Testing the feasibility of a **CO**ro**N**ary a**N**gioplasty d**EC**ision **T**ool **(CONNECT)**

A cluster randomised controlled feasibility study of CONNECT: a patient decision aid designed to improve the quality of shared decision-making for planned coronary angioplasty.

Registration: ISRCTN13802038

Statistical Analysis Plan Version 1

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1. Introduction

This statistical analysis plan (SAP) is written in conjunction with the International Conference on Harmonisation topic E9 [1] and trial documents (Protocol, case report form (CRF) and Data Validation Specifications). The SAP will guide the statistician during the statistical analysis of all quantitative outcomes in order to answer the objectives of the study.

1.1. Background and rationale

Patient Decision Aids (PtDAs) are evidence-based interventions known to be effective in improving the quality of shared decision-making.

The CONNECT feasibility study is a cluster randomised controlled feasibility study with an embedded qualitative study. Eight clusters (NHS Trusts providing planned coronary angioplasty in England) will be recruited and randomised to the control or intervention arm at a 1:3 allocation ratio. Six clusters will implement a digital Patient Decision Aid 'CONNECT' and two clusters will provide usual care only. Questionnaires will be administered before and after delivery of intervention or control.

The overarching aim of this study is to determine whether it is feasible to conduct a cluster Randomised Controlled Trial (c-RCT) to test the effectiveness of CONNECT for improving shared decision-making for patients with stable angina.

The quantitative and qualitative data collected will enable us to assess:

1) the feasibility of delivering CONNECT in the planned coronary angioplasty patient pathway;
2) explore the acceptability of CONNECT to patients and cardiology teams;
3) assess the feasibility and acceptability of trial procedures.

1.2. Objectives

The primary objective of this study is to determine the feasibility of proceeding to a definitive trial.

We will achieve this aim by the completion of the following objectives:

1) Determine the feasibility of recruitment and retention.
2) Evaluate willingness to be randomised.
3) Determine diversity and inclusivity of sample.
4) Explore the characteristics and appropriateness of questionnaires as outcome measures for c-RCT.
5) Estimate the Intra-cluster Correlation Coefficient and sample size calculation for a c-RCT.
6) Explore the practical implementation of CONNECT.
7) Evaluate the acceptability of CONNECT and study procedures.

2. Study Methods

2.1. Trial design

This is a two group, unblinded, multi centre, parallel cluster randomised controlled feasibility study with an embedded qualitative study. Clusters will be NHS Trusts that provide planned coronary angioplasty treatment for adults. Eight clusters will be recruited and randomised to the control or intervention arm at a 1:3 allocation ratio. Participants (n=320; 40 per cluster) will be patients with stable angina who are on the waiting list for planned coronary angioplasty or planned diagnostic coronary angiography with the potential to proceed immediately to treatment with coronary angioplasty ("angio query proceed"). Participants recruited from clusters in the intervention arm will receive the digital PtDA 'CONNECT'. Participants recruited from clusters in the control arm will

receive usual care. Questionnaires will be administered before and after delivery of intervention or control.

2.2. Randomisation

The eight Cardiology Departments are the units of analysis and will be randomised using stratified block randomisation with an allocation ratio of 3:1 to the intervention group and block size of four. Cardiology Departments will be stratified as appropriate, by factors such as the presence, or absence, of on-site surgical provision.

There will be no blinding, as the intervention will be delivered by the research nurse and cardiology teams. Randomisation will be conducted by the study statistician (RS) and the statistician will conduct the randomisation blinded.

2.3. Sample size

2.3.1. Pilot trial sample size

From each cluster a non-probability sample of 40 consecutive patient participants (320 in total) will be recruited. A formal power calculation is not required for a feasibility study as testing intervention effectiveness is not the aim. However, the sample size should be sufficient to estimate the uncertain critical parameters: Standard Deviation (SD) of the primary outcome, recruitment/consent rates, ICC and the average cluster size needed to inform the design of the future full-scale c-RCT with sufficient precision. A minimum of 8 clusters in total is needed to best estimate the ICC [2]. Using Swiger's formula for the variance of the ICC [3], the precision gain of the ICC estimate diminishes after 30-50 patients per cluster. As more clusters with fewer patients is preferred, an average of 40 patients from each cluster will be recruited, leading to a total sample of 320 patients. Allowing for a median consent rate of 70% [4], a total of 457 patients will be approached to participate, approximately 57-58 per cluster. This sample size will be efficient to estimate the feasibility outcomes.

On average, each cluster will have 5-10 cardiologists, who will see about 400-1000 patients per year. Approximately 30,500 patients per year have planned CA for stable angina. There are 98 UK NHS cardiac centres that perform CA. This suggests, on average, 312 patients are eligible per cluster. Accounting for a median consent rate of 70% [4], 218 patients could be consented in one year. Therefore, 40 patients per cluster within 12 months should be feasible.

2.3.2. Full trial sample size

For the anticipated primary clinical outcome (Decisional Conflict Scale) at follow up, the ICC for patients treated within the same site will be estimated using a marginal or random effects model.

At present, we have no valid or reliable estimates for the critical parameters for the sample size calculation for the future c-RCT (hence the need for this feasibility study). However, assuming an ICC of 0.05 [5] and an effect size of 0.3-0.4 for the anticipated primary outcome [6,7], preliminary estimates suggest the full c-RCT with 90% power, significance level of 5% (two-sided) and allowing for variable cluster size, between 24 to 42 clusters would be needed, with an average cluster size of 40 patients per year, equating to 914 to 1618 patients in total.

2.4. Framework

This study will use a precision framework.

2.5. Statistical Interim analyses and stopping guidance

This study has no planned interim analysis or early stopping.

2.6. Timing of final analysis

Analysis will be conducted when all data is in house and has been checked.

2.7. Outcomes

2.7.1. Feasibility outcomes

See section 1.2

2.7.2. Clinical outcomes

The patient questionnaires:

- The Decisional Conflict Scale
- Angioplasty Knowledge questionnaire
- Preparation for Decision-Making Scale (10-item version)
- Perceived Involvement in Care Scale

2.7.3. Overview of feasibility study uncertainties and outcomes

Table 1: Overview of feasibility study uncertainties and outcomes

Uncertainty	Outcomes
Feasibility of cluster recruitment and their willingness to participate	• Number of Cardiology Departments approached, the number of responses to the 'Expression of Interest', and the number willing to participate. • Recruitment rate (Number of Cardiology Centres recruited in 4 months).
Feasibility of patient participant recruitment and retention	• Number of eligible patient participants, approached, consented, and recruited. • Recruitment rate (Number of patients recruited per month, per site). • Retention rate, defined as the proportion completing the anticipated primary outcome questionnaires (Decisional Conflict Scale questionnaire at T2). • Attrition (loss of participants who were assigned to intervention or control). • Rates of MACE and hospital readmission within 30-days of discharge.
Diversity and inclusivity of sample	• Characteristics of Cardiology Departments: geographical location, Index of Multiple Deprivation (IMD), size of cardiology workforce, presence or absence of on-site surgical cover, annual volume of planned angio/coronary angioplasty procedures. • Patient participant demographics: age, gender, ethnicity, level of social support, health and E-literacy, cardiac diagnosis, co-morbidities. • Number of non-English speaking participants requiring interpreter services (verbal and/or translation of documents). • Number of participants without access to digital technology (including smartphones, tablets, laptops, and the internet).
Characteristics and appropriateness of questionnaires as outcome measures in the future c-RCT	• Response rate (Number of participants who completed and returned the questionnaires divided by number of participants in the sample). • Item response rate (Number of valid responses divided by total number of responses requested).
Intra-cluster Correlation Coefficient (ICC) and sample size calculation for full scale c-RCT	• Estimate of the ICC of the Decisional Conflict Scale at T2 using a marginal or random effects model. • The full c-RCT sample size will be calculated based on estimates of the effect size (alongside previous research), the standard deviation and the ICC from the anticipated primary outcome analysis.

Practicality of implementing CONNECT in NHS settings	CONNECT implementation:
	• Number of participants who access CONNECT.
	• Percentage of pre-assessment clinic visits in which the CONNECT summary was used during the consultation.
	• Qualitative analysis of training session minutes and interview transcripts to summarise:
	  ○ Potential variations in usual-care patient pathway for planned coronary angioplasty.
	  ○ Practicalities of providing a digital PtDA in the NHS.
	  ○ Barriers and enablers to integrating the CONNECT summary.

Reasons for non-consent to study participation	Qualitative analysis to summarise: • Reasons for Cardiology Departments nonparticipation. • Reasons for patient nonparticipation.

Uncertainty	Outcomes
Acceptability of CONNECT and study procedures	Qualitative analysis of interviews to explore: • Self-reported adherence to CONNECT and how it was used by patients at home and during the pre-assessment clinic. • Barriers and enablers to recruitment and using CONNECT at home and during pre-assessment clinic. • Understanding, appropriateness, and potential burden of questionnaire completion.

2.7.4. Data collected and timing of outcomes

Measures	Enrolment	Baseline (T1)	Post Pre-Assessment (T2)
Brief Health Literacy Screening Tool (Chew et al 2004)	X		
eHealth Literacy Scale (Norman & Skinner 2006)	X		
Decisional Conflict Scale (O'Connor, A. 2010)		X	X
Coronary Angioplasty Knowledge questionnaire. (Researcher Team generated)		X	X
Preparation for Decision-Making Scale (Bennett et al. 2010)			X
Perceived Involvement in Care Scale (Lerman et al. 1990)			X

Enrolment: After informed consent for study participation.
Baseline: Before using CONNECT at least 1 week before Pre-Assessment Clinic.
Post Pre-Assessment Clinic: After pre-assessment, but before coronary angio/angioplasty procedure.

Data collected:

Study logs: Patient identification Log, Screening Log, Enrolment/Withdrawal Log, and Pre-Assessment Log.

Participant demographic and clinical details: age, sex, ethnicity, live alone, employment status, internet access, scheduled procedure and treatment received, MACE, 30-day readmission after procedure, CAD presentation, CV history, smoking status, presence of comorbidities.

Health literacy questionnaires (n=2): BRIEF 3-item health literacy tool, 8-item eHealth Literacy Scale.

Timepoint 1 patient reported questionnaires (n=2): 9-item knowledge questionnaire, 10-item decisional conflict scale.

Timepoint 2 patient reported questionnaires (n=4): Repeated knowledge questionnaire with 4 extra questions about access to information and CONNECT, repeated 10-item decisional conflict scale, 10-item preparation for decision making scale, 13-item perceived involvement in care scale.

CONNECT use: Google analytics data.

3. Statistical Principles

3.1. Confidence intervals and P-values

As the trial is a pragmatic parallel group RCT data will be reported and presented according to the CONSORT 2010 statement [8] and the CONSORT extension for pilot and feasibility studies [9]. As a pilot/feasibility study the main analysis will be mainly descriptive and focus on confidence interval estimation and not formal hypothesis testing. Results will be presented with their associated 95% confidence intervals. As this is a feasibility study and it's not powered to detect differences, P- values will not be used.

No methods for multiplicity adjustment will be used in this study.

3.2. Adherence and Protocol Deviations

Adherence to CONNECT will be defined as: The percentage of patient participants in the intervention arm who report being able to successfully access CONNECT. This will be determined from the pre-assessment clinic study log.

A further secondary adherence measure will be the percentage of patient participants who take the personal summary to the pre-assessment consultation. We will present appropriate summary statistics for the rate of adherence in the intervention arm.

In addition, there will be google analytics data which will also be analysed to help determine adherence. This data will include:

- Number of visits to the website (in total or for a particular month/ period of time).
- Average time spent on the website.
- Average time spent on different sections of the website.
- The most viewed parts of the website.
- The section of the website where people leave (customer journey end).

3.3. Analysis populations

The Intention To Treat (ITT) population includes all patients for whom consent is obtained and who are randomised to treatment. This is the primary analysis set and endpoints will be summarised for the ITT population unless stated otherwise.

The Per Protocol (PP) population includes all patients who accessed CONNECT on the treatment arm. This is a secondary analysis set.

3.4. Withdrawal/Follow up

As a study progresses there may be a change in participants preferred level of participation. A participant may decide that they no longer wish to contribute with the study and cease involvement in any ongoing data collection. Participants may also be withdrawn from the study by the research or clinical care team due to clinical deterioration (e.g., hospitalisation). In these scenarios, data that has already been collected before change of status/withdrawal will be analysed unless participants specifically ask for it to be deleted. Any change of status/withdrawal will be recorded (date of withdrawal, reason and type of withdrawal) in the site Case Report Form and the Chief Investigator informed. As this is a feasibility study, participants who have a change of status/or are withdrawn will not be replaced. The number and percentage of patients withdrawing will be reported (as a proportion of all patients withdraw) by randomised group.

3.5. Baseline patient characteristics

The baseline demographics and clinical characteristics of the patients will be reported. For the continuous variables (e.g. age) either mean and SD will be presented or median and inter quartile range (IQR) depending on the distribution of the data. The number of observations used in each calculation will be presented alongside the summaries.

All baseline summaries will be presented in appropriate tabular form.

Data will be collected on the following: age, sex, ethnicity, health and digital literacy level, live alone, employment status, internet access, CAD presentation, CV history, smoking status, and presence of comorbidities.

4. Analysis

4.1. Analysis methods

As this is a feasibility study the main analysis will be predominantly descriptive and focus on confidence interval estimations rather than formal hypothesis testing. The baseline demographics and clinical characteristics of the patients will be reported overall and by randomised group. For the continuous variables (e.g., age) either mean and SD will be presented or median and inter quartile range (IQR) depending on the distribution of the data. The number of observations used in each calculation will be presented alongside the summaries.

We will look at differences between groups for the anticipated primary outcome (Decisional Conflict Scale). A random effects model (or another appropriate method) will be used to estimate the difference between the two treatment groups adjusting for age, sex, health literacy score, living alone, health burden (number of co-morbidities) and baseline decisional conflict scale score as fixed effects and hospital as a random effect to account for clustering. This difference and its associated 95% confidence interval will be used to check that the likely effect is within a clinically relevant range (as confirmation that it is worth progressing with the full trial) and to inform the sample size calculation for the definitive study as outlined previously. Similar analyses will be conducted for other secondary endpoints.

For the anticipated primary outcome (Decisional Conflict Scale) at follow up, the ICC for patients treated with the same site will be estimated using a marginal or random effects model.

The mean/median for anticipated primary and secondary outcomes (e.g. Coronary Angioplasty Knowledge questionnaire) at baseline and post-pre-assessment (along with its variability) will be reported for all participants.

4.1.1. Stop go criteria

Details of the ‘Stop’/'Change'/’Go’ criteria derived from data collected in this feasibility study will determine progression to a future large-scale evaluation (c-RCT).

Below is a table of the revised progression Criteria for the CONNECT feasibility study. The criteria were agreed with the study advisory group (SAG) prior to starting recruitment. These criteria will be used to determine whether a full c-RCT would be feasible.

Progression Criteria	**Green-Go**	**Amber-Maybe**	**Red-Stop**	**Proposed action if Amber targets are attained**
Cluster recruitment targets: Number of Cardiac Centres recruited in the first 3 months of the study.	8	5-7	≤4	Review reasons for non-participation on EoI document and consider alternative strategies.

Progression Criteria	Green-Go	Amber-Maybe	Red-Stop	Proposed action if Amber targets are attained
Patient recruitment targets: Average number of patients recruited per month, per cluster.	3+	2	≤1	Review recruitment processes and reasons for non-consent. Consider alternative strategies.
Adherence targets: % of the patient sample who access CONNECT before pre-assessment clinic. *	60%+	25%-60%	<25%	Review qualitative data for reasons for non-adherence. Consider strategies to improve CONNECT engagement. Consider developing a non-digital version of CONNECT if non-adherence is largely due to low digital literacy levels.
Retention targets: % of the patient sample who complete the study.	80%+	60%-80%	<60%	Review attrition reasons and identify strategies to prevent before full c-RCT.
Willingness to be randomised: % of Cardiac Centres who responded to the EOI that are willing to be randomised in the future c-RCT.	80%	60%-80%	<60%	Review reasons for non-participation on EoI document and consider alternative strategies and/or trial designs, such as delayed-intervention trial.
Anticipated Primary Outcome acceptability: Average % item completion of the Time Point 2 Decisional Conflict Scale questionnaire. †	80%+	60%-80%	<60%	Review the outcome measures with PPI group and revise ahead of c-RCT.
Patient and Cardiology Health Professional acceptability of CONNECT and study procedures.	-	-	-	Review qualitative data on patient and cardiology health professional acceptability of CONNECT.
Adverse events: Adverse events linked to using CONNECT.	-	-	-	There are no known serious adverse events linked to using a patient decision aid such as CONNECT. We will review any patient-reported negative effects of using CONNECT during the pre-assessment clinic. Treatment may continue without the use of CONNECT.

**Based on data from a study that found 62% patient uptake of a smartphone app to self-test vision (Korot E, Pontikos N, Drawnel FM, Jaber A, Fu DJ, Zhang G, Miranda MA, Liefers B, Glinton S, Wagner SK, Struyven R, Kilduff C, Moshfeghi DM, Keane PA, Sim DA, Thomas PBM, Balaskas K. Enablers and Barriers to Deployment of Smartphone-Based Home Vision Monitoring in Clinical Practice Settings. JAMA Ophthalmol. 2022 Feb 1;140(2):153-160. doi: 10.1001/jamaophthalmol.2021.5269).*

†Based on data from a Randomised Controlled Trial of a patient decision aid for angina, in which the lowest item response rate for the post-visit decisional conflict scale (DCS) was 83% (21 responses missing for the Effective subscale of the DCS; total sample n=124). Coylewright M, Dick S, Zmolek B, et al. Percutaneous Coronary Intervention Choice Decision Aid for Stable Coronary Artery Disease: A Randomized Trial. Circulation Cardiovascular quality and outcomes 2016 2016/11/03. DOI: 10.1161/circoutcomes.116.002641.

This information along with the acceptability of the study design and protocol to patients; patient recruitment and attrition/retention rates will enable us to determine whether or not the definitive c-RCT is feasible.

There are no planned sensitivity or subgroup analyses.

4.2. Missing data

As this a feasibility study, no methods to deal with missing data will be used.

We will report the number of patients who had complete data for each of the key parameters (each outcome measure) for each time-point by treatment group and overall.

For patient questionnaires, the item response rate at each visit (Enrolment, T1, T2) will be reported. Response rate will be measured as a fraction of the total number of items.

4.3. Additional analyses

There will be no additional analyses.

4.4. Harms

It will be the responsibility of the local PI to report any adverse events and escalate to the Chief Investigator as required. The occurrence of an adverse event caused by being in the intervention or control seems very unlikely.

We will record MACE, (acute myocardial infarction, death due to a cardiac or unknown cause, emergency revascularization, ventricular arrhythmia, or cardiogenic shock) that participants may suffer as a complication of treatment with “angio query proceed” or planned coronary angioplasty and hospital readmission within 30 days of treatment. However, this will not be recorded as an adverse event.

Any adverse events will be reported with their number/rate and associated 95% CI. There are no known serious adverse events linked to using a patient decision aid such as CONNECT. Patient-reported negative effects of using CONNECT will be reported during the participant’s pre-assessment clinic appointment. Treatment may continue without the use of CONNECT.

4.5. Statistical Software

All analyses will be conducted using the statistical software package R.

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