution between these attributes allows investigation of the rate at which clinicians would trade off one attribute for another. For example, it allows investigation of questions such as, what increase in risk would clinicians accept for a given increase in health outcome. A relevant example in the case of thrombolysis might include the degree of risk a clinician would accept for an improvement in level of dependency. The DCE will also examine variation in decision-making by clinician factors such as age, experience, clinical background and attitude to risk (using a six item version [39] of the Jackson Personality Inventory Risk-taking subscale [19]). Choice models estimated from DCEs can also be used to predict the probability with which a vignette with particular attribute levels will be chosen, or in our case, recommended for thrombolysis. DCEs are widely used in the health sector [40] including clinical decision making in areas such as clinical recommendation of contraceptive type [41]. DCEs have been undertaken in the field of stroke medicine (e.g. to explore patient preferences for early rehabilitation management)[42], but none have examined the factors that influence clinicians' decisions to offer thrombolysis.

1.2 Rationale for the current study

Stroke remains one of the leading causes of death and disability in the UK[43]. Thrombolysis with rtPA is a cost-effective treatment for acute ischaemic stroke but unwarranted geographical and inter-professional variation exists in use of thrombolysis in the UK, despite the existence of the National Stroke Strategy[43], NICE guidelines[1], licensing criteria[21] and a strong evidence base[1-3]. Such variation is unlikely to be accounted for by different patient populations, but rather by different application of decision making about offering thrombolysis, based on interpretation and understanding of patient variables on the one hand, and on variables relating to the individual decision-makers (such as experience, cognitive biases) on the other hand. The proposed study will capture information on which patient and clinician factors influence clinicians' willingness to treat ischaemic stroke patients using thrombolysis, as well as determining their level of influence. By understanding how clinicians internally and externally negotiate the often difficult trade-offs between risks and benefits in different patients, we can optimise appropriate use of thrombolysis and better support risk communication, consent and decision-making with patients. Predicted outcomes of the research will include immediate benefits for service delivery by: (i) translating learning into postgraduate training and continuing professional development; (ii) supporting implementation of a decision support tool we have recently developed to support decision-making in thrombolysis; and (iii) informing the content and interpretation of audit and evaluation programmes. As well as improving stroke patient outcomes by better supporting clinicians in the decision to offer thrombolysis with rtPA, the study is likely to lead to cost savings for the NHS by ensuring that the patients most likely to benefit, receive thrombolysis and those for whom there is an increased risk of harm do not.

2.0 Aims and Objectives

2.1 Aim
To identify what factors contribute to variation in, and influence, clinicians' decision making about intravenous thrombolysis for acute ischaemic stroke, given what is already known about the most effective and safe use of the treatment, in order to inform programmes that seek to influence clinical behaviour and decision-making.

2.2 Objectives
(i) to determine which patient factors influence clinical decision making about the offer of thrombolysis;
(ii) to identify and quantify the trade-offs clinicians make regarding the decision to offer thrombolysis;
(iii) to determine which clinical factors influence clinical decision making about the offer of thrombolysis (e.g. clinician experience, setting, personality type);
(iv) to influence clinicians' behaviour by translating learning into continuing professional development activity, national clinical guidelines, supporting implementation of an existing thrombolysis decision support tool, and informing clinical audit and evaluation programmes (SSNAP).

The study will capture information on medical judgement and choice to illuminate the decision making processes underpinning clinicians' willingness to offer thrombolysis with the overall aim of optimising care for acute stroke patients by better supporting risk communication, consent and decision-making with patients and their families.

3.0 Methods

3.1 Study Design
DCEs explore the trade-offs between competing factors within decision making by eliciting participants' preferences and the relative importance of those factors [9, 37]. The DCE will be conducted with stroke physicians and neurologists in secondary care and specialist stroke centres and will involve the following stages:

3.2 Exploratory work to establish factors influencing decision making (determining attributes & levels)
In depth exploratory work, usually involving qualitative methods and literature review, is an important first stage in a DCE to establish the attributes (characteristics of the decision making model) and levels (magnitude of those characteristics)[44]. Much of this background exploratory work, which is essential to the design of a high quality DCE, has already been undertaken as part of a NIHR programme grant[34]. We will draw on previously completed work by the project team, including existing qualitative interview data on the views and experiences of stroke clinicians about thrombolysis decision making, as well as ethnographic data collected through non participant observation and data from the usability testing of the DASH decision support tool[18, 34, 45]. Systematic review of these data will identify key influences on decision making to inform the experimental design of the DCE and will enhance external validity. We already have evidence on the broad range of patient attributes that are important (such as age, gender, history of stroke, severity of stroke (NIHSS score); stroke onset time to treatment, systolic blood pressure; diabetes; history of hypertension; blood glucose; recent infarction on CT/MRI scan; aspirin monotherapy; and aspirin plus clopidogrel) but will undertake additional qualitative interviews with non-expert clinicians (defined here as recently appointed stroke consultants) to determine the appropriate set and levels of attributes. The value of interviewing non-expert clinicians is that they may be more likely to make explicit certain aspects of decision making that a more expert clinician could take for granted and may fail to disclose.

Face-to-face, semi-structured interviews will be conducted with up to ten non-expert clinicians; these will be audio-recorded and transcribed verbatim. Our sampling strategy will be purposive to

include clinicians from the local cardiovascular network and beyond. Because thrombolysis rates are relatively high in the North East of England, we will also approach clinicians from another cardiovascular network with lower rates of thrombolysis, (based on figures from national audit reports). We will recruit five clinicians locally and five from other networks; the latter will be interviewed by telephone. Participants will be asked to reflect on their clinical experience where thrombolysis was considered, in particular they will be asked to think back to grey/borderline/difficult cases and to talk through the decision making process, trade-offs made and influencing factors. Additional prompts will include: influential factors beyond guidelines and licensing criteria; experiences of adverse events; communicating risks and benefits of thrombolysis; attitude to risk; colleagues' views and experiences; and approaches and norms within practice setting. Anonymised transcripts will be coded thematically and analysed using a framework approach[46] to establish the range of attributes (and levels) to be included in the DCE. This will be particularly important for possible 'grey' areas, such as age, where age > 80 years is a contraindication in the licensing criteria but arguments have been made that physiological/functioning age is more important than chronological age[47]. Special consideration will be given to patient factors that are not part of the underlying predictive model, such as social circumstances and prior functional status, together with other factors that may the incorporated or influence clinical decision-making (for example, better clinical expertise and perceptions of the evidence base). In short, these interviews will be used to identify any additional patient attributes and clinician related factors that might influence decision-making that are not accounted for in our existing qualitative data.

3.3 Experimental Design: A fractional factorial design will be used to combine attributes and levels to construct hypothetical patient scenarios, in the form of vignettes. The narrative format of vignettes, rather than the traditional tabular lists of attributes and levels, will be used in order to increase participant engagement[48]. For each vignette, participants will be asked whether they would offer treatment or not, rather than making a choice between two different case vignettes. To enhance validity, all scenarios will be discussed with stroke physicians in the study advisory group to ensure that they are plausible and clinically appropriate, and provide an appropriate range and variety of cases. To enhance validity (and allow comparison of model predictions to actual choices), a subsection of vignettes will be based, as closely as possible, on real cases identified through SITS-UK (thrombolysed cases only)[49] and a database of anonymised cases (both treated and non-treated) collected as part of local audit. Vignettes will include CT scans to make the scenarios as close to actual clinical situations as possible. Importantly, our experimental design will allow us to include a number of vignettes that show variation in patient factors that are likely to be most sensitive to differing decisions, that is those difficult, 'grey zone' cases.

3.4 Development of DCE survey: The vignettes will be reduced to a manageable number using experimental design techniques (fractional factorial design) and incorporated into a survey. Within the survey the case vignettes will be preceded by a series of questions on possible covariates such as clinician age, grade/seniority, experience with rtPA, experience of adverse events associated with use of thrombolysis, personality type/risk aversion (using the Jackson Personality Inventory Risk-taking subscale[19, 39]).

3.5 Programming of online version of the survey: The DCE will be programmed into an online survey to enhance ease and speed of survey dissemination (for efficiency purposes this will be outsourced to an independent company). The survey will be designed to be short, straightforward and easy to complete; usability issues will be assessed during the piloting stage.

3.6 Pilot DCE: The survey will be pretested, with a convenience sample of up to eight clinicians, to establish the clinical validity of the vignettes, examine participants' understanding and check how long the survey takes to complete[50]. This will address practical issues, such as length of the survey to avoid response fatigue[10, 37], optimal presentation of choice sets, and views on how to make the website easier to use[10]. Pretesting will include a think aloud approach[51], using a subset of vignettes, to facilitate adaptation of the survey instrument.

3.7 Data collection and Sampling: We will recruit clinicians via the British Association of Stroke Physicians (BASP, total sample size n=350) and aim to maximise response rate with reminders at two and four months. An invitation to participate, together with an information sheet, will be distributed to members of BASP with a link to the online survey. CP, who is a member (and ex-chair) of the BASP Training and Education Committee, will facilitate this approach. Whilst sampling through BASP will capture the great majority of decision makers on thrombolysis in the UK, we will extend our sample by inviting members of the BASP trainees' group to participate (once again facilitated by CP). To increase numbers and broaden representation, we also plan to circulate the invitation nationally via the cardiovascular network. To take account of diversity in how services are delivered (i.e. in some cases emergency department (ED) specialist physicians may have independent responsibility for decision making about thrombolysis), we will also distribute the invitation to participate via the Society for Acute Medicine to include ED specialists with responsibilities for thrombolysis. Importantly eligibility for participation in the survey will be defined as the potential participant having independent responsibility for decision making about thrombolysis. ED specialists involved only in discussions about the offer of thrombolysis will be excluded. To ensure that these criteria are adhered to, a question about the respondent's role in decision making will be included in the introductory questions of the survey.

Optimal sample size requirements for the limited dependent variable models of the nature estimated in DCEs depend on knowledge of the true choice probabilities, which are not known prior to undertaking the research[52]. However, previous DCE studies have shown that robust choice models can be estimated from sample sizes between 50-100 respondents.[53, 54]. Each clinician will be presented with up to 16 vignettes.

3.8 External Validity

High levels of external validity have been demonstrated in DCEs in a number of areas in which DCEs have been applied, including in health, environment, and transport settings[52, 55]. For example, in a study of physicians' prescribing decisions, stated preference responses to hypothetical scenarios were shown to align with revealed preference (i.e. preferences under simulated conditions aligned with actual behaviour)[55]. Our approach to ensuring high levels of external validity in this study is multi-fold. First, we will draw upon existing evidence from interview and ethnographic work to identify the full range of attributes (and levels) likely to influence decision making. Second, we will design the choice set to mimic as closely as possible the decision of interest. This will be in the form of a binary choice (decision to offer thrombolysis or not), as this reflects clinical practice in that clinicians are faced with one patient at a time and must decide whether or not to offer thrombolysis. Similarly vignettes (as opposed to a traditional tabular list of attributes and levels that are commonly used in DCEs) more closely reflect the way in which clinicians receive information about their patients, thereby increasing the realism of the decision task. Clinicians tend to be familiar (and likely more comfortable) with vignettes as they are regularly used in training and continuing professional development. Consequently, participating clinicians are unlikely to treat the exercise as a test and thus behave differently to how they would in the real world. That said, we will make it clear in the information sheet preceding the DCE survey that all responses will be anonymised and individuals will not be judged on their responses against guideline/licensing criteria. The importance of honest, 'uncensored' responses will be reiterated in information about the survey, as well as within the survey instrument itself. Furthermore, we will undertake in-depth pilot work to establish the clinical face and content validity, and ease of understanding and accessibility of the vignettes. The clinical members of the research team will be further involved in this important component to ensure that the vignettes in the final survey are acceptable to clinicians and possess maximal clinical face/content validity.

Stated preferences to offer/withhold thrombolysis for patients in hypothetical scenarios in the DCE will be compared with thrombolysis decisions in actual practice settings (using anonymised cases identified through local audit data (both treated and non-treated cases) and patient registries such as SITS-UK (treated cases only)[49]

3.9 Data Analysis

The data will be modelled in a random utility theory framework using limited dependent variable modelling. The decision to offer thrombolysis will be modelled as a function of the attributes of the hypothetical patient and the characteristics of the decision makers. This will allow investigation of which characteristics of the patients have a positive effect and which have a negative effect on the decision to offer thrombolysis, as well as which characteristics of the decision makers (e.g. age, experience of offering thrombolysis, attitudes to risk etc.) have a positive or negative impact on the decision to offer thrombolysis. Heterogeneity will be explored using random coefficients and scale-adjusted latent class modelling. Using the preferred model (based on goodness of fit criteria such as Akaike or Bayesian information criterion)[17], marginal rates of substitution will be calculated to quantify the rate at which decision makers are prepared to trade off one attribute for another, which also allows investigation of the relative importance, or ranking, of the characteristics of patients to the decision to offer thrombolysis[44]. Predicted probability analysis will investigate the probability of offering thrombolysis using clinically relevant values on the attribute levels.

Ideally, as part of our analyses, we would like to compare the characteristics of responders with non-respondents to detect the possibility of non-response bias. However, the possibility of such comparisons is limited as BASP do not collect demographic information about their members. Concerns about response bias will depend on overall response rates. In a previous survey conducted by one of our co-applicants and distributed though BASP a response rate of 72%[56] was achieved, indicating that a good response can be expected from clinicians with a specific interest in this area. We will design and develop the survey and invitations to maximise response rates based on best practice in survey design and drawing on the experiences of our co-applicants. In addition, we will fully describe the characteristics of responders to our survey which will allow an approximate assessment of whether or not the sample is representative of the wider population of physicians who make decisions about thrombolysis. We will also consult the Royal College of Physicians census data on the average age and gender of stroke physicians and emergency department specialists to assess the representativeness of our sample.

We will also model the population-level impact of patient-related attributes identified in the DCE as statistically significant drivers and inhibitors of decisions to offer thrombolysis, in terms of losses and gains in Quality Adjusted Life Years (QALYs) from treatment with and without thrombolysis.

QALYs for individual patients with specific attributes (stroke onset time to treatment, systolic blood pressure, diabetes, stroke severity, age, gender, prior stroke, signs of current infarction on pre-treatment scan, blood glucose, aspirin and clopidogrel, aspirin monotherapy, weight and history of hypertension) are calculated in the DASH II decision analytic model as a function of modified Rankin values (functional independence, dependence and death) at three months and with reference to life tables with actuarial data on life expectancy in terms of absolute age. Patient-related attributes (and associated levels) identified as drivers and inhibitors in the DCE (e.g., gender [male, female) and 15 mm/Hg intervals in systolic blood pressure), which are also present in the DASH II decision analytic model[34], will be used to estimate how changing the levels across each patient-related attribute (holding other levels of attributes constant in the DASH II decision analytic model using the range of levels of attributes in the DCE and/or lower quartile, median, upper quartile and modal values for patients treated with thrombolysis in the SITS-UK database) impacts on QALY gains/losses for patients treated with and without thrombolysis. In addition, this method would be used to estimate the marginal cost-effectiveness of treating patients with and without the criterion identified in the DCE.

4.0 Dissemination and projected outputs: Translating findings for patient benefit

The DCE will be used to establish which attributes described in the vignettes are taken account of by clinicians when deciding to offer thrombolysis; which of these attributes act as facilitators to, or have a positive impact on the decision to offer thrombolysis, and which act as barriers, or reduce the likelihood of offering thrombolysis; and how these influence the appropriate use of thrombolysis. These data will be used to increase *appropriate* use of thrombolysis for patient benefit by influencing clinicians' behaviour via three routes.

First, the findings will be incorporated into postgraduate training and continuing professional development about thrombolysis. This will be undertaken through the development, revision and sharing of training materials with the regional cardiovascular networks who host the NHS Stroke Improvement Programme, so that training for stroke physicians and teams can incorporate the study findings [11-14]. Results will also be presented at the British Association of Stroke Physicians annual training event. In addition, co-applicants GAF and CP will organise two national stroke thrombolysis master-classes, which will embed the vignettes into case-based learning for an audience of 50 stroke clinicians. CP is the curriculum development representative on the Stoke Medicine Specialty Advisory Committee and will ensure that the findings influence the content of the national curriculum for Stroke Medicine trainees.

Second, building on the outputs of the DASH programme grant which included the development of a decision support tool [15], the findings will be used to support implementation of decision support. In the DASH programme we have developed a risk communication and decision support tool that is available on the web, via an iPad and through an iPhone application. In pilot work this has proven highly valued by both clinicians and patients/carers as a result of its capacity to support better understanding of the risk/benefit balance based on individual clinical characteristics of patients, using an embedded high-quality decision analytical model, and via presentation of the risks and benefits using evidence-based risk communication methods. The findings of this study will enable the development of tutorial information to embed within the DASH II support tool, with the aim of optimising its use as a clinical training aid. Information on factors known to promote or inhibit clinicians' offering thrombolysis, and their appropriateness, will be included within the tutorial in order to optimise use. Providing additional information and support to clinicians will lead to better support for risk communication, consent and decision-making about thrombolysis with patients.

Third, we will link the study outputs to national clinical audit (SSNAP). Through this mechanism it is possible that the study findings can be used to determine whether additional data items (e.g. use of decision support tools; records of thrombolysis training) should be routinely collected about thrombolysis at a national level and they will also help in the interpretation of the findings of the national audit.

The findings will also be disseminated as conference presentations, peer reviewed papers and reports to the Stroke Research Network, the Intercollegiate Stroke Working Party and the Royal College of Physicians in order to be considered for inclusion in the National Clinical Guidelines.

5.0 Plan of investigation and timetable

Significant Milestones

Month 1: Approvals from Newcastle University and Research and Development Departments of the relevant trusts
Month 2: Exploratory work completed
Month 6: Experimental design and survey produced
Month 8: Program online version of the survey
Month 10: Pilot work completed
Month 16: Data collection completed
Month 19: Analysis completed
Month 24: Translating findings for patient benefit and dissemination phase completed

6.0 Project management

The study will be conducted in accordance with the Research Governance Framework for Health and Social Care under the guidance of our Project Advisory Group. The Project Advisory Group (including all members of the research team, plus three independent members, one of whom will act as chair) will meet six times during the study period to provide advice on the study design, interpretability of the survey and issues relating to sampling, interpretation and dissemination of the study findings (EL will participate by teleconference/Skype). The Project Advisory Group is composed of all members of the research team (three stroke physicians, each contributing complementary expertise; three health economists; a health psychologist and a research leader in

the field of shared decision making) working alongside four independent experts and representatives from the Stroke Research Network, North East Cardiovascular Network, the Stroke Association and the Society for Acute Medicine. Collaboration with emergency medicine specialists will provide opportunities to gain insights into alternative models of service delivery.

A smaller core group (the project management group) will meet more frequently to address issues as they arise and to feed into all stages of the DCE with an increased frequency of meetings during the design and analysis phases. Importantly, the project management group will include two patient/carer representatives who will be invited to attend all project management meetings and will advise on issues relating to commenting on the design of DCE, the range of scenarios included and their presentation; hosting of the DCE including review of information and consent text for participants; critique of the web user interface; and dissemination strategies. On a day to day basis the research associate will be accountable for project management, under the supervision of LT, DF and EL, and will draw on good communications with the wider advisory group to update on progress and milestones achieved.

7.0 Ethical Issues

According to the most recent guidance on governance arrangements for research ethics committees [57] it is not within the scope of an NHS Research Ethics Committee to review or give an opinion on research projects involving only clinicians. Since no "potential research participants will be identified from, or because of, their past or present use of the services" nor will they be identified from "their status as relatives or carers of past or present users of these services", NHS ethical approval is not required (p.9)[57]. Approval will, however, be obtained from the Research and Development Departments of the relevant trusts for the interviews in the exploratory phase of the DCE. In addition, approval will be sought from the Newcastle University Research Ethics Committee.

With regard to this initial exploratory phase to inform design of the DCE, written consent will be obtained in advance from clinicians. All potential participants will be provided with information about the study and there will be an opportunity to address questions to the researchers prior to participation. They will be informed that their participation is entirely voluntary and that they are free to withdraw at any time without reason. With regard to the DCE survey, an information screen will precede the online survey, which will include a brief project description, and participants will be made aware that their consent is implied through completion of the survey. All personal identifiers will be removed to protect anonymity.

Newcastle University requires that primary research data should be held for 10 years. Storage arrangements for all relevant data materials will be in accordance with the Data Protection Act 1998 and with the University Information Security Guidelines. Should the researchers become privy to any information that would indicate malpractice or misconduct, or suggest that any individual was in danger of harm, this information will be disclosed to the appropriate personnel. A statement to this effect will be included in the information sheets and consent forms.

8.0 Public and Patient Involvement

Our earlier work, which will shape the design of the DCE, was heavily informed by the involvement of stroke service users; for example, patients/family members were involved in development of the decision support tool for thrombolysis in the NIHR programme grant[34]. Two patient/carer representatives from the Patient, Carer and Public Involvement Panel of the Stroke Research Network will be recruited to the project management group to advise on all aspects of the study (not simply the consultation and dissemination phases). Based on INVOLVE guidance[58], patient and carer representatives will be compensated for their time spent preparing for and attending eight project management meetings. By linking with the North East Stroke Research Network, The Stroke Association and the North East Cardiovascular Network, the views of stroke service users and their carers will be embedded throughout the project; representatives from each organisation will be invited to join our broader Project Advisory Group.

The proposal was reviewed by the Patient, Carer and Public Involvement Panel within the Stroke Research Network and the NIHR Stroke Research Network Acute Clinical Study Group (which has patient/public representatives).

9.0 Funding

This work is funded by the National Institute for Health Research Health Services and Delivery Research Programme: Project 12/5001/45.

References

1. National Institute for Health and Clinical Excellence. *Alteplase for the treatment of acute ischaemic stroke, NICE technology appraisal guidance 122*, 2007.
2. The Third International Stroke Trial (IST-3) collaborative group. *The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial.* Lancet, 2012. **379**: p. 2352-63.
3. Wardlaw, J.M., Murray, V., Berge, E., del Zoppo, G., Sandercock, P., Lindley, R.L., Cohen, G. *Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis.* Lancet, 2012. **379**: p. 2364-72.
4. Royal College of Physicians Intercollegiate Stroke Working Party. *National Sentinel Stroke Clincial Audit 2010, Round 7. Public Report for England, Wales and Northern Ireland.* 2011.
5. Royal College of Physicians. *SINAP-latest results, January - March 2012*. Available from: http://www.rcplondon.ac.uk/latest-results.
6. Dirks, M., Niessen, L.W., Koudstaal, P.J., et al. the members of the Delphi panel on indications and contraindications for intravenous thrombolysis in acute ischaemic stroke, *Intravenous thrombolysis in acute ischaemic stroke: from trial exclusion criteria to clinical contraindications. An international Delphi study.* J Neurol Neurosurg Psychiatry, 2007. **78**: p. 685–689.
7. Kwan J, H., Sandercock P. *A systematic review of barriers to delivery of thrombolysis for acute stroke.* Age Ageing, 2004. **33**: p. 116-21.
8. Ciccone, A. *Consent to thrombolysis in acute ischaemic stroke: from trial to practice.* Lancet Neurology, 2003. **2**(6): p. 375-8.
9. Louviere, J.J., Lancsar, E. *Choice experiments in health: the good, the bad, the ugly and toward a brighter future.* Health Economics, Policy and Law, 2009. **4**: p. 527–546.
10. van Helvoort-Postulart, D., van der Weijden, T., Dellaert, B.G.C., de Kok, M., von Meyenfeldt, M.F., Dirksen, C.D. *Investigating the complementary value of discrete choice experiments for the evaluation of barriers and facilitators in implementation research: a questionnaire survey.* Implementation Science, 2009. **4**: p. 10.
11. NHS Stroke Improvement Programme. [Accessed 26th June 2012]; Available from: http://www.improvement.nhs.uk/stroke/.
12. British Association of Stroke Physicians (BASP). [4th July 2012]; Available from: www.basp.ac.uk.
13. Joint Royal Colleges of Physicians Training Board. J. *Stroke Medicine (Sub Specialty), Curriculum and Assessment*. [Accessed 16th July 2012]; Available from: http://www.jrcptb.org.uk/specialties/st3-spr/pages/stroke-medicine.aspx.
14. Royal College of Physicians. *National Clinical Guidelines for Stroke*. [16th July 2012]; Available from: http://www.rcplondon.ac.uk/resources/stroke-guidelines.
15. Flynn, D., Nesbitt, D., McMeekin, P., Kray, C., Stobbart, L., Ford, G.A., Rodgers, H., Price, C., Thomson, R.G. *Development and Testing of a Computerised Decision Support and Risk Communication Tool for Thrombolytic Treatment in Acute Stroke Care*, in *6th International Shared Decision Making Conference: Bridging the gap between research and practice: patient pull or clinician push?*2011: Maastricht, The Netherlands.
16. Royal College of Physicians. *Sentinel Stroke National Audit Programme (SSNAP)*. 2012; Available from: https://audit.rcplondon.ac.uk/sentinelstroke/page/page.aspx?pc=welcome.
17. Ryan, M., Gerard, K., Amaya-Amaya, M. *Using Discrete Choice Experiments to Value Health and Health Care*2008, Dordrecht: Springer.
18. Murtagh, M.J., Burges-Watson, D., Jenkings KN, Lie MLS, Mackintosh JE, Ford, G.A., Thomson, R.G. *Situationally-sensitive knowledge translation and relational decision making in hyperacute stroke: a qualitative study* PLoS ONE, 2012. **7**(6): p. e37066.
19. Paunonen, S.V., Jackson, D. N. *The Jackson Personality Inventory and the five-factor model of personality* Journal of Research in Personality, 1996. **30**(1): p. 42-59.
20. Flynn, D., McMeekin P., Ford, G.A., et al. *Development of a decision analytic model (DAM) to support decision making and risk communication for thrombolytic treatment in acute stroke care.* Cerebrovasc Dis, 2011. **31**(2): p. 34.

21. Boehringer Ingelheim. *Press release Arvice: Stroke. Boehringer Ingelheim gains approval of extended 4.5 hour time-window for Actilyse® in acute ischaemic stroke for majority of EU countries*. 2011 [26th July 2012]; Available from: http://www.boehringeringelheim.com/news/news_releases/press_releases/2011/04_november_2011_alteplase.html.
22. Hacke, W., Kaste, M., Bluhmki, E., et al. for the ECASS Investigators, *Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke.* The New England Journal of Medicine, 2008. **359**(13): p. 1317-29.
23. Grol, R., Grimshaw, J. *From best evidence to best practice: effective implementation of change in patients' care.* Lancet, 2003. **362**(9391): p. 1225-30.
24. Cabana, M.D., Rand, C.S., Powe, N.R., Wu, A.W., Wilson, M.H., Abboud, P.A., Rubin, H.R. *Why don't physicians follow clinical practice guidelines? A framework for improvement.* JAMA 1999. **282**(15): p. 1458-65.
25. Meurer, W.J., Majersik, J.J., Frederiksen, S.M., Kade, A.M., Sandretto, A.M., Scott, P.A. *Provider perceptions of barriers to the emergency use of tPA for Acute Ischemic Stroke: A qualitative study.* BMC Emergency Medicine, 2011. **11**(5).
26. Brown, D.L., Barsan, W.G., Lisabeth, L.D., Gallery, M.E., Morgenstern, L.B. *Survey of emergency physicians about recombinant tissue plasminogen activator for acute ischemic stroke.* Ann Emerg Med, 2005. **46**: p. 56-60.
27. Mulley, A.G. *Inconvenient truths about supplier induced demand and unwarranted variation in medical practice.* BMJ, 2009. **20**(339): p. b4073.
28. Sandercock, P., Lindley, R., Wardlaw, J., Dennis, M., Innes, K., Cohen, G., Whiteley, W., et al.; the IST-3 collaborative group. *Update on the third international stroke trial (IST-3) of thrombolysis for acute ischaemic stroke and baseline features of the 3035 patients recruited.* Trials, 2011. **12**: p. 252.
29. Bluhmki, E., Chamorro, A., Dávalos, A., Machnig, T., Sauce, C., Wahlgren, N., Wardlaw, J., Hacke, W. *Stroke treatment with alteplase given 3·0—4·5 h after onset of acute ischaemic stroke (ECASS III): additional outcomes and subgroup analysis of a randomised controlled trial.* The Lancet Neurology, 2009. **8**(12): p. 1095-1102.
30. Toni, D., Lorenzano, S., Puca, E., Prencipe, M. *The SITS-MOST registry.* Neurol Sci, 2006. **27**: p. S260–S262.
31. Lees, K.R., Bluhmki, E., Kummer, R., Brott, T.G., Toni, D., Grotta, J.C., et al. *Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS and EPITHET trials.* Lancet, 2010. **375**: p. 1695-1703.
32. Hancock, H.C., Mason, J.M., Murphy, J.J. *Using the method of judgement analysis to address variations in diagnostic decision making.* BMC Research Notes, 2012. **5**: p. 139.
33. Flynn, D., Murtagh, M., Stobbart, L., Rodgers, H., Ford, G.A., Thomson, R.G., *A Review of Decision Support Interventions for Thrombolysis in Acute Stroke.* Cerebrovascular Diseases, 2010. **29**(Suppl 2): p. 208.
34. Ford, G.A., Rodgers, H., Thomson, R., et al., *Development and evaluation of hyperacute services for patients with acute stroke.* NIHR Programme Grant, RP-PG-0606-1241, 2007-2012.
35. Flynn, D., van Schaik, P., van Wersch, A., et al., *Non-medical influences upon medical decision-making and referral behaviour: an annotated bibliography*2003, Westport, CT: Prager Publishers.
36. Tverskey, A., Kahneman, D., *Judgement under uncertainty: heuristics and biases.* Science, 1972. **185**: p. 1124-31.
37. Ryan, M., Gerard, K., *Using discrete choice experiments to value health care programmes: current practice and future research reflections.* Applied Health Economics and Health Policy, 2003. **2**(1): p. 55-64.
38. Bachmann, L.M., Mühleisen, A., Bock, A., ter Riet, G., Held, U., Kessels, A.G.H., *Vignette studies of medical choice and judgement to study caregivers' medical decision behaviour: systematic review.* BMC Medical Research Methodology, 2008. **8**: p. 50.
39. Pearson, S.D., Goldman, L., Orav, E.J., Guadagnoli, E., Garcia, T.B., Johnson, P.A., Lee, T.H., *Triage decisions for emergency department patients with chest pain: do physicians' risk attitudes make the difference?* J Gen Intern Med, 1995. **10**(10): p. 557-64.
40. de Bekker-Grob, E.W., Ryan, M. & Gerard, K. , *Discrete choice experiments in health economics: a review of the literature.* Health Economics 2012. **21**: p. 145-172.
41. Knox, S.A., Viney, R., Street, D., Haas, M., Fiebig, D.G., Weisberg, E., Bateson, D. , *What's good and bad about contraception? A comparison of the values placed on features of contraceptive products by women consumers and GP providers.* PharmacoEconomics (forthcoming), 2012.
42. Laver, K., Ratcliffe, J., George, S., Lester, L., Walker, R., Burgess, L., Crotty, M., *Early rehabilitation management after stroke: what do stroke patients prefer?* J Rehabil Med, 2011. **43**(4): p. 354-8.
43. Department of Health, *National Stroke Strategy*, 2007.
44. Lancsar, E., Louviere, J., *Conducting Discrete Choice Experiments to Inform Healthcare Decision Making: A User's Guide.* Pharmacoeconomics, 2008. **26**(8): p. 661-677.

45. Mackintosh, J.E., Burges-Watson, D., Lie, M.L.S. et al. *Patient Perspectives on decision making about thrombolysis in the hyperacute stroke setting*. in *5th International Shared Decision Making Conference*. 2009. Boston.
46. Pope, C., Ziebland, S., Mays, N., *Qualitative research in health care: Analysing qualitative data* BMJ, 2000. **320**: p. 114-6.
47. Ford, G.A., *Current controversies: thrombolysis for patients with acute ischaemic stroke aged over 80.* Journal of the Royal College of Physicians Edinburgh, 2010. **40**: p. 49-53.
48. Ryan, M., *Discrete choice experiments in health care.* British Medical Journal, 2004. **328**(14): p. 360-361.
49. Safe Implementation of Treatment- International Stroke Thrombolysis Registry (SITS-ISTR). July 18th 2012]; Available from: https://sitsinternational.org/.
50. Ratcliffe, J., Buxton, M., McGarry, T., et al., *Patients' preferences for characteristics associated with treatments for osteoarthritis.* Rheumatology, 2004. **43**(3): p. 337-45.
51. Ericsson, K., Simon, H., *Verbal reports as data* Psychological Review, 1980. **87**(3): p. 215–251.
52. Louviere, J.J., Hensher, D.A., Swait, J.D. , *Stated choice methods analysis and application* 2000, Cambridge Cambridge University Press.
53. King, M., Hall, J., Lancsar, E., et al., *Patient preferences for managing asthma: Results from a discrete choice experiment Health Economics*, 2007. **16**: p. 703-717.
54. Ratcliffe, J., *Public preferences for the allocation of donor liver grafts for transplantation. Health Economics* 2000. **9**: p. 137-48.
55. Mark, T., Swait, J., *Using stated preference and revealed preference modelling to evaluate prescribing decisions.* Health Econ, 2004. **13**(6): p. 563-73.
56. Rodgers, H., Dennis, M., Cohen, D., Rudd, A. , *British Association of Stroke Physicians: benchmarking survey of stroke services* Age Ageing, 2003. **32**(2): p. 211-7.
57. DH Research and Development Directorate (England) National Institute for Social Care and Health Research (Wales) Chief Scientist Office (Scotland) R&D Division Public Health Agency (Northern Ireland), *Governance arrangements for research ethics committees: a harmonised edition*, 2011, Department of Health: London.
58. INVOLVE, *A guide to reimbursing and paying members of the public who are actively involved in research.* http://www.invo.org.uk/pdfs/completepaymentguideupdated060509.pdf, 2009.
59. van Schaik, P., Flynn, D., van Wersch, A,. Douglass, A., Cann, P., *Influence of Illness Script Components and Medical Practice on Medical Decision Making. .* Journal of Experimental Psychology: Applied, 2005. **11**(3): p. 187–199.