HEALTH TECHNOLOGY ASSESSMENT

VOLUME 18 ISSUE 44 JULY 2014
ISSN 1366-5278

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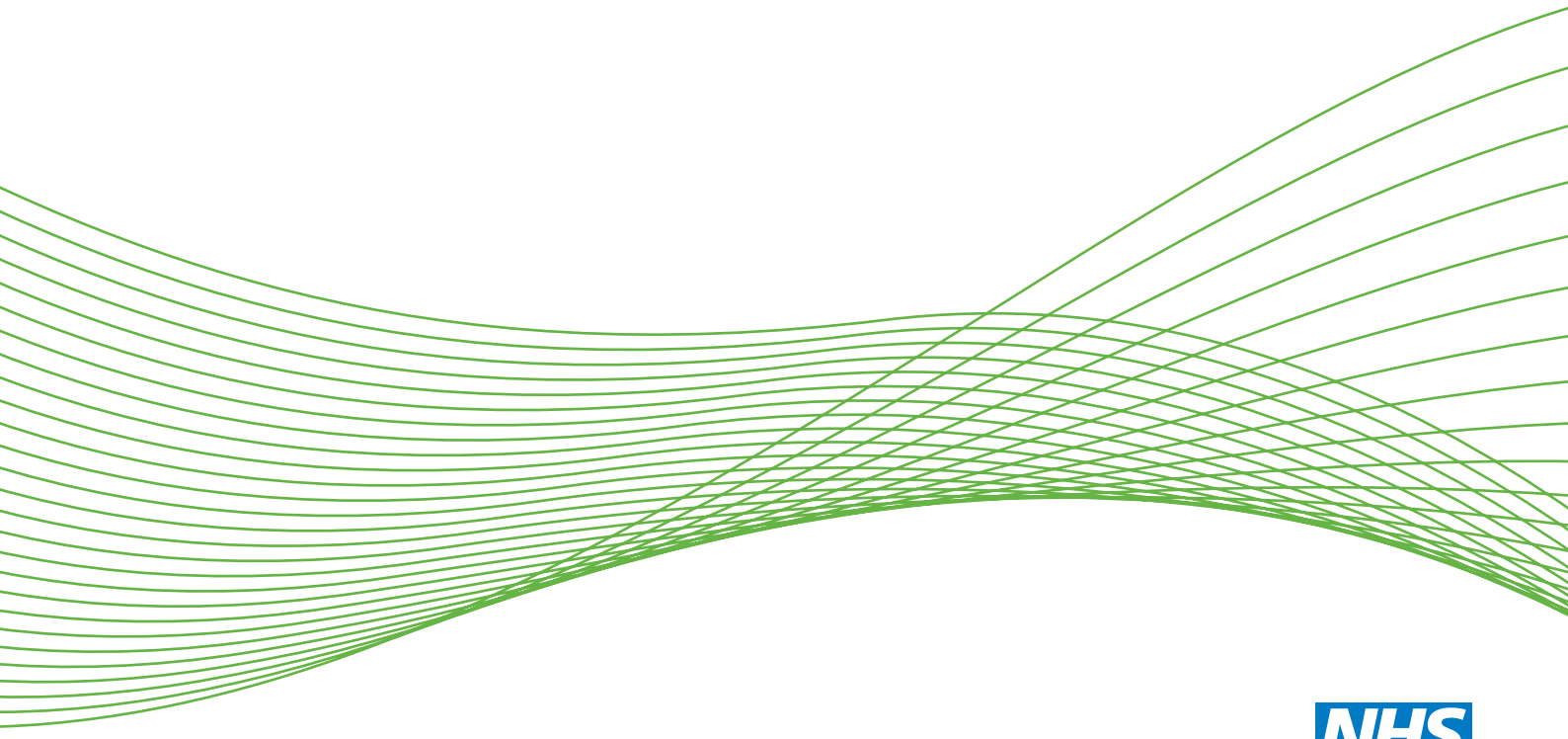

NHS
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DOI 10.3310/hta18440

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Declared competing interests of authors: none

Published July 2014
DOI: 10.3310/hta18440

This report should be referenced as follows:

Rogers CA, Pike K, Campbell H, Reeves BC, Angelini GD, Gray A, *et al.* Coronary artery bypass grafting in high-RISk patients randomised to off- or on-Pump surgery: a randomised controlled trial (the CRISP trial). *Health Technol Assess* 2014;**18**(44).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (SciSearch®) and *Current Contents®*/ Clinical Medicine.

Health Technology Assessment

HTA EME

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Five-year impact factor: 5.804

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index and is assessed for inclusion in the Database of Abstracts of Reviews of Effects.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: nihredit@southampton.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

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This report

This issue of *Health Technology Assessment* contains a project originally commissioned by the MRC but managed by the Efficacy and Mechanism Evaluation Programme. The EME programme was created as part of the National Institute for Health Research (NIHR) and the Medical Research Council (MRC) coordinated strategy for clinical trials. The EME programme is funded by the MRC and NIHR, with contributions from the CSO in Scotland and NISCHR in Wales and the HSC R&D, Public Health Agency in Northern Ireland. It is managed by the NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC) based at the University of Southampton.

The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from the material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, the MRC, NETSCC, the HTA programme, the EME programme or the Department of Health. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health.

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Abstract

Coronary artery bypass grafting in high-RISk patients randomised to off- or on-Pump surgery: a randomised controlled trial (the CRISP trial)

Chris A Rogers,[1]* Katie Pike,[1] Helen Campbell,[2] Barnaby C Reeves,[1] Gianni D Angelini,[3] Alastair Gray,[2] Doug G Altman,[4] Helen Miller,[1] Sian Wells[1] and David P Taggart[5] on behalf of the CRISP investigators[†]

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Background: Coronary artery bypass grafting (CABG) is the treatment of choice for patients with multivessel coronary artery disease (CAD). Evidence from randomised controlled trials (RCTs) in low-risk populations shows that 'off-pump' CABG is at least as safe as 'on-pump' CABG, but high-quality trial data in high-risk populations are lacking.

Objectives: To test the hypothesis that, in high-risk patients, off-pump coronary artery bypass grafting (OPCABG) reduces mortality and morbidity without causing a higher risk of reintervention compared with on-pump coronary artery bypass grafting (ONCABG).

Design: Open parallel-group RCT with a 1 : 1 allocation ratio and expertise-based randomisation.

Setting: Eight specialist cardiac surgery centres in the UK and one specialist centre in Kolkata, India.

Participants: Patients with an additive European system for cardiac operative risk evaluation score (EuroSCORE) of ≥ 5, undergoing non-emergency isolated CABG via a median sternotomy.

Interventions: CABG without cardiopulmonary bypass (CPB), i.e. OPCABG on the beating heart, or CABG with CPB, i.e. ONCABG on a chemically arrested heart.

Main outcome measures: Primary outcome – a composite of death or serious morbidity [all-cause mortality, myocardial infarction (MI), stroke, prolonged initial ventilation, sternal wound dehiscence] within 30 days of surgery. Secondary outcomes – quality of life (QoL) [Rose Angina Questionnaire, Canadian Cardiovascular Society (CCS) angina class, European QoL-5 Dimensions (EQ-5D), Coronary Revascularisation Outcome Questionnaire (CROQ)] and resource utilisation.

Results: The organisation of a tertiary cardiac surgery service in the UK presented several barriers to recruitment. Referral information was often inadequate to confirm eligibility. Limited surgeon participation at a centre, the need to meet referral-to-treatment performance targets and complex referral pathways did not support an expertise-based allocation. Urgent patients waiting for surgery in local 'feeder' hospitals were often not transferred until late the night before surgery, which limited the time available to take

consent and organise the surgery on an expertise basis. Several elective patients declined to take part because they wanted the surgeon they had met when the surgery was first discussed in clinic to operate. Several initiatives were explored to boost recruitment. After 10 months of recruitment, the trial design was modified to permit both within-surgeon and expertise-based randomisation within a centre. However, this did not have sufficient impact and the trial was stopped on the grounds of futility after 106 patients (< 2% of the target sample size) had been recruited in 18 months. Ninety-eight patients were included in the trial analyses, six patients were withdrawn and two died before surgery. In both groups, 6% of patients experienced the primary outcome [adjusted odds ratio (OR) (OPCABG to ONCABG) 1.07; 95% confidence interval (CI) 0.27 to 4.14]. QoL scores at 4–8 weeks post surgery were similar in the two groups. Patients randomised to OPCABG had a shorter stay in the intensive care unit and in hospital after surgery (median 26.0 vs. 27.7 hours in intensive care and 7 vs. 8 days in hospital).

Conclusions: The Coronary artery bypass grafting in high-RISk patients randomised to off- or on-Pump surgery (CRISP) trial was not successful for a range of logistical reasons. However, the experience gained is of value for the design and conduct of future trials. The surgical community have polarised views. A qualitative evaluation of the reasons behind the views held by the advocates of the two techniques is an area for future research.

Trial registration: Current Controlled Trials ISRCTN29161170.

Funding: This project was funded by the Medical Research Council/National Institute for Health Research (NIHR) Efficacy and Mechanism Evaluation programme and will be published in full in *Health Technology Assessment*; Vol. 18, No. 44. See the NIHR Journals Library website for further project information.

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List of abbreviations

ACE	angiotensin-converting enzyme
AE	adverse event
AF	atrial fibrillation
AKI	acute kidney injury
ARB	angiotensin receptor blocker
BBS	Best Bypass Surgery
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CCS	Canadian Cardiovascular Society
CI	confidence interval
CICU	cardiac intensive care unit
CK-MB	creatine kinase MB isozyme
CLRN	comprehensive local research network
CORONARY	CABG off- or on-pump revascularisation trial
CPB	cardiopulmonary bypass
CRF	case report form
CRISP	Coronary artery bypass grafting in high-RISk patients randomised to off- or on-Pump surgery
CRISPSw	(1) all-cause death after Cardiac surgery, (2) new onset Renal failure, (3) MI, (4) Stroke, (5) Prolonged initial ventilation and (6) Sternal wound dehiscence
CROQ	Coronary Revascularisation Outcome Questionnaire
DMSC	Data Monitoring and Safety Committee
ECG	electrocardiograph
EQ-5D	European Quality of Life-5 Dimensions
EuroSCORE	European system for cardiac operative risk evaluation score
HDU	high-dependency unit
HR	hazard ratio
IABP	intra-aortic balloon pump
ICC	intraclass correlation coefficient
IQR	interquartile range
LV	left ventricle/ventricular
LVAD	left ventricular assist device
MD	mean difference
MI	myocardial infarction
NYHA	New York Heart Association
ONCABG	on-pump coronary artery bypass graft
OPCABG	off-pump coronary artery bypass graft
OR	odds ratio
PCI	percutaneous coronary intervention
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
REC	Research Ethics Committee
ROOBY	Randomised On/Off Bypass trial
RR	relative risk
RRT	renal replacement therapy
SAE	serious adverse event
SD	standard deviation
TIA	transient ischaemic attack
TSC	Trial Steering Committee
VF	ventricular fibrillation
VT	ventricular tachycardia

Scientific summary

Background

Despite advances in medical therapy and percutaneous coronary interventions (PCIs) there is good evidence that coronary artery bypass grafting (CABG) offers superior survival and freedom from repeat intervention in patients with multivessel coronary artery disease (CAD). Conventional CABG uses cardiopulmonary bypass (CPB) ('on-pump') to support the circulation while the heart is temporarily stopped. CPB causes a systemic inflammatory response syndrome, which can contribute to mortality and overt morbidity, particularly in higher-risk patients. Evidence from randomised controlled trials (RCTs) in low-risk populations shows that 'off-pump' CABG (OPCABG) on the beating heart is at least as safe as 'on-pump' CABG (ONCABG). There are consistent findings from large observational studies that OPCABG appears to reduce mortality and morbidity in high-risk patients.

Objectives

The Coronary artery bypass grafting in high-RISk patients randomised to off- or on-Pump surgery (CRISP) trial was set up to test the hypothesis that OPCABG in high-risk patients reduces mortality and morbidity, without causing a higher risk of reintervention.

Methods

Study design

An international, multicentre, open, parallel-group RCT of isolated OPCABG versus ONCABG in high-risk patients with an additive European system for cardiac operative risk evaluation score (EuroSCORE) of ≥ 5.

Settings and participants

Specialist cardiac surgery centres in the UK and overseas. Patients with an additive EuroSCORE of ≥ 5 undergoing non-emergency isolated CABG surgery via a median sternotomy incision.

Interventions

Trial patients were randomised to

(a) CABG without CPB (OPCABG) on the beating heart or
(b) CABG with CPB (ONCABG) on a chemically arrested heart.

The anaesthetic technique and method of myocardial protection used was in accordance with established local protocols.

Randomisation

The preferred method of randomisation was expertise based, i.e. patients were randomised to surgery carried out by an experienced OPCABG surgeon or to an experienced ONCABG surgeon. Surgeons were eligible if they had a stated preference and were sufficiently experienced in their preferred technique (had performed at least 100 operations).

Allocations were concealed and stratified by centre and cohort minimisation was used to minimise imbalance of key prognostic factors across the groups. Patients were randomly assigned in a 1 : 1 ratio.

Outcomes

The primary outcome was a composite end point of death or serious morbidity within 30 days of surgery. The components were (1) all-cause mortality, (2) new-onset renal failure, (3) myocardial infarction (MI), (4) stroke, (5) prolonged initial ventilation and (6) sternal wound dehiscence. New-onset renal failure was defined as a postoperative creatinine level of > 200 µmol/l, a percentage increase from preoperative creatinine of ≥ 40% and the need for renal replacement therapy (RRT). Blood test results (of troponin I, troponin T or creatine kinase MB isoenzyme) and the pre- and postoperative electrocardiographs were adjudicated by an independent committee who were blinded to the allocation of OPCABG or ONCABG, and MI was defined on consensus of the adjudicators. Stroke was defined as new, acute, focal neurological deficit thought to be of vascular origin with signs or symptoms lasting longer than 24 hours and confirmed by a neurologist. Prolonged ventilation was defined as ≥ 96 hours, excluding any periods of reintubation. Sternal wound dehiscence was defined as requiring non-pharmacological intervention (e.g. V.A.C.® dressing or reoperation).

Secondary outcomes were:

(a) quality-of-life (QoL) assessment at recruitment and 4–8 weeks after surgery, measured using the Rose Angina Questionnaire, Canadian Cardiovascular Society (CCS) angina class, European QoL-5 Dimensions (EQ-5D) and Coronary Revascularisation Outcome Questionnaire (CROQ)
(b) resource utilisation, determined by hospital resources during index admission.

Follow-up

All patients were followed up 4–8 weeks after surgery.

Sample size

The study sample size was set at 5418 patients (2709 per group). The expected incidence of the composite primary outcome, based on data from the Bristol and Oxford cardiac databases, was 9.3%. A sample size of 5418 patients had 90% power to detect a 30% reduction in relative risk (RR) with 5% statistical significance (two tailed).

Statistical analyses

Analyses were carried out on the basis of intention to treat. All treatment comparisons are presented as effect sizes with 95% confidence intervals (CI) and *p*-values of < 0.05 were considered statistically significant. All models were adjusted for age, sex and operative priority as fixed effects and surgeon as a random effect. Adverse events (AEs) were grouped by the treatment received, rather than by the treatment allocated.

Results

Patient screening

From October 2009 to March 2011, a total of 787 patients were assessed for potential inclusion in the trial. Six hundred and eighty-one were excluded: 523 were ineligible, 82 were eligible but not approached, 74 did not consent and two were omitted for other reasons. The main reasons for non-consent were 'personal' or wanting a specific type of surgery or surgeon.

Recruitment

A total of 106 patients were recruited from eight centres in the UK and one centre in Kolkata, India. Patient follow-up was completed in June 2011. A total of 39 surgeons participated: 19 were ONCABG specialists and 20 were OPCABG specialists. It was estimated that each centre would recruit at least six patients per month. However, this target was not met at any participating centre and the study was closed to recruitment in March 2011 at the request of the funder.

Barriers to recruitment

Five key barriers to recruitment were identified:

1. The number of participating surgeons. Recruitment using an expertise-based randomisation system was severely hampered if only two surgeons in a centre were taking part.
2. Access to potentially eligible patients. In some centres, urgent inpatients were transferred several days before surgery, which provided sufficient time to gain the patient's consent and organise the surgery. In other centres, patients were not transferred until late on the day before surgery and the time frame for recruitment was invariably too short.
3. Referral system. Some centres operated a generic referral system for all patients (i.e. patients were placed in a pool) while in other centres there was a mixture of generic and named referrals, but the vast majority were named referrals. Surgeons were reluctant to 'share' patients referred to them whom they had met in clinic.
4. Targets. The need to meet referral-to-treatment targets and other local performance targets.
5. Insufficient information in the referral letter to determine eligibility. The EuroSCORE is made up of several components and frequently the information provided on referral was inadequate to allow the score to be calculated accurately.

Outside the UK, the main barriers that hampered the set-up were (1) obtaining approved translations of essential documents, (2) insurance/indemnity issues and (3) the limited per-patient funding available.

Actions taken and proposals to increase recruitment

Many initiatives were explored to overcome these barriers to recruitment, but these were largely unsuccessful. In August 2010 it was agreed that the study design should be changed from expertise-based randomisation to within-surgeon randomisation. However, several OPCABG experts were unwilling to operate ONCABG on high-risk patients so it was subsequently decided to allow both methods of randomisation within a centre.

Other changes to the trial design were also considered:

(a) Widening the inclusion criteria. There was no support for this.
(b) Changes to the primary outcome. A proposal to extend the composite 30-day outcome to include (1) reoperation for bleeding, (2) low cardiac output, (3) new onset of atrial arrhythmia and (4) replacing new-onset renal failure with the less severe acute kidney injury (AKI). It was estimated that the increased incidence of this revised composite outcome would have reduced the target sample size to 1094 patients.
(c) Seeking Research Ethics Committee (REC) approval to randomise eligible patients prior to consent. This was not pursued owing to (1) ethical concerns, (2) the potential for bias and the opportunity for the surgeon to influence the patient's decision to participate or not and (3) potential for imbalance between the groups if the consent rates differed between those allocated to an ONCABG or OPCABG expert.

A recovery plan which included the proposed extended composite primary end point was considered by the National Institute for Health Research-Efficacy and Mechanism Evaluation (NIHR-EME) Board in February 2011. The proposal was not accepted and the trial was closed.

Withdrawals

Eight of the 106 randomised patients were excluded from the analysis population, six withdrew prior to surgery and two died prior to surgery.

Protocol deviations

Four patients randomised to OPCABG received ONCABG and there were no crossovers from ONCABG to OPCABG.

Patient follow-up

Follow-up data 4–8 weeks after surgery were obtained for all patients.

Baseline data and operative characteristics

The median EuroSCORE was 6 [interquartile range (IQR) 5–8], the median age 77.1 years (IQR 71.9–80.6) and 23% of patients were female. Approximately half (45%) of procedures were classified as urgent.

Fewer patients in the OPCABG group than in the ONCABG group had three or four grafts (63% vs. 79%). There were no deaths during surgery.

Primary outcome

In both groups, 6 out of 49 (12%) patients experienced the composite primary outcome. The estimated treatment effect, adjusted for age, sex, operative priority and surgeon, was odds ratio (OR) 1.07 (95% CI 0.27 to 4.14; $p = 0.93$). The most commonly occurring component was MI (which occurred in six patients).

Secondary outcomes

Quality-of-life data were similar in the two groups. On average, patients in the OPCABG group scored slightly higher than in the ONCABG group on the EQ-5D visual analogue scale and on the CROQ, albeit with no statistically significant differences [EQ-5D mean difference (MD) = 4.92, (95% CI −0.94 to 10.8; $p = 0.11$); CROQ core total MD = 1.10, (95% CI −0.97 to 3.17; $p = 0.30$)].

On average, resource use was greater for patients randomised to ONCABG. They spent longer in surgery (median 3.4 vs. 3.2 hours), were ventilated for longer (median 7.1 vs. 5.7 hours), spent longer in cardiac intensive care unit (CICU) (median 27.7 vs. 26.0 hours) and stayed longer in hospital (median 8 vs. 7 days) than patients randomised to OPCABG.

Adverse events and postoperative complications

There were 74 expected AEs, eight of which were classified as serious. There were fewer events in patients who received OPCABG [32 (1 serious) vs. 42 events (7 serious)]. There were also fewer unexpected AEs in the OPCABG group [24 (12 serious) vs. 44 events (24 serious)]. The most common complications were atrial fibrillation (AF), superficial wound infections and respiratory infections. There were four deaths (two in each group), three of which occurred more than 30 days after surgery.

Discussion

Main findings: study conduct

The main findings are that expertise-based randomisation is challenging to implement. For a range of logistical reasons, the trial failed to recruit to time and target and was closed prematurely.

Some of the challenges faced were due to the context and nature of the service provision in the UK. Cardiac surgery is a tertiary service. As a consequence, patients are referred from a large geographical area and a significant proportion of referrals are urgent inpatients. The information provided at referral was often limited, making the assessment of eligibility difficult. Elective patients were often unwilling to take part because they wished to stay with the surgeon they met at their first appointment. The availability of an expert surgeon to carry out the operation within a time scale that does not breach local and national targets for treatment, and the willingness or otherwise of surgeons to work together and ‘share’ their patients, are potential barriers to recruitment into any trial using expertise-based randomisation.

Main findings: study results

The CRISP trial did not find statistically significant differences between the OPCABG and ONCABG groups owing to the limited power. However, the question that the trial set out to address remains important.

The Cochrane review, published in 2012, acknowledged that mainly patients with low risk of postoperative complications were enrolled in the trials reviewed.

The two largest trials to compare ONCABG and OPCABG, the Randomised On/Off BYpass (ROOBY) and CABG off- or on-pump revascularisation (CORONARY) trials, have been published since the CRISP trial began. The ROOBY trial has been severely criticised because it recruited predominantly low-risk patients and many of the OPCABG surgeons were inexperienced. The CORONARY trial, the largest trial to date, had more experienced surgeons and recruited a higher proportion of higher-risk patients, although < 20% of participants had a EuroSCORE of > 5.

The Cochrane meta-analysis was updated to include the results from the CORONARY and CRISP trials. The RRs were death 1.18 (95% CI 0.98 to 1.40), MI 0.96 (95% CI 0.82 to 1.12), stroke 0.80 (95% CI 0.61 to 1.06) and renal complication 0.92 (95% CI 0.70 to 1.21). Data from three trials in high-risk patients (total $n = 534$) were also combined with the CRISP results. This analysis suggested a lower risk of death with OPCABG in the early postoperative period (RR 0.46, 95% CI 0.20 to 1.04; $p = 0.06$) and a comparable risk to 3 years (RR 0.90, 95% CI 0.32 to 2.58; $p = 0.85$). The risk of a MI was also reduced in the early postoperative period (RR 0.59, 95% CI 0.33 to 1.06; $p = 0.077$).

Strengths and limitations

Despite the failure of CRISP to recruit to target, the options to improve recruitment were thoroughly tested. We believe that expertise-based randomisation is the only way to evaluate established surgical procedures when there are strongly held preferences but collective equipoise; however, it may not be feasible in a tertiary referral setting.

The final study size is a clear weakness although the trial methodology was strong; the value of the trial data is their contribution to meta-analyses.

Lessons for the future

If we were setting up CRISP now, there are many things that we would do differently. First, we would design the trial in two phases, with a feasibility phase followed by a main trial phase. This design is being used in other surgical areas of difficult-to-do trials.

Second, we would include a qualitative research element in order to gain a full understanding of the barriers to recruitment and the extent of the equipoise. The strength of the bond formed between surgeon and patient at that first consultation would also be explored through interviews with patients.

Third, we would focus recruitment equally towards UK and overseas centres from the beginning of the trial. Many of the barriers to recruitment experienced in the UK may not be such a problem overseas. Fewer than 5% of patients recruited to the CORONARY trial were from the UK and the biggest contributors were India and China (1307 and 781 patients, respectively).

Future research

The answer to the question whether OPCABG offers an additional benefit over ONCABG in a high-risk population is unclear. The trial evidence in high-risk patients suggests the outcomes are similar although the collective evidence across all trials suggests the risk of death is higher with OPCABG. The views of members of the surgical community are polarised. A qualitative evaluation of the reasons behind the views held by the advocates of the two techniques is an area for future research.

One explanation for the polarisation is the belief that ‘it’s in the surgeon’s hands’. If the surgeons are true ‘experts’, then one may anticipate no difference in outcomes between the two methods. An individual patient data meta-analysis of the trial data, classifying patients according to the characteristics/experience of the surgeon, could test this hypothesis.

Conclusion

We believe there is still a role for expertise-based randomisation to evaluate established treatments when there are strong practitioner preferences and both treatments are used. The CRISP trial was not successful but there are valuable lessons to be learnt for the future from the CRISP experience.

Trial registration

Current Controlled Trials ISRCTN29161170.

Funding

This project was funded by the Medical Research Council/NIHR-EME programme and will be published in full in *Health Technology Assessment*; Vol. 18, No. 44. See the NIHR Journals Library website for further project information.

Chapter 1 Introduction

Background and rationale

Despite advances in medical therapy and percutaneous coronary interventions (PCIs) there is good evidence that coronary artery bypass grafting (CABG) offers superior survival and freedom from repeat intervention in patients with multivessel coronary artery disease (CAD).[1–5] For example, in the published New York State registry of almost 60,000 patients, after risk stratification for cardiac and non-cardiac comorbidity, there was a significant reduction in mortality (absolute difference of 5%) and a sevenfold reduction in the need for repeat interventions at 3 years in patients undergoing CABG rather than PCI using stents.[2] Predictions that drug-eluting stents will significantly reduce the need for CABG are premature because, although these stents reduce the incidence of restenosis compared with bare metal stents, three large meta-analyses have shown that they do not improve survival or reduce the incidence of subsequent myocardial infarction (MI).[6–8] There are two reasons why CABG is likely to remain a superior treatment to PCI over the longer term: (1) CABG protects whole zones of proximal myocardium (as the graft is placed to the midcoronary vessel beyond all proximal disease);[9] and (2) PCI frequently results in incomplete revascularisation, which adversely affects survival proportional to the incompleteness of revascularisation.[10] Currently around half a million patients worldwide undergo CABG each year. There is a real possibility that these numbers will increase with a growing elderly population, an increasing epidemic of diabetes and obesity which all predispose to the development of CAD, and an increasing realisation that PCI may merely delay definitive treatment.

Conventional CABG uses cardiopulmonary bypass (CPB) ('on-pump') to support the circulation while the heart is temporarily stopped. CPB causes a systemic inflammatory response syndrome, which leads to multiorgan dysfunction, and, although mild and reversible in most, can contribute to mortality and overt morbidity, particularly in higher-risk patients.[11–19] Evidence from randomised controlled trials (RCTs) in low-risk populations shows that 'off-pump' CABG (OPCABG) is at least as safe as 'on-pump' CABG (ONCABG) in terms of mortality and that it reduces several aspects of morbidity but may lead to a higher need for subsequent reintervention.[11–14]

However, the exclusion of high-risk patients from these RCTs is of key importance because there are consistent findings from large observational studies that OPCABG appears to reduce mortality and morbidity in such patients.[15–19] These studies, summarised in *Table 1*, have used propensity scoring and/or logistic regression to take account of different baseline characteristics in the OPCABG and ONCABG groups but are still prone to all the limitations of non-randomised studies.

Only 15–20% of all CABG in Europe and the USA are performed as OPCABG owing to concerns that it may result both in fewer grafts and in lower graft patency. The Prague-4 RCT of 400 patients in a single centre reported similar 30-day clinical outcomes but a reduction in 1-year saphenous vein graft patency (49% in OPACBG group vs. 59% in ONCABG group) in the OPCABG group.[20] In contrast, in the Surgical Management of Arterial Revascularisation Therapies trial, a single-centre, single-surgeon RCT of 197 patients, Puskas *et al.*[21] reported 1-year angiographic graft patencies of 94% for OPCABG (mean of 3.2 grafts) and 96% for ONCABG (mean of 3.4 grafts). In the Beating Heart Against Cardioplegic Arrest Studies,[22] two single-surgeon RCTs of 401 patients in total, 7-year follow-up has shown graft patency of 86.2% and 85.4%, respectively.

TABLE 1 Five observational studies of OPCABG vs. ONCABG in propensity matched higher-risk patients reporting reduced mortality with OPCABG

Reference number	Effect measure	Number of patients		Mortality (%)		OPCABG risk reduction in mortality (%)	*p*-value
		ONCABG	OPCABG	ONCABG	OPCABG		
15	O/E ratio for death	106,423	11,717	1.02	0.81	20	0.001
16	O/E ratio for death	10,631	1929	1.25	0.61	49	0.001
17	Bayes' risk based mortality	5163	2223	2.9	1.4	52	0.001
18	Death within 30 days among patients with a EuroSCORE of > 6	510	510	5.9	3.1	47	0.04
19	Mortality in 422 very high-risk patients	211	211	11	4	64	< 0.05

EuroSCORE, European system for cardiac operative risk evaluation score; O/E, observed/expected.

Past research

Research published before commencement of the trial

When the Coronary artery bypass grafting in high-RISk patients randomised to off- or on-Pump surgery (CRISP) trial was conceived, there had been two meta-analyses[11,12] and two consensus statements[13,14] addressing the issue of OPCABG versus ONCABG. The key summary points of these, and of two other meta-analyses[23,24] published before recruitment to CRISP began, are reproduced below. It should be noted that these papers report, in effect, analyses of the same primary data from RCTs. Two earlier meta-analyses,[25,26] with fewer patients and listed in several publications, were statistically less rigorous and are not described.

Meta-analysis 1: Cheng *et al.* 2005[11]

In this meta-analysis of 37 RCTs (3369 patients) of OPCABG versus ONCABG, no significant differences were found for 30-day mortality [odds ratio (OR) 1.02, 95% confidence interval (CI) 0.58 to 1.80], MI (OR 0.77, 95% CI 0.48 to 1.26), stroke (OR 0.68, 95% CI 0.33 to 1.40), renal dysfunction (OR 0.58, 95% CI 0.25 to 1.33), intra-aortic balloon pump (IABP) requirement, wound infection, rethoracotomy or reintervention. However, OPCABG significantly decreased atrial fibrillation (AF), transfusion, inotrope requirements, respiratory infections, ventilation time, intensive care unit stay and hospital stay. Patency and neurocognitive function results were inconclusive. In-hospital and 1-year direct costs were higher for ONCABG. Therefore, this meta-analysis demonstrates that mortality, stroke, MI and renal failure were not statistically significantly reduced in OPCABG; however, selected short- and mid-term clinical and resource outcomes were improved compared with ONCABG.

Meta-analysis 2: Wijeysundera *et al.* 2005[12]

These authors carried out a meta-analysis of 37 RCTs (3449 patients) and 22 risk-adjusted (logistic regression or propensity score) observational studies (293,617 patients). In RCTs, OPCABG was associated with a reduced incidence of AF and trends towards reduced 30-day mortality (OR 0.91, 95% CI 0.45 to 1.83) and reduced incidence of stroke (OR 0.52, 95% CI 0.25 to 1.05) and MI (OR 0.79, 95% CI 0.50 to 1.25). Observational studies showed OPCAB to be associated with reduced 30-day mortality (OR 0.72, 95% CI 0.66 to 0.78) and a reduced incidence of stroke (OR 0.62, 95% CI 0.55 to 0.69), MI (OR 0.66, 95% CI 0.50 to 0.88) and AF (OR 0.78, 95% CI 0.74 to 0.82). At 1–2 years, OPCABG was associated with trends toward reduced mortality, but also increased repeat revascularisation (RCT: OR 1.75, 95% CI 0.78 to 3.94; observational: OR 1.35, 95% CI 0.76 to 2.39). The conclusions that can be

drawn include that the RCTs did not find, aside from AF, the statistically significant reductions in short-term mortality and morbidity demonstrated by observational studies.[12] These discrepancies may be due to differing patient-selection and study methodology. Future studies must focus on improving research methodology, recruiting high-risk patients and collecting long-term data.

Meta-analysis 3: Sedrakyan *et al.* 2006[23]

This was a meta-analysis of 41 RCTs (3996 patients) of OPCABG versus ONCABG. No statistically significant differences were found for mortality [relative risk (RR) 0.96, 95% CI 0.58 to 1.60], MI (RR 0.80, 95% CI 0.54 to 1.19), renal failure (RR 0.61, 95% CI 0.26 to 1.45), reintervention (RR 1.90, 95% CI 0.92 to 3.90) or recurrence of angina. However, OPCABG significantly decreased AF (RR 0.70, 95% CI 0.57 to 0.84), stroke (RR 0.52 95% CI 0.37 to 0.74) and wound infection.

Meta-analysis 4: Moller *et al.* 2008[24]

In this meta-analysis of 66 RCTs (5537 patients) of OPCABG versus ONCABG, no significant differences were found for mortality (RR 0.98, 95% CI 0.66 to 1.44), MI (RR 0.95, 95% CI 0.65 to 1.37), repeat revascularisation (RR 1.34, 95% CI 0.83 to 2.18) or stroke (RR 0.62, 95% CI 0.32 to 1.19); however, OPBCABG significantly decreased AF (RR 0.69, 95% CI 0.57 to 0.83). To increase the strength of evidence regarding which method to prefer, large RCTs with longer-term follow-up and blinded outcome assessment, recruiting consecutive high-risk patients, are needed.

American Heart Association scientific statement: Sellke *et al.* 2005[13]

One of the most hotly debated and polarising issues in cardiac surgery has been whether CABG without the use of CPB or cardioplegia (OPCABG) is superior to that performed with the heart–lung machine and the heart chemically arrested (standard CABG). Various clinical trials are reviewed comparing the two surgical strategies, including several large retrospective analyses, meta-analyses and the randomised trials that address different aspects of standard CABG and OPCABG.[13] Although definitive conclusions about the relative merits of standard CABG and OPCABG are difficult to reach from these varied randomised and non-randomised studies, several generalisations may be possible. Nevertheless, there appear to be trends in most studies. These trends include less blood loss and need for transfusion after OPCABG, less myocardial enzyme release after OPCABG up to 24 hours, less early neurocognitive dysfunction after OPCABG and less renal insufficiency after OPCABG. Fewer grafts tend to be performed with OPCABG than with standard CABG. Length of hospital stay, mortality rate and long-term neurological function and cardiac outcome appear to be similar in the two groups. To answer definitively the remaining questions of whether either strategy is superior, and in which patients, a large-scale prospective randomised trial is required.

Recommendations of the National Heart, Lung, And Blood Institute working group on the future direction in cardiac surgery. Off-pump coronary artery bypass: Baumgartner *et al.* 2005[14]

Although CPB may reduce the technical difficulty of performing CABG surgery, it also contributes to the risk of specific complications, such as perfusion-related embolisation, hypoperfusion, generalised inflammatory response and anaemia. Consequently, a number of surgeons perform OPCABG, in which CPB is avoided, in an effort to avoid perfusion-related complications. Definitive data establishing the superiority of one technique over the other are lacking. Retrospective reviews of large databases suggest that OPCABG is associated with a decrease in risk-adjusted mortality and morbidity. Smaller prospective, randomised clinical trials comparing OPCABG with pump-based CABG have produced varying results, even when only graft patency is examined. Such conflicting information has led to adoption of OPCABG in a haphazard manner that poorly serves the large patient population with CAD. Currently, fewer than 25% of coronary revascularisations are performed without CPB and this percentage of OPCABG procedures has not increased over the last 3 years. A large, multicentre, randomised clinical trial comparing OPCABG and CABG is needed to resolve uncertainty regarding their relative benefits.

Although these meta-analyses of RCTs showed clinically important effect sizes (similar to those in the observational studies), they were underpowered for statistical significance. The CRISP trial was set up to test the hypothesis that, in high-risk patients, OPCABG reduces mortality and morbidity without causing a higher risk of reintervention, with the aim of recruiting almost 50% more patients than included in the meta-analyses.

Research published after commencement of the trial

There have been eight further meta-analyses and a Cochrane systematic review published since 2009, when recruitment to the CRISP trial began.[27–35] Six of the meta-analyses were restricted to RCTs,[27–30,33,35] one considered both RCTs and observational studies[32] and the other was a meta-analysis of propensity score analyses.[31] The largest of these meta-analyses, which was similar in size to the Cochrane systematic review (86 RCTs, 9906 patients), examined the association between outcome and risk.[30] Superior results with OPCABG were reported in patients with a lower ejection fraction for mortality and the incidence of AF, but not for the incidence of stroke or MI. No effect modification was seen for age and sex.

The Cochrane review published in 2012[34] includes 86 RCTs (10,716 patients). It includes results from four large trials (> 300 participants) published since the previous meta-analysis by the same group:[24] the Medicine angioplasty or surgery study,[36] the Randomised On/Off BYpass (ROOBY) trial,[37] the Best Bypass Surgery (BBS) trial[38] and the Danish On-pump Off-pump Randomisation Study (DOORS; published in abstract form only).[39] The review does not include the more recently published CABG off- or on-pump revascularisation (CORONARY) trial.[40] All-cause mortality to 30 days (death within 30 days of surgery) favoured OPCABG, but not significantly so (RR 0.63, 95% CI 0.33 to 1.20). However, when including follow up beyond 30 days, a significantly increased risk of death with OPCABG was found (RR 1.24, 95% CI 1.01 to 1.53). There was no difference with respect to MI, either in the first 30 days (RR 1.16, 95% CI 0.83 to 1.64) or overall (RR 1.00, 95% CI 0.80 to 1.26). In contrast, the risk of stroke in the first 30 days was reduced (RR 0.56, 95% CI 0.32 to 0.99) but, again, a difference in overall risk was not found (RR 0.76, 95% CI 0.54 to 1.06). OPCABG conferred a non-significantly increased risk of coronary reintervention (RR 1.25, 95% CI 0.94 to 1.65) and a significantly reduced risk of postoperative AF (RR 0.78, 95% CI 0.63 to 0.96); the incidence of renal insufficiency was similar (RR 0.86, 95% CI 0.62 to 1.20). On average, OPCABG patients had fewer distal anastomoses (−0.28, 95% CI −0.40 to −0.16). The authors acknowledged that mainly patients with low risk of postoperative complications were enrolled and patients with three-vessel coronary disease and impaired left ventricular (LV) function were under-represented. The majority of trials were assessed as having a high risk of bias owing to the open-label design. There was no heterogeneity in all-cause mortality between trials with a low risk of bias. Within this subgroup of trials, both single-surgeon, single-centre and multicentre trials were represented. The review did not consider subgroups of patients because the trials did not report results of subgroups and included only three trials focusing on high-risk patients.[38,41,42] The authors concluded that ONCABG should be the standard treatment but that OPCABG should be considered for patients with contraindications to aortic cannulation and cardiac arrest. They also suggested that large high-quality RCTs recruiting experienced surgeons and focusing on patients with impaired ventricular function and in whom ONCABG is contraindicated are needed.

The Canadian-led CORONARY trial recruited 4752 patients from 79 centres in 19 countries.[40] The trial had a coprimary composite outcome of death, non-fatal stroke, non-fatal MI or new renal failure requiring dialysis at 30 days after randomisation. There was no significant difference in the rate of this primary composite outcome [hazard ratio (HR) 0.95, 95% CI 0.79 to 1.14] or in any of its individual components. OPCABG significantly reduced the rates of blood transfusion (RR 0.80, 95% CI 0.75 to 0.85), reoperation for bleeding (RR 0.61, 95% CI 0.40 to 0.93), acute kidney injury (AKI) (RR 0.87, 95% CI 0.80 to 0.96) and respiratory complications (RR 0.79, 95% CI 0.63 to 0.98) but increased the rate of early repeat revascularisations (HR 4.01, 95% CI 1.34 to 12.0).

Aims and objectives

The CRISP trial was set up to address the limitations highlighted in the meta-analyses, namely to test the hypothesis that OPCABG in high-risk patients reduces mortality and morbidity, without causing a higher risk of reintervention. It complemented the CORONARY trial, which recruited predominantly lower-risk patients. Overall, 5.6% of CORONARY trial participants had impaired LV function (impairment was defined as LV function < 35%) and only 17.7% had a European system for cardiac operative risk evaluation (EuroSCORE) of > 5.[40]

This report describes the results of the CRISP trial. The trial closed early, on the grounds of futility, after less than 2% of the target sample size had been reached. The challenges faced and the outcomes for the small cohort of patients recruited are described.

Chapter 2 Methods

Study design

The CRISP trial was a designed as an international, multicentre, open, parallel-group RCT of isolated OPCABG versus ONCABG in high-risk patients with an additive EuroSCORE of ≥ 5. The study received research ethics approval (reference 08/MRE00/58) and was registered (reference ISRCTN29161170).

The preferred method of randomisation when CRISP was set up was expertise based, i.e. patients were randomised to surgery carried out by an experienced off-pump surgeon or by an experienced on-pump surgeon. Evaluating surgical interventions using an expertise-based trial design was first proposed in 1980,[43] but was rarely used until more recently.[44] The advantages of an expertise-based design have been discussed in detail by Devereaux *et al.*,[45] Cook[46] and in the orthopaedic setting by Scholtes *et al*.[47] The rationale for choosing an expertise-based design for the CRISP trial was as follows: individual surgeons, because of their training and experience, are generally more proficient in a particular technique and so are likely to use primarily a single surgical approach. This could compromise the validity of a conventional RCT as the surgical expertise may be skewed toward the technique which is best established, most widely used or easiest to perform; a conventional RCT also has limited applicability since, by design, only surgeons experienced in OPCABG can take part. Surgical procedures that require a 'learning curve' are clearly disadvantaged as a minimum number of cases need to be performed and considerable experience is needed before a surgeon feels at ease with both techniques. Unless participating surgeons have expertise in both procedures, there is also a potential for differential crossover in the two arms of the trial (i.e. more crossovers in one direction than the other). OPCABG is less frequently performed than ONCABG, technically more demanding and may have a more prolonged 'learning curve'. Previous conventional RCTs have been criticised for recruiting 'inexperienced' OPCABG surgeons, resulting in poor OPCABG results with an excess of graft occlusion and not the best ONCABG surgeons.[48] Expertise-based randomisation was chosen to avoid these problems. The surgeon eligibility criteria for participation in the CRISP trial are described in *Settings*.

Changes to trial design after commencement of the trial

After CRISP had been recruiting for 10 months, the Trial Steering Committee (TSC), in reviewing the recruitment challenges CRISP was experiencing at the time (see *Chapter 3, Barriers to recruitment* for further detail), agreed that the randomisation method should be relaxed and that both expertise-based and within-surgeon randomisation should be permitted, but with expertise-based randomisation remaining the preferred option when staff availability and logistics permitted its use. The CRISP randomisation system was then updated to record prospectively which allocation method, expertise based or within surgeon, was intended to be used for each patient recruited.

Participants

Eligibility criteria

Patients having isolated CABG surgery were eligible if they satisfied the following criteria:

- additive EuroSCORE of ≥ 5[49]
- non-emergency surgery
- operation to be carried out via a median sternotomy
- written informed patient consent.

Patients with an additive EuroSCORE of five or more are at higher risk of mortality and morbidity. The EuroSCORE is made up of 17 components:

- Age (one additive EuroSCORE point per 5 years from age 60 years).
- Sex (one additive EuroSCORE point if female).
- Chronic obstructive pulmonary disease (one additive EuroSCORE point if on bronchodilators or steroids for lung disease).
- Extracardiac arteriopathy (two additive EuroSCORE points if claudication, carotid stenosis > 50%, previous or planned surgery of the abdominal aorta, limb artery or carotid).
- Neurological dysfunction (two additive EuroSCORE points if disease severely affects ambulation or day-to-day function).
- Previous cardiac surgery (three additive EuroSCORE points if pericardium opened previously).
- Creatinine (two additive EuroSCORE points if > 200 µmol/l).
- Active endocarditis (three additive EuroSCORE points if on antibiotics for endocarditis).
- Critical preoperative state [three additive EuroSCORE points if on inotropes, IABP, acute renal failure (oliguria < 10 ml/hour), aborted sudden death, intermittent positive-pressure ventilation, ventricular tachycardia (VT), ventricular fibrillation (VF)].
- Unstable angina (two additive EuroSCORE points if on intravenous nitrates until arrival in operating theatre).
- Left ventricular ejection fraction (one additive EuroSCORE point if between 30% and 50%, three additive EuroSCORE points if < 30%).
- Recent MI (two additive EuroSCORE points if MI < 90 days before surgery).
- Pulmonary hypertension (two additive EuroSCORE points if systolic pulmonary artery pressure > 60 mmHg).
- Emergency surgery required (two additive EuroSCORE points).
- Not isolated CABG (two additive EuroSCORE points if major cardiac procedure with or without CABG).
- Surgery on the thoracic aorta (three additive EuroSCORE points if ascending, arch or descending aorta).
- Post-MI ventricular septal defect (four additive EuroSCORE points).

Note that the last four components are exclusion criteria from the trial and, therefore, patients would not accrue any EuroSCORE points from these components.

Patients having isolated CABG surgery were *not* eligible if they satisfied any of the following criteria:

- additive EuroSCORE of < 5
- emergency operation (immediate revascularisation for haemodynamic instability)
- concomitant cardiac procedure with CABG
- operation to be carried out via an incision other than a median sternotomy (e.g. anterolateral left thoracotomy)
- known contraindication to ONCABG or OPCABG (e.g. calcified aorta, calcified coronaries, small target vessels).

Changes to trial eligibility criteria after commencement of the trial

Following the first CRISP investigators meeting, held in November 2009, participant age of < 70 years was removed as an exclusion criterion. This change was implemented from January 2010.

Settings

Patients were recruited to the CRISP trial from specialist cardiac surgery centres in the UK and Kolkata, India.

The preferred method of randomisation for CRISP was expertise-based randomisation (see *Study design*). Surgeons at participating centres using this preferred method were eligible to join CRISP if they had a stated preference for either OPCABG or ONCABG and were approved by the TSC as being sufficiently experienced in their preferred technique (i.e. at least 100 operations).

If, after detailed discussion with the research team, it was agreed that expertise-based randomisation was not possible at a centre, stratified within-surgeon randomisation was used. Centres and surgeons that planned to use within-surgeon randomisation required approval from the TSC (prior to the randomisation criteria being relaxed part-way through the trial; see *Study design*). The surgeons concerned were required to provide evidence that they have expertise in both techniques (at least 100 operations carried out using each method) and that they used both techniques with similar frequency.

Interventions

Trial patients were randomised to

(a) CABG without CPB, i.e. OPCABG on the beating heart, via a median sternotomy incision, or
(b) CABG with CPB, i.e. ONCABG on a chemically arrested heart, via a median sternotomy incision.

The anaesthetic technique and method of myocardial protection used were in accordance with established local protocols. These aspects were not specified in the trial protocol as there is a consistent 30-day mortality of around 2% for CABG across most UK centres, suggesting that minor differences in anaesthetic technique and methods of myocardial protection do not have a major influence on perioperative mortality. Surgical details were recorded on the case report form (CRF).

The only requirement was that the centre/surgeon followed the randomisation allocation. If it proved necessary to convert from OPCABG to ONCABG during the operation, this was recorded on the CRF.

Outcomes

Primary outcome

The primary outcome was a composite end point of death or serious morbidity (CRISPSw) within 30 days of surgery (i.e. up to and including day 30). The components were (1) all-cause death after **C**ardiac surgery, (2) new onset **R**enal failure, (3) M**I**, (4) **S**troke, (5) **P**rolonged initial ventilation and (6) **S**ternal **w**ound dehiscence.

New-onset renal failure was defined as a postoperative creatinine value of > 200 µmol/l, a percentage increase from preoperative creatinine of $\geq 40\%$ and the need for renal replacement therapy (RRT). Dialysis/haemofiltration during CPB only did not constitute a requirement for RRT, and any patient who received RRT in the month prior to surgery was not eligible for this end point. The highest creatinine prior to any RRT was measured, along with preoperative and day 2 postoperative creatinine measurements for all patients.

Myocardial infarction was defined by (1) troponin I level of > 0.5 µg/l or troponin T level of > 0.2 µg/l and new pathological Q-waves with documented new wall motion abnormalities except in the septum, (2) creatine kinase MB isozyme (CK-MB) level of ≥ 10 upper limit of normal (non-Q MI), or

(3) electrocardiographic (ECG) changes consistent with infarction (new significant Q-waves ≥ 0.04 cm or a reduction in R-waves of > 25%, in at least two contiguous leads). It was originally intended that if blood results did not indicate a MI but ECG suggested a MI had occurred, then the results would be adjudicated by an independent committee masked to the randomised allocation. However, after a blinded review of the data, it was decided that blood results and preoperative and postoperative ECGs for all patients would be adjudicated in this manner and MI defined on consensus of the adjudicators. ECG and blood samples (troponin T or troponin I, when possible; CK-MB was only used only if these tests were not available) were taken for the assessment of cardiac markers on day 5 postoperatively and all tests were redone if there was any indication of a suspected MI at any other time.

Stroke was defined as new acute focal neurological deficit thought to be of vascular origin, with signs or symptoms lasting longer than 24 hours and confirmed by a neurologist. Imaging was encouraged to further delineate between an ischaemic or haemorrhagic event.

Prolonged ventilation was defined as 96 hours or more, excluding any periods of reintubation following the initial extubation.

Sternal wound dehiscence was defined as requiring non-pharmacological intervention (e.g. vacuum-assisted closure dressing or reoperation). Any component events that occurred either prior to surgery or > 30 days after surgery were recorded but not included in the 30-day composite outcome.

Secondary outcomes

Secondary outcomes were:

(a) duration of cardiac intensive care unit (CICU) stay during the index hospital admission (excluding any periods when the patient was returned to CICU after initial discharge), calculated as the time from operation end to initial discharge from CICU
(b) duration of hospital stay during index hospital admission, calculated as the time from operation to discharge from the cardiac unit
(c) quality-of-life (QoL) assessment at recruitment and 4–8 weeks after surgery, measured using Rose Angina Questionnaire (short),[50] Canadian Cardiovascular Society (CCS) angina class,[51] European QoL-5 Dimensions (EQ-5D)[52] and Coronary Revascularisation Outcome Questionnaire (CROQ)[53]
(d) resource utilisation, determined by hospital resources during index admission
(e) cost-effectiveness, determined by within-trial cost per CRISPSw event averted, extrapolated cost per life-year gained and per quality-adjusted life-year (QALY) gained.

In addition, UK centres were randomised such that all patients operated at that centre received one of three different EQ-5D questionnaires: (1) the standard EQ-5D three-level questionnaire, (2) an extended five-level version with descriptors for all five levels, (3) an extended five-level version with descriptors for just the three original levels[54] (see *Appendix 2*). An intended substudy of CRISP was to compare patient responses using the three scoring systems in patients undergoing coronary surgery.

Adverse events

Expected events were specified in the CRISP protocol (see *Appendix 3*). The protocol states that events listed are expected in the period from surgery and discharge from hospital after the operation. Any event outside this window is considered unexpected. Expected events were captured through purpose-designed CRFs (see *Appendix 4*). Unexpected events were captured in free-text format.

Changes to trial outcomes after commencement of the trial

Some small changes were made after the trial commenced at the recommendation of the Data Monitoring and Safety Committee (DMSC). First, the need to independently adjudicate blood test and ECG results for inconsistencies in the reporting of the MI primary outcome element was added. Second, in order to reduce any possible systematic bias, the definition of the new onset renal failure primary outcome element was

changed from the need for RRT alone to the need for RRT and the fulfilment of clinical creatinine criteria. Finally, the collection of patient-reported CCS angina class was added to complement the Rose angina class also being collected.

The original intention of the trial was to follow-up patients for 1 year post surgery, but this was reduced to 4–8 weeks owing to the premature termination of the trial. Amendments were required to secondary outcomes to accommodate this: (1) all QoL outcomes were changed from assessment at recruitment, 4–8 weeks and 1 year post surgery to recruitment and 4–8 weeks alone; (2) resource use was changed from during 1 year to during the index hospital admission and (3) intended secondary outcomes of survival free from death or serious morbidity at 1 year and survival at 3 months were removed.

Sample size

The study sample size was set at 5418 patients (2709 per group). Pooled data collected from Bristol and Oxford cardiac databases were used to inform the sample size calculation. The data suggested an expected incidence of the composite primary outcome of 9.3% for patients with a preoperative EuroSCORE of ≥ 5. As all patients randomised to a given surgeon under expertise-based randomisation will have had their operations using the same technique, they cannot be regarded as independent of each other. Assuming that 80 surgeons would take part in the trial, the resultant intraclass correlation coefficient (ICC) was estimated from data from Bristol and Oxford cardiac databases to be 0.005. Using these assumptions, a sample size of 5418 patients had 90% power to detect a 30% reduction in RR with 5% significance (two tailed).

The DMSC periodically reviewed the safety data. At the start of the trial, two interim analyses of clinical outcomes were proposed: (1) when 50% of participants had been followed up to 30 days and (2) when 50% of participants had completed the trial (i.e. had been followed up for 12 months after surgery, the end of follow-up according to the original trial design). It was proposed that the trial should continue as planned unless there was a statistically significant difference between the two surgical approaches, with $p \leq 0.001$. These interim analyses were not undertaken owing to the premature termination of the trial (see *Chapter 3, Decision to close the trial early*).

Randomisation

Randomised treatment allocations were internet based and generated by Sealed Envelope Ltd, London, UK.[55] Allocations were stratified by centre and cohort-minimisation used to minimise imbalance of key prognostic factors (age, sex, urgency of operation, poor LV function, impaired renal function, previous stroke, redo CABG and significant pulmonary disease) across the OPCABG and ONCABG groups. Patients were randomly assigned in a 1 : 1 ratio.

Using an internet-based randomisation system ensured that allocations were concealed until all data that could uniquely identify the patient, confirm eligibility and establish stratification and cohort minimisation groups were entered. Access to the system was password protected and only available for designated site staff. Randomisation was carried out after the trial co-ordinator or research nurse had obtained written informed patient consent. The timing of expertise-based randomisation was carefully chosen to leave enough time to schedule the surgery, but also to minimise the time between randomisation and surgery and, therefore, reduce the possibility of outcome events or cancellation of surgery occurring in this period. Within-surgeon randomisation was usually carried out as close as possible to surgery. Any patients who were unexpectedly rescheduled retained their study numbers and randomised allocation and every effort was taken to ensure the rescheduled operation was carried out by an appropriate surgeon participating in the trial, according to the randomisation method used and the assigned allocation.

Blinding

It was not possible to blind the surgeons or those involved in the postoperative care of the patients. However, at most centres, postoperative care follows strict protocols that are not ONCABG or OPCABG specific. Patients were not explicitly informed of their allocation and the external signs of surgery were similar for both groups. The careful choice of objective, clinically defined primary outcome components should minimise bias. In addition, the individuals undertaking the adjudication of MI data were masked to the treatment allocation.

Data collection

Data collection was performed both while the patient was under the care of the cardiac unit and again at their standard 4–8 week postoperative outpatients appointment to identify any elements of the primary outcome and/or adverse events (AEs). Data were collected from clinical records by research nurses and/or clinical trial co-ordinators. Purpose-designed CRFs were used to record data at each stage of a patient's journey through the trial (see *Appendix 4*), with the key data collection points being pre surgery, the period from surgery to discharge and the routine 4–8-week follow-up appointment. Completed CRFs were then entered into the trial database via a password-protected web–based interface.

A bespoke trial database was designed using SQL server (2008). The database was intended to act as both a data storage facility and a trial management resource. For example, the database issued reminders when 4–8 week postoperative assessments were due, managed payment schedules to sites and provided facilities for tracking the progress of serious adverse event (SAE) reporting. Owing to the intended large sample size, a considerable amount of data validation was applied to the database. The validation rules were determined as a result of detailed discussions between clinical trial co-ordinators, research nurses, statisticians and database developers working on the study and were refined following any feedback from sites. Validation broadly included rules such as (1) the correct ordering of any dates and times, e.g. the date and time of CICU, high-dependency unit (HDU) or ward admission must be after the operation end date and time but prior to hospital discharge; (2) agreement of data on postoperative complications between the study CRFs and SAE forms for sponsor reporting, e.g. if there is an AE classified as serious on the CRFs an SAE form should be completed; (3) patient details (e.g. sex, age) and stratification/cohort minimisation data entered on the study CRFs should match that entered on the internet-based randomisation system; and (4) miscellaneous validation of related data recorded on different CRF pages, e.g. if the patient is recorded as being reintubated twice, there should be two reintubation and re-extubation dates and times entered on the relevant CRF. See *Appendix 4*, *Figure 1*, for an example of a message to the user if validation rules were not met.

Statistical methods

Analyses of the primary and secondary outcomes were carried out on the basis of intention to treat (ITT). The analysis (ITT) population consisted of all randomised patients excluding patients who died prior to surgery, patients who withdrew prior to surgery as it was decided not to perform surgery and patients who withdrew at any time and were unwilling for any data collected to be used. Continuous variables were summarised using the mean and standard deviation (SD) [or median and interquartile range (IQR) if the distribution was skewed] and categorical data were summarised as a number and percentage. All treatment comparisons are presented as effect sizes with 95% CIs, and p-values of < 0.05 from likelihood-ratio tests have been considered statistically significant. However, as the trial was stopped early, it was very underpowered to detect clinically important differences.

It was intended to adjust all formal comparisons of OPCABG versus ONCABG for surgeon and the factors used in the cohort minimisation. However, owing to the reduced sample size and resultant low event rates

of some of the cohort minimisation factors, all models were adjusted for age, sex and operative priority as fixed effects and surgeon as a random effect. All underlying model assumptions were checked using standard methods (e.g. residual plots, tests for normality or for proportional hazards). Outlying observations that meant models did not fit the data adequately were excluded from analyses and are indicated in table footnotes.

The primary analysis is the proportion of patients experiencing the composite outcome of death or major morbidity (CRISPSw) up to 30 days and has been analysed using logistic regression with the treatment effect reported as an OR. Component events have been presented separately by occurrence pre or post hospital discharge. The duration of CICU stay and hospital stay were analysed as time to event outcomes, with patients who die prior to CICU/hospital discharge censored at the time of their death. Comparisons were performed using Cox proportional hazards models and treatment comparisons are presented as HRs. The validity of the assumption of proportional hazards was tested and, if violated, a model with a time-dependent covariate (the interaction term between the treatment and the survival time) was used. Random effects terms were fitted via the use of shared frailty terms.[56]

For all QoL data, standard rules have been used to derive outcome measures. Rose angina and CCS angina class both result in ordinal outcomes ranging from no angina symptoms to ordered grades of angina symptoms. EQ-5D data are in two sections, the first consisting of five ordinal questions (which, for the patients who used the standard EQ-5D questionnaire, is converted into an EQ-5D single summary index) and the second a visual analogue scale. Finally, data from CROQ questionnaires are used to derive seven continuous scores, including an overall 'core total' score.

Rose and CCS angina class data at 4–8 weeks post surgery have been dichotomised into any angina symptoms versus no angina symptoms. Treatment groups have been compared using logistic regression, adjusting for the appropriate preoperative angina class as a categorical outcome, with treatment effects reported as ORs. Formal statistical comparisons of treatment effects have been performed only if > 10 patients in total experience the angina outcome (with at least one event in each treatment group). Responses to the five EQ-5D ordinal questions have been tabulated but no formal analyses undertaken (see *Appendix 2*, *Table 21*). EQ-5D single summary index and visual analogue scale data and the CROQ core total score have been analysed using linear mixed effects methodology. Pre and postoperative values were modelled jointly to avoid the necessity to either exclude cases with missing preoperative measures or to impute missing preoperative values. Multivariate normal models were fitted incorporating separate parameter estimates for the mean baseline response and for each treatment at the 4–8 week time point (i.e. saturated model with time fitted as a categorical variable).

Safety data have been reported on the safety population, defined as all randomised patients excluding patients who withdrew prior to surgery, as it was decided not to perform surgery, and patients who withdrew at any time and were unwilling for any data collected to be used. Expected events (i.e. listed in the study protocol as expected prior to hospital discharge following cardiac surgery) and unexpected events (any event not listed in the protocol occurring before discharge and any event occurring after hospital discharge) have been tabulated separately (see *Tables 15–17*), with events that meet the criteria (prolonged an ongoing hospitalisation/resulted in hospitalisation, resulted in death, was life-threatening or resulted in persistent or significant disability/incapacity) of a SAE identified. Events have been presented and grouped by the treatment received, rather than the treatment allocated, and no formal comparisons between treatment groups have been made.

No formal corrections have been made for multiple testing, but the number of statistical comparisons has been limited and our interpretation of the results takes into account the magnitude and consistency of effect estimates. No subgroup or sensitivity analyses were performed. A planned subgroup analysis to compare the treatment effect in patients with an additive EuroSCORE of < 8 and ≥ 8 was planned but not performed owing to the early termination of the trial.

Missing data in all tables are indicated by footnotes. There were no missing data for the primary outcome or the time to event outcomes. Missing data for QoL outcomes were infrequent (< 5%) and, therefore, cases with missing postoperative values have been excluded from analyses. For cases with complete postoperative but missing preoperative data, the joint modelling of continuous data avoids the necessity to impute such data under the assumption that data are missing at random, but for categorical data the most common category across both treatment groups has been imputed. Owing to the low levels of missing data, it was judged that more complex missing data approaches (e.g. multiple imputation) would be unlikely to recover any additional information.

All statistical models were fitted in Stata version 12.0 (StataCorp LP, College Station, TX, USA). All other analyses and data management were performed in SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Health economics

Given the early cessation of the trial (see *Chapter 3, Decision to close the trial early*), unit cost estimates for valuing resource utilisation data had not yet been collected. This, plus the small sample sizes at trial cessation, precludes the calculation of the costs associated with each method of CABG, as well as estimates of cost-effectiveness. Resource utilisation data reported for each arm of the trial are, therefore, limited to key items consumed during the index hospital admission for surgery, including duration of operation, duration on ventilation, time in CICU, time in HDU and time on a ward.

Following general guidance issued by the National Institute for Health and Care Excellence, continuous data are presented using mean and SDs for each group. Differences between groups are presented using the mean difference (MD) and 95% (bootstrapped) CI for the difference.

Chapter 3 Results

Centres

The CRISP trial planned to recruit patients from 40 centres, 20 in the UK and 20 overseas. In the recruitment period from October 2009 to March 2011, patients were recruited from eight centres in the UK and one centre in India. A total of 39 surgeons participated: 19 ONCABG specialists and 20 OPCABG specialists. The number of surgeons at each centre ranged from two to nine (*Table 2*). The proportion of consultant surgeons at a centre participating in CRISP ranged from 20% to 100%.

In addition to the nine participating centres, a further five UK centres (University College London; Sussex Cardiac Centre, Brighton; The Cardiothoracic Centre, Liverpool; Nottingham University Hospital; and South Tees Hospital, Middlesbrough) had the necessary approvals in place to start but had not recruited any trial participants before the study closed to recruitment in March 2011 at the request of the funder (see *Decision to close the trial early*). Two UK centres, in Edinburgh and Cardiff, and 10 overseas centres were at various stages of the research approvals process when the study closed (see *Appendix 1*).

Screened patients

A total of 787 patients were assessed for potential inclusion in the trial. Six hundred and eighty-one were excluded: 523 were ineligible, 82 were eligible but not approached, 74 were approached but did not consent and two were omitted for other reasons. The numbers of patients screened, found to be ineligible, not approached, did not consent and randomised are given by centre in *Table 3* and demonstrate different proportions of ineligible patients between centres (range 0% to 76%). This reflects the fact that some centres did not screen all potential patients.

The majority of ineligible patients [493 out of 523 (94%)] had an additive EuroSCORE of < 5. Other reasons for ineligibility, non-approach and non-consent are given in *Figure 1*. Reasons for eligible patients not being approached included (1) cancellations and transfers to another surgeon's list, (2) a decision not to operate, (3) time constraints and (4) a surgeon's decision.

The main reason given for patients declining to take part was personal reasons, followed by the patient having a preference for a specific surgeon.

Even at the Bristol and Oxford centres, where the screening data were most complete, 75 and 39 eligible patients, respectively, were identified each year on average: significantly fewer than the average 300 eligible patients identified retrospectively from an institutional database of all cardiac procedures over the same period in Bristol. The main reasons for the deficit were (1) not all surgeons were participating in CRISP, (2) only willing OPCABG surgeons could participate if logistical problems (e.g. time constraints or surgeon unavailability) required a within-surgeon allocation, (3) other trials were recruiting from the same pool of patients in the same time period (although CRISP was prioritised over other trials in Bristol).

TABLE 2 CRISP centres and number of participating surgeons by centre

	Number of surgeons	
Centre	ONCABG surgeons	OPCABG surgeons
Basildon	1	2
Blackpool	2	3
Bristol	3	6
King's College	3	1
Oxford	1	1
Papworth	1	1
Sheffield	2	1
Wolverhampton	4	2
India	2	3
Total	19	20

TABLE 3 Screening data by centre

		Excluded from study						
		Ineligible		Not approached	Did not consent	Other reason	Randomised	
Centre	Screened (*n*)	*n*	%[a]	*n*	*n*	*n*	*n*	%[a]
Basildon	13	2	15	1	4	0	6	46
Blackpool	44	17	39	2	4	0	21	48
Bristol	436	330	76	39	41	0	26	6
King's College	64	40	63	11	7	1	5	8
Oxford	132	93	70	15	5	0	19	14
Papworth	48	22	46	12	9	0	5	10
Sheffield	27	17	63	1	1	1	7	26
Wolverhampton	17	2	12	1	3	0	11	65
India	6	0	0	0	0	0	6	100
Total	787	523	66	82	74	2	106	13

a Percentage of screened patients.

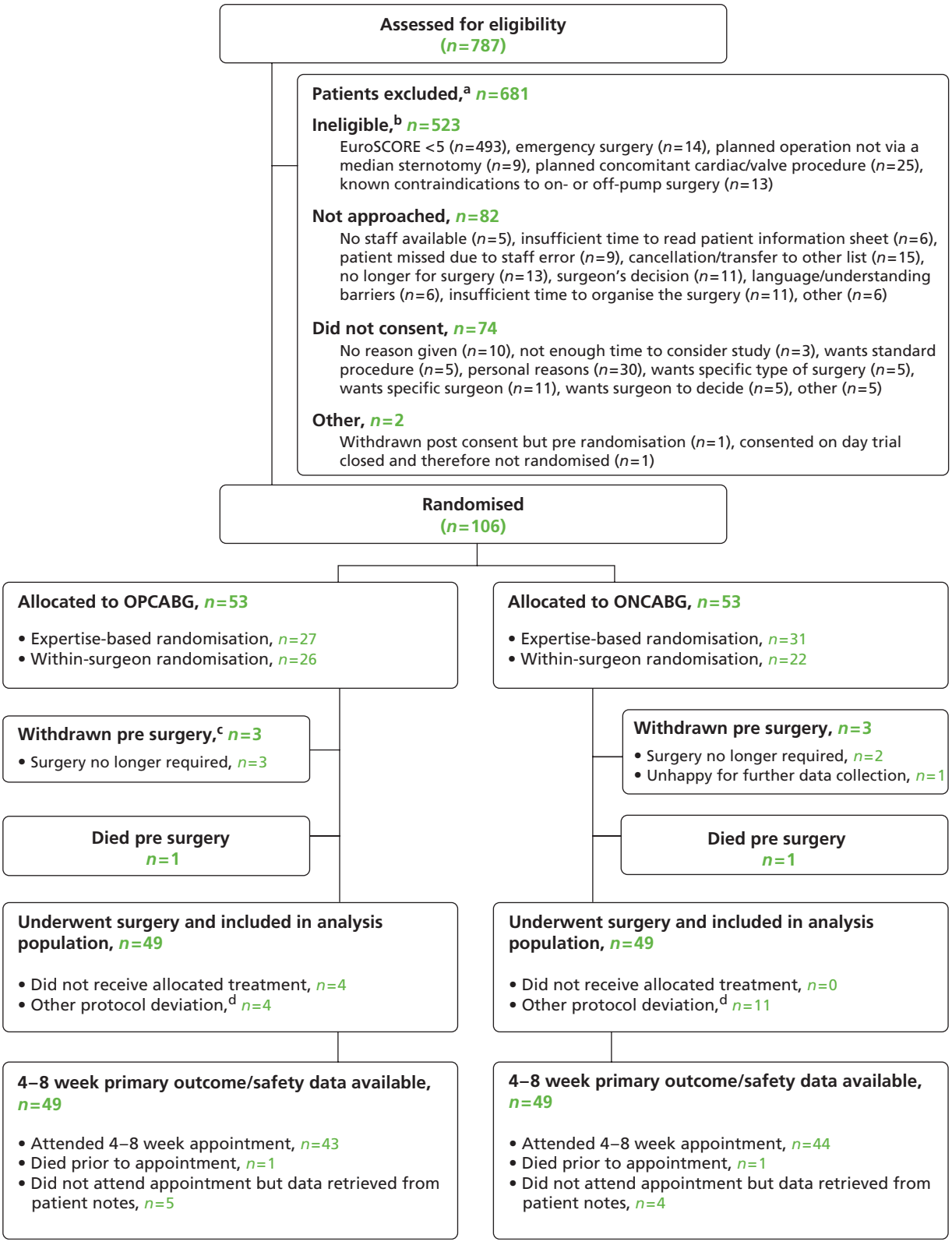

FIGURE 1 Flow of participants. a, The exclusions section is incomplete as not all sites have entered full screening data; b, some patients may be ineligible for more than one reason; c, one further patient (not included on flowchart) withdrew pre surgery but was happy for data collection to continue; therefore, the patient is included in all applicable analyses (for details of all withdrawals see *Table 8*); and d, for further details see *Table 9*.

Recruitment

A total of 106 eligible patients were recruited into the study from October 2009 to March 2011. Patient follow-up was completed in June 2011. The study was closed to recruitment in March 2011 at the request of the funder (see *Decision to close the trial early*).

Recruitment pathway

The logistics of identifying eligible patients, recruiting them into the trial and organising the surgery within an expertise-based allocation framework was recognised as the key challenge for participating centres. It was acknowledged that the recruitment pathway could vary between centres in order for them to meet this challenge while continuing to work and operate within national and local protocols. The recruitment pathway envisaged before commencement of the trial, modelled on the recruitment pathway at the Bristol centre, is described in *Figure 2*.

When presenting the study at site initiation visits it became apparent that this exact model would not be applicable at all centres. The model developed at Wolverhampton, where the majority of referrals are to a named surgeon, is shown in *Figure 3*.

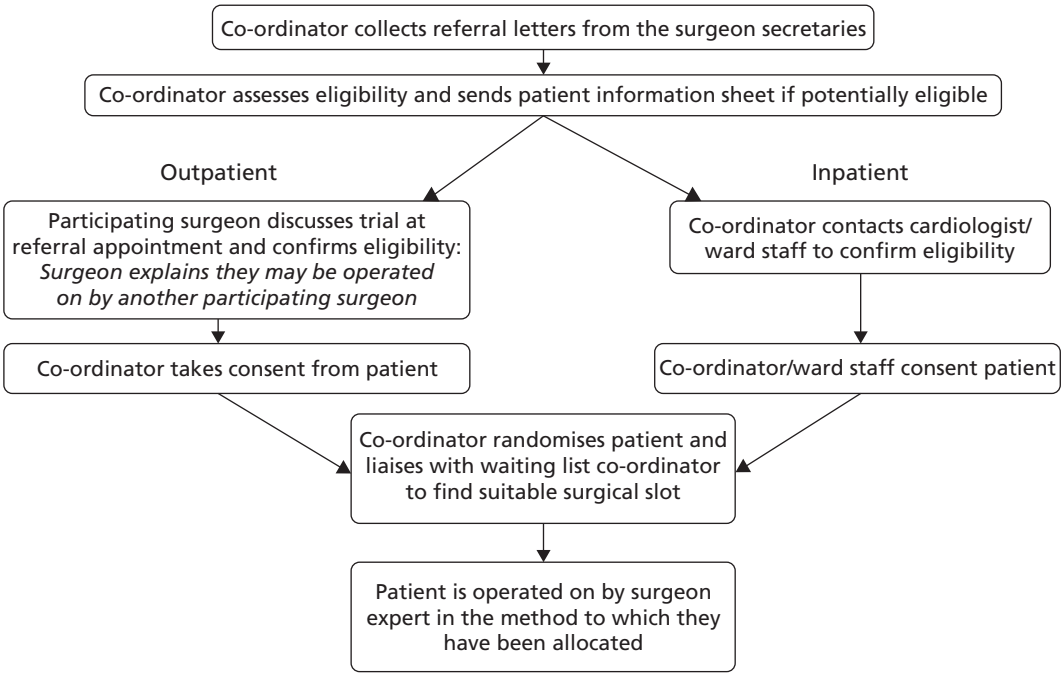

FIGURE 2 Recruitment pathway (Bristol model).

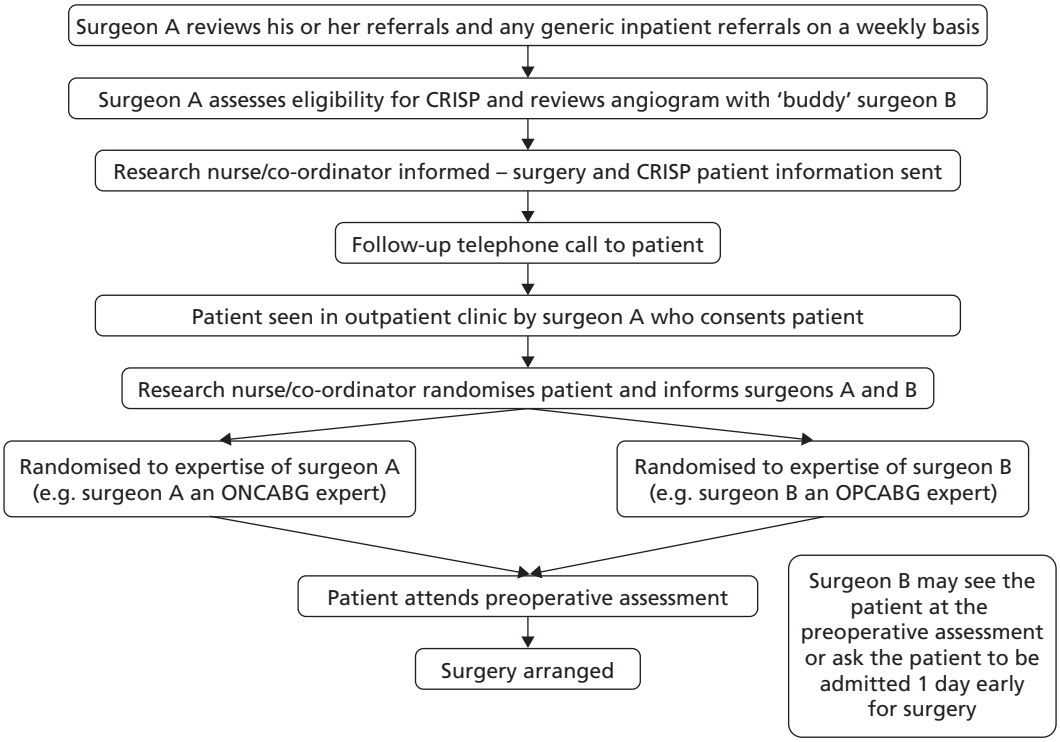

FIGURE 3 Recruitment pathway (Wolverhampton model).

Recruitment rate

When the CRISP trial was designed, it was estimated that each centre would recruit at least six patients per month. This estimate was based on data from the Bristol and Oxford centres, where between 200 and 300 eligible patients underwent CABG each year. Based on previous trials, it was anticipated that 40% of eligible patients would be recruited,[22] which would have resulted in an annual recruitment rate of between 80 and 120 patients per year. This target was not met at any participating centre. Two centres (Blackpool and Bristol) recruited five patients in 1 month and three centres (Blackpool, Wolverhampton and India) each recruited four patients in 1 month. The number of patients recruited by month and centre is shown in *Table 4* and cumulative predicted and actual recruitment is shown in *Figure 4*.

TABLE 4 Number of patients recruited by month and centre

	Month of randomisation																	
	2009		2010												2011			
Centre	November	December	January	February	March	April	May	June	July	August	September	October	November	December	January	February	March	Total
Basildon	0	0	1	3	0	0	0	0	0	0	2	0	0	0	0	0	0	6
Blackpool	0	0	0	0	0	0	4	5	2	2	2	0	1	0	3	1	1	21
Bristol	1	1	1	3	0	1	2	1	2	1	3	1	5	0	1	2	1	26
King's College	0	0	0	0	0	0	0	0	0	0	1	1	0	0	1	1	1	5
Oxford	0	0	0	0	3	3	3	1	1	1	3	1	2	1	0	0	0	19
Papworth	0	0	0	1	0	0	1	0	0	0	2	1	0	0	0	0	0	5
Sheffield	0	0	0	0	0	0	0	1	1	2	1	0	0	1	0	1	0	7
Wolverhampton	0	0	0	0	0	0	0	0	0	0	4	2	0	3	0	2	0	11
India	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	4	6
Total	1	1	2	7	3	4	10	8	6	6	18	6	8	5	5	9	7	106

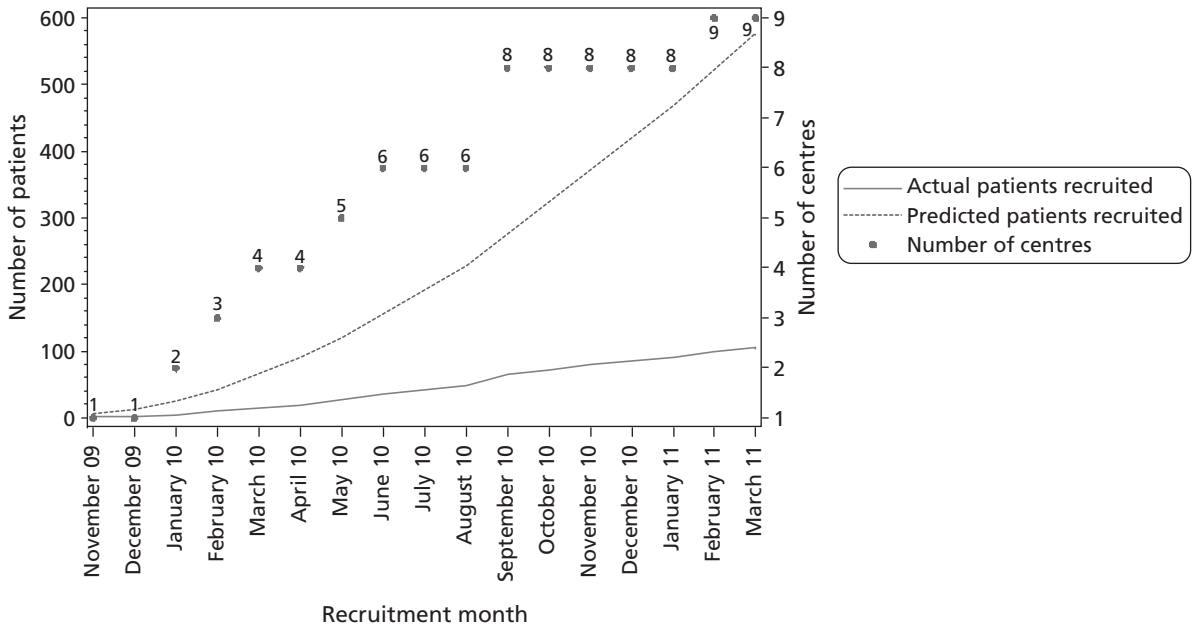

FIGURE 4 Predicted and actual recruitment. The predicted number of patients assumes six patients recruited per centre per month (predictions in study protocol).

Barriers to recruitment

During study visits to centres and through a survey of the UK centres, we sought to gain information on the characteristics and key challenges of the recruitment process at each of the CRISP centres. The information provided by the UK study centres is summarised in *Table 5*. The centres not listed did not respond. Five key barriers to recruitment emerged from the information gathered:

1. The number of participating surgeons. Recruitment using an expertise-based randomisation system was severely hampered if only two surgeons in a centre were taking part.
2. Access to potentially eligible patients. In some centres, urgent inpatients were transferred to the specialist cardiac centre several days before surgery, which provided sufficient time to gain the patient's consent and organise the surgery. In other centres, patients were not transferred until late on the day before surgery and the time window for recruitment was invariably too short.
3. Referral system. Some centres operated a generic referral system for all patients (i.e. patients were placed in a pool) while, in other centres, there was a mixture of generic referrals and referrals to a named surgeon. In some centres, the vast majority were named referrals. Surgeons were reluctant to 'share' patients referred to them whom they had met in clinic, as they believed that the patients would want to stay with the surgeon they had met.
4. Targets. The need to meet referral-to-treatment targets and other performance targets imposed locally.
5. Insufficient information in the referral letter to determine eligibility. The EuroSCORE is made up of several components, and frequently the information provided on referral was inadequate to allow the score to be calculated accurately.

The trial team and the participating centres worked hard to try and overcome these challenges. Meetings with referring cardiologists were arranged to increase awareness of the trial and the importance of providing complete referral data. Despite the team providing purpose-designed stickers with tick-boxes that could be added to the referral letters, the quality of the referral data did not improve. Options for seeking consent from urgent inpatients before the transfer to the cardiac centre were explored in the centres with a policy of transferring urgent inpatients the night before surgery. However, this proved unsuccessful; for example, in the Bristol area, the lead research nurse for the comprehensive local research

TABLE 5 Key challenges of the recruitment process

Centre	Patient pool	Recruitment opportunities and key challenges	Participating surgeons
Basildon	Aimed to recruit from urgent patient pool because few (< 20%) of the elective patients would be eligible (EuroSCORE of ≥ 5)	Urgent inpatients referred for surgery are transferred to the cardiac centre at least 3 days prior to surgery. Patients would be recruited, randomised and the surgery arranged in this 3-day window	One ONCABG, two OPCABG
Blackpool	Approximately 200 operations in eligible patients per year. Aimed to recruit from urgent patient pool because elective patients are allocated to a surgeon on the basis of their 'geographic patch' and the centre was of the opinion that patients want to stay with the allocated surgeon they meet in clinic	Inpatients referred for surgery are transferred to the cardiac centre several days prior to surgery. Patients would be recruited, randomised and the surgery arranged in this window. Soon after recruitment started, the centre stopped screening elective patients for the trial	Two ONCABG, three OPCABG
Bristol	Approximately 200 to 300 operations in eligible patients per year. Aimed to recruit eligible patients from both the elective and urgent inpatient pool		Three ONCABG, six OPCABG
King's College	Aimed to recruit eligible patients primarily from the elective patient pool	Urgent inpatients waiting in a 'feeder' hospital are not transferred to the cardiac centre until the night before surgery, which does not give enough time for patients to be given trial information, make a decision and the surgery to be arranged according to an expertise-based allocation	Three ONCABG, one OPCABG
Oxford	Patients are referred to named surgeons. The centre was of the opinion that patients want to stay with the allocated surgeon they meet in clinic	With only two surgeons participating, patients can only be recruited and randomised using an expertise-based allocation when both surgeons are available to operate, otherwise national or local protocols could be breached	One ONCABG, one OPCABG
Papworth		With only two surgeons participating, patients can be recruited and randomised using an expertise-based allocation only when both surgeons are available to operate. Otherwise national or local protocols could be breached	One ONCABG, one OPCABG
Sheffield	Aimed to recruit from urgent patient pool	Urgent inpatients referred for surgery are transferred to the cardiac centre a couple of days prior to surgery. Patients would be recruited, randomised and the surgery arranged in this window	Two ONCABG, one OPCABG
University College, London[a]		No specific research nurse or trial co-ordinator support was available – the centre was dependent on secretarial staff to run the trial. The centre was encouraged to contact the CLRN for research support	
Wolverhampton	The majority of patients are referred to a named surgeon	Established a buddy system to facilitate recruitment and the allocation within the expertise-based allocation framework	Four ONCABG, two OPCABG

CLRN, comprehensive local research network.
a No screening or recruitment took place at University College London.

network (CLRN) was not comfortable with asking her team of local research nurses to explain and seek consent for a trial that was taking place in another hospital. The option of a research nurse from the cardiac centre visiting the feeder hospital was also explored, but, in the UK, this requires explicit research and development approval at the feeder hospital, the need to identify a local principal investigator at each feeder hospital and the agreement of the patient's referring cardiologist. As there was no research funding available and no cardiac surgeon with an interest in the trial employed at the feeder hospitals, this proved impossible to achieve. The study had ethical approval to allow trial information to be faxed to a feeder hospital to allow potential participants time to consider the trial in advance any discussion with a surgeon and this approach was used at the Bristol centre. However, at other centres, e.g. Basildon, faxing patient information to feeder hospitals was not permitted.

In the centres outside the UK, the main barriers that hampered the set-up were (1) obtaining approved translations and back-translations of all essential documents, (2) insurance/indemnity issues (some centres, particularly in North America, required additional insurance/indemnity, which had cost implications) and (3) the per-patient funding available, which several potential investigators felt was insufficient.

Actions taken to increase recruitment

In August 2010, the TSC agreed that the expertise randomisation was a significant barrier to recruitment and that to alleviate the logistical challenges and improve recruitment, a change to within-surgeon randomisation was needed. The TSC agreed that the study could still deliver important data with the revised design and was mindful that the CORONARY trial[40] also began with an expertise-based design and changed to a within-surgeon allocation to alleviate recruitment difficulties (Professor David Taggart, University of Oxford, 2010, personal communication).

This TSC decision was communicated to CRISP centres via a study newsletter. Several OPCABG experts expressed their concerns about the decision. A significant number indicated that they would not be willing to operate ONCABG on high-risk patients and so they were effectively withdrawing from the trial. At a further meeting, held in October 2010, the TSC reviewed this feedback and agreed that a balance was needed, whereby recruitment could be improved through within-surgeon randomisation (thereby overcoming some logistical challenges by allowing late referrals to be included and recruitment to continue when the ONCABG expert is unavailable) and some expertise-based randomisation (to maintain the trial's unique design and allow all participating surgeons to remain in the trial). They therefore agreed to allow both methods of randomisation within a centre and the randomisation database was changed to record prospectively the randomisation method to be used for each recruited patient.

In summer 2010, the study team asked the Research Ethics Committee (REC) to allow an amendment relaxing the time between a potential participant being provided with the patient information sheet and consent being requested. When REC approval was first sought, this time was set at a minimum of 24 hours. The REC agreed to this time restriction being removed to allow urgent cases identified at short notice to be included in the study, provided patients were given sufficient time to consider the information and ask any questions.

Proposals to increase recruitment

The CRISP study team, the DMSC and TSC were all mindful that, even after relaxing the randomisation criteria and removing the 24-hour 'thinking time' restriction, the target 5418 of patients recruited was unlikely to be achieved in a realistic time scale. In order to address this, other changes to the trial design were considered.

- Widening the inclusion criteria. There was no support for this. It was agreed that the trial needed to focus on high-risk patients.
- Changes to the primary outcome to reduce the study size (two alternative changes to the primary outcome were considered).

- Replacing the composite end point with a new primary end point: time from surgery to 'fitness for hospital discharge'. The definition of fitness was made up of six objective components, chosen to avoid the subjective non-clinical factors associated with hospital discharge that can bias open trials. The six components (precise definitions for each of the components were to be agreed) proposed were:
  - normal temperature
  - normal pulse
  - normal rate of respiration
  - normal oxygen saturation
  - bowels opened since surgery
  - ability to walk 70 m or a flight of stairs (or reach pre surgery level of fitness if unable to do this pre surgery).
- Each component would be assessed on a daily basis from the medical notes, with the first day on which all the criteria were met being defined as day the patient was deemed 'fit for discharge'. Sample size calculations suggested that a 2-day difference in median time to fitness (8 vs. 10 days) could be detected with a sample size of approximately 1000 patients (with 90% power).
- The TSC felt that use of a fitness for discharge measure could demonstrate a material benefit, in terms of costs, as well as acting as a surrogate for the major clinical end point events included in the composite primary end point. However, the DMSC members were less convinced. The DMSC agreed that the end point should be changed in such a way that would allow a reduction in the sample size but was not in favour of a fitness for discharge measure on the grounds that it was not 'major' enough for such a large trial, that the scientific community would not value its clinical significance and that it favoured OPCABG.
- Extending the composite 30-day outcome to include (1) reoperation for bleeding, (2) low cardiac output, (3) new onset of atrial arrhythmia and (4) replacing new-onset renal failure with the less severe AKI. It was estimated that this revised composite outcome would have had occurred in approximately 30% of patients and that this increased incidence would have reduced sample size from 5418 to 1094 patients (90% power to detect a 30% reduction in RR). This option was presented to the funder (see *Decision to close the trial early*).

- Seeking REC approval to randomise eligible patients prior to consent – this was suggested by several investigators as a solution to the logistic challenges of expertise-based randomisation that would allow the patient to meet the allocated expert surgeon in clinic prior to surgery. It was not pursued for several reasons, (1) ethical concerns, (2) the potential for bias and the opportunity for the surgeon to influence the patient's decision to participate or not and (3) potential for imbalance between the groups if the consent rates differed between those allocated to an ONCABG or OPCABG expert.

Decision to close the trial early

After the TSC meeting in August 2010, which was attended by representatives from the funder, the study team were asked to prepare a recovery plan. This plan, which included the following recommendations, was submitted to the funder in September 2010.

- The original research question remained very important to surgeons, and to the NHS, and was substantially different from the question being addressed by the CORONARY trial.
- The primary end point should be revised to reduce the study size, as it was anticipated that recruitment would need to be extended to the year 2015 in order to reach the original target study size. A revised protocol, with a change to the primary end point (see *Proposals to increase recruitment*), would have allowed the two main aspects of the research question: (1) efficacy of off- versus on-pump methods in high-risk patients and (2) the methods compared among both off- and on-pump surgeons, to be answered within a shorter time frame and with significant saving of research costs.

Following further discussions regarding the primary end point with the TSC and DMSC in October and November 2010, respectively, this was followed up with a detailed proposal for the revised primary end point, based on extending the composite end point to include (1) reoperation for bleeding, (2) low cardiac output, (3) new onset of atrial arrhythmia and (4) replacing new-onset renal failure with the less severe AKI (see *Proposals to increase recruitment*). Using this revised end point, with revised recruitment rates based on the CRISP experience (two to three patients per centre per month) and recruiting from 20 centres, rather than the original target of 40 centres, the trial team estimated that the revised target sample size could be achieved by December 2012, with a financial saving of approximately £500,000 owing to the reduced sample size.

This recovery plan was considered by the NIHR-EME Board in February 2011 and the trial team were informed in March 2011 that the CRISP trial was to close. The Board did not feel that it would have funded the trial with the proposed revised end point and also owing to the overlap with the US funded CORONARY trial. The last CRISP patient was randomised on 11 March 2011.

Recruited patients

Screening data are compared between ineligible, eligible but non-consenting and randomised patients in *Table 6*. Ineligible patients were on average younger, less likely to be female and less likely to have preoperative conditions that result in higher additive EuroSCORE, e.g. chronic pulmonary disease, extracardiac arteriopathy, unstable angina or recent MI.

Differences in randomisation practices between centres are shown in *Table 7*. There was wide variation in the proportion of patients randomised using expertise-based randomisation and the median times from randomisation to surgery, although the numbers of randomised patients per centre are small. Overall, patients were randomised earlier using expertise-based randomisation (median 17.5 days prior to surgery, IQR 7–42 days) than using within-surgeon randomisation (median 3.5 days, IQR 1–16 days).

The numbers of urgent and elective patients recruited varied across centres (see *Table 7*). In Blackpool and the centre in India, the patients were predominantly urgent cases (20 out of 21 in Blackpool and 6 out of 6 in India), while in Oxford and Wolverhampton the majority were elective (15 out of 19 and 9 out of 11, respectively). At the other centres, similar numbers of elective and urgent cases were recruited.

Patient withdrawals

Eight of the 106 randomised patients were excluded from the analysis population: six patients withdrew prior to surgery and two patients died prior to surgery. Therefore, 98 patients underwent surgery and have been included in the principal analysis population, 49 in the OPCABG group and 49 in the ONCABG group (see *Figure 1*).

Five patients were withdrawn because it was decided that surgery was no longer required and one patient withdrew on the day of randomisation with no further details given. A further patient (OPCABG group) also withdrew their consent preoperatively owing to anxiety that they were not randomised to ONCABG; however, they were happy to be followed-up and for their data to be used and so remained in the analysis cohort. *Table 8* shows a summary of withdrawals; for full details, see *Appendix 2*, *Table 20*.

TABLE 6 Comparisons of ineligible, non-consenting and randomised patients

	Ineligible (*N* = 523)		Eligible but non-consenting (*N* = 74)		Randomised (*N* = 106)	
Eligibility criteria	***n***	**%**	***n***	**%**	***n***	**%**
Urgent operation	228	44	26	35	50	47
EuroSCORE of ≥ 5	30	6	74	100	106	100
EuroSCORE, median (IQR)	3 (1–3)	–	6 (5–8)	–	6 (5–8)	–
Age						
< 60 years (0 points)	132	25	0	0	2	2
60–64 years (1 point)	118	23	0	0	5	5
65–69 years (2 points)	109	21	6	8	11	10
70–74 years (3 points)	115	22	19	26	18	17
75–79 years (4 points)	42	8	31	42	34	32
80–84 years (5 points)	4	1	15	20	31	29
85–89 years (6 points)	3	1	3	4	5	5
90–94 years (7 points)	0	0	0	0	0	0
≥ 95 years (8 points)	0	0	0	0	0	0
Female (1 point)	70	13	24	32	25	24
Chronic pulmonary disease (1 point)	25	5	10	14	14	13
Extracardiac arteriopathy (2 points)	16	3	16	22	32	30
Neurological dysfunction (2 points)	2	0	3	4	3	3
Previous cardiac surgery (3 points)	3	1	2	3	3	3
Serum creatinine level > 200 µmol/l (2 points)	10	2	2	3	3	3
Active endocarditis (3 points)	0	0	0	0	0	0
Critical preoperative state (3 points)	4	1	2	3	3	3
Unstable angina (2 points)	6	1	7	9	11	10
LV function[a]						
Good (> 50%) (0 points)	371	81	47	66	60	57
Moderate (30–50%) (1 point)	71	16	17	24	41	39
Poor (< 30%) (3 points)	15	3	7	10	5	5
Pulmonary hypertension[b] (2 points)	5	1	0	0	5	5
Recent MI (2 points)	55	11	28	38	53	50

a Sixty-nine patients with missing data (66 ineligible and three eligible but refused consent).
b One patient with missing data (ineligible).

TABLE 7 Randomisation data by centre

	Randomised	Expertise-based randomisation		Time from randomisation to surgery[a,b]		Operative priority	
Centre	*n*	*n*	%[c]	Median	IQR	Elective[d]	Urgent[d]
Basildon	6	4	67	2	1–14	3 (1)	3 (3)
Bristol	26	15	58	35.5	2–43	16 (13)	10 (2)
Blackpool	21	17	81	10	8–17	1 (0)	20 (17)
King's College	5	0	0	1	0–3	4 (0)	1 (0)
Oxford	19	12	63	5	1–34	15 (9)	4 (3)
Papworth	5	2	40	11	0–34	4 (2)	1 (0)
Sheffield	7	2	29	10	4–43	4 (1)	3 (1)
Wolverhampton	11	0	0	26	11–50	9 (0)	2 (0)
India	6	6	100	1	1–1	0 (0)	6 (6)
Total	106	58	55	10	2–37	56 (26)	50 (32)

a Overall times from randomisation to surgery: expertise-based randomisation (50 patients): median 17.5 days, IQR 7–42 days; within-surgeon randomisation (48 patients): median 3.5 days, IQR 1–16 days.
b Eight patients with missing data (six withdrawals pre surgery and two deaths pre surgery): Basildon, one patient; Blackpool, four patients; Oxford, two patients; and India, one patient.
c Percentage of randomised patients.
d Numbers in brackets are the numbers of patients recruited using expertise-based randomisation. Urgent patients are defined as those waiting in hospital for surgery. From the 2008 National Adult Cardiac Surgical Database Report:[57] the percentage of all non-emergency/salvage isolated CABG procedures (i.e. including those with a EuroSCORE of < 5) that were urgent procedures was 31%.

TABLE 8 A summary of the withdrawals

	Randomised to OPCABG (*N* = 53)		Randomised to ONCABG (*N* = 53)		Overall (*N* = 106)	
Withdrawal	*n*	%	*n*	%	*n*	%
Any withdrawal	4	8	3	6	7	7
Decision taken by						
Patient	1	–	1	–	2	–
Clinician	3	–	2	–	5	–
Reason for withdrawal						
Surgery no longer required	3	–	2	–	5	–
Type of surgery allocated to	0	–	1	–	1	–
Patient did not give reason	0	–	1	–	1	–
Other reason	1	–	1	–	2	–

Protocol deviations

There were 21 protocol deviations in 19 patients (*Table 9*). Four patients randomised to OPCABG did not receive their allocation and there were no crossovers in the ONCABG group. Reasons for not receiving the allocated treatment were (1) development of ST segment on ECG during manipulation of the heart, (2) unplanned additional procedure required, (3) VF/VT arrest and (4) myocardial ischaemia with ST changes and low blood pressure. Other types of protocol deviations were (1) patient did not meet eligibility criteria ($n = 4$), (2) the operating surgeon was not on the approved list of trial surgeons ($n = 6$), (3) expertise-based randomisation was used but the surgeon was not an expert in the allocated surgery type ($n = 6$), and (4) within-surgeon randomisation was used with an ONCABG surgeon ($n = 1$). Data on all patients for whom there was a protocol deviation were included in the trial analyses on an intention-to-treat basis.

Patient follow-up

Follow-up data 4–8 weeks after surgery were obtained for all 98 patients in the principal analysis population: 87 patients attended their follow-up visit, two patients died prior to their visit and nine did not attend but data were retrieved from their clinical notes and/or general practitioners.

TABLE 9 Protocol deviations

	Randomised to OPCABG ($N = 49$)		Randomised to ONCABG ($N = 49$)		Overall ($N = 98$)	
Protocol deviation	***n***	**%**	***n***	**%**	***n***	**%**
Any protocol deviation	***8***	***16***	***11***	***22***	***19***	***19***
Did not receive allocated treatment[a]	4	8	0	0	4	4
Did not meet eligibility criteria[b]	3	6	1	2	4	4
Surgeon not on list of trial surgeons – expertise-based randomisation	0	0	6	12	6	6
Surgeon not on list of trial surgeons – within-surgeon randomisation	0	0	0	0	0	0
Expertise-based randomisation used but the surgeon not an expert in allocated surgery type	2	4	4	8	6	6
Within-surgeon randomisation used with ONCABG surgeon[c]	0	0	1	2	1	1

a Reasons for not receiving allocated treatment: development of ST segment on ECG during manipulation of the heart, unplanned additional procedure required, VF/VT arrest, myocardial ischaemia with ST changes and low blood pressure.
b Three patients (in the OPCABG group) did not meet the eligibility criteria owing to receiving additional procedures (mitral valve repair + left atrial maze + left appendage excision, suprapubic catheter, ligation of right lung bulla). The remaining patient (in the ONCABG group) was operated as an emergency. All patients were eligible at the time of consent but their status changed prior to surgery.
c Patient originally randomised using within-surgeon randomisation under an OPCABG surgeon and allocated to ONCABG. However, the surgery date was subsequently changed and the new surgeon was an ONCABG surgeon.Two patients were classified as protocol deviations for more than one reason. One patient (in the OPCABG group) did not receive the allocated reason and did not meet the eligibility criteria. One patient (in the ONCABG group) did not meet the eligibility criteria and expertise-based randomisation was used with the surgeon, not an expert, in the allocated surgery type.

Numbers analysed

Ninety-eight patients in the principal analysis population were included in all tables of demographic and operative characteristics and analyses of the primary outcome and duration of CICU/hospital stay. Ninety-seven patients were included in QoL analyses: (1) 90 patients with both preoperative and 4–8 weeks postoperative data, (2) six patients with preoperative data only and (3) one patient with postoperative data only. One hundred patients were included in the safety analyses: the 98 patients in the principal analysis population plus the two patients who died prior to surgery.

Baseline data and operative characteristics

Patient demographics and preoperative characteristics are presented in *Table 10*. The median EuroSCORE was 6 (IQR 5–8), the median age 77.1 years (IQR 71.9–80.6 years) and 23 patients (23%) were female. Most patients (95%) had good or moderate LV function and low proportions of patients (< 15%) experienced the remaining EuroSCORE components, with the exception of extracardiac arteriopathy (32%) and recent MI (49%). The majority of patients were non-diabetic (76%), were past or current smokers (62%) and had triple-vessel disease (77%). Approximately half (45%) of procedures were classified as urgent. Characteristics were generally similar between the two groups. However, more patients in the OPCABG group than in the ONCABG group had New York Heart Association (NYHA) functional classification of heart failure as Grade I (46% vs. 20%, respectively) and no patients in the OPCABG group had an abnormal heart rhythm or a pacemaker, but five patients in the ONCABG group had an abnormal heart rhythm and four had a pacemaker. Conversely, slightly more patients in the OPCABG group had > 50% disease in the left main stem and hypertension requiring treatment (39% vs. 27% and 84% vs. 76%, respectively). In addition, angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) II and beta blocker use was more common in the OPCABG group (82% vs. 65% and 84% vs. 65%, respectively). Finally, the average heart rate was lower in the OPCABG group [median 63 beats per minute (b.p.m.) (IQR 58–72 b.p.m.) vs. median 70 b.p.m. (IQR 60–85 b.p.m.)].

Operative characteristics are given in *Table 11*. Fewer patients had three or four grafts in the OPCABG group (63% vs. 79%, respectively). Use of the partial aortic clamp was more frequent in the ONCABG group than in the OPCABG group (88% vs. 65%, respectively) and use of a cell saver more frequent in the OPCABG group than in the ONCABG group (78% vs. 47%, respectively). More patients in the ONCABG group were paced than in the OPCABG group (27% vs. 14%, respectively) and more received red blood cell transfusions (31% vs. 16%, respectively). The blood product activated factor VII, which may or may not be given postoperatively, was not given to any participants in this cohort. There were no clear differences in terms of the grafts used and there were no deaths during surgery. The duration of the operation measured from the start of the operation (knife to skin) to the end of the procedure (patient leaves theatre) was slightly shorter in the OPCABG group (median 3.2 hours, IQR 2.7–3.9 hours) than in the ONCABG group (median 3.4 hours, IQR 3.0–4.2 hours). The MD was 0.22 of an hour (approximately 13 minutes).

TABLE 10 Patient demography and past history

Patient characteristic	Randomised to OPCABG (*N* = 49)		Randomised to ONCABG (*N* = 49)		Overall (*N* = 98)	
	n	%	*n*	%	*n*	%
EuroSCORE						
EuroSCORE, median (IQR)	6 (5–8)	–	6 (6–8)	–	6 (5–8)	–
EuroSCORE components						
Age (years)[a]						
Median (IQR)	76.1 (73.0–80.6)	–	77.7 (71.7–80.6)	–	77.1 (71.9–80.6)	–
Mean (SD)	76.4 (5.8)	–	75.7 (7.7)	–	76.1 (6.8)	–
Sex,[a] female (1 point)	11	22%	12	24%	23	23%
Chronic pulmonary disease (1 point)	5	10%	8	16%	13	13%
Extracardiac arteriopathy (2 points)	15	31%	16	33%	31	32%
Neurological dysfunction (2 points)	1	2%	2	4%	3	3%
Previous cardiac surgery[a] (3 points)	2	4%	1	2%	3	3%
Serum creatinine > 200 µmol/l[a] (2 points)	2	4%	1	2%	3	3%
Active endocarditis (3 points)	0	0%	0	0%	0	0%
Critical preoperative state (3 points)	0	0%	3	6%	3	3%
Unstable angina (2 points)	7	14%	3	6%	10	10%
LV function[a]						
Good (> 50%) (0 points)	30	61%	27	55%	57	58%
Moderate (30–50%) (1 point)	17	35%	19	39%	36	37%
Poor (< 30%) (3 points)	2	4%	3	6%	5	5%
Pulmonary hypertension[a] (2 points)	1	2%	3	6%	4	4%
MI within last 90 days (2 points)	25	51%	23	47%	48	49%
Other cardiac history						
NYHA[b]						
I	22	46%	10	20%	32	33%
II	17	35%	20	41%	37	38%
III	8	17%	18	37%	26	27%
IV	1	2%	1	2%	2	2%
Previous MI at any time	35	71%	34	69%	69	70%
Time between MI and surgery (months),[c] median (IQR)	1 (0–3.5)	–	1 (0–3)	–	1 (0–3)	–
Congestive cardiac failure	1	2%	1	2%	2	2%
Previous PCI	6	12%	10	20%	16	16%

TABLE 10 Patient demography and past history (*continued*)

Patient characteristic	Randomised to OPCABG (*N* = 49)		Randomised to ONCABG (*N* = 49)		Overall (*N* = 98)	
	n	%	*n*	%	*n*	%
Doppler carotid stenosis ≥ 70%						
No	16	33%	18	37%	34	35%
Yes	7	14%	5	10%	12	12%
Not known	26	53%	26	53%	52	53%
Heart rhythm[d] (sinus)	49	100%	44	90%	93	95%
Pacemaker[e]	0	0%	4	8%	4	4%
Number of vessels with coronary disease						
Single	1	2%	0	0%	1	1%
Double	9	18%	12	24%	21	21%
Triple	38	78%	37	76%	75	77%
Quadruple	1	2%	0	0%	1	1%
> 50% disease in left main stem	19	39%	13	27%	32	33%
Other cardiac history	8	16%	7	14%	15	15%
Non-cardiac history						
BMI (kg/m^2), mean (SD)	26.8 (4.3)	–	27.6 (5.2)	–	27.2 (4.7)	–
Smoking status						
No	18	37%	19	39%	37	38%
Ex-smoker > 1 month	26	53%	26	53%	52	53%
Yes	5	10%	4	8%	9	9%
Diabetes[f]	11	22%	13	27%	24	24%
Hypertension requiring treatment	41	84%	37	76%	78	80%
Haemofiltration/dialysis	0	0%	0	0%	0	0%
Previous stroke[a]	3	6%	5	10%	8	8%
Previous stroke or TIA	6	12%	7	14%	13	13%
Peripheral vascular disease	5	10%	7	14%	12	12%
Urgent operative priority[a,g]	20	41%	24	49%	44	45%
Preoperation tests						
Creatinine (μmol/l), median (IQR)	101 (87–121)	–	99 (87–116)	–	101 (87–121)	–
Haemoglobin (g/dl), mean (SD)	13.0 (1.6)	–	12.6 (1.8)	–	12.8 (1.7)	–
Mean arterial pressure (mmHg), mean (SD)	92.2 (13.0)	–	90.4 (13.4)	–	91.3 (13.2)	–
Heart rate (b.p.m.), median (IQR)	63 (58–72)	–	70 (60–85)	–	66 (59–75)	–

continued

TABLE 10 Patient demography and past history (*continued*)

Patient characteristic	Randomised to OPCABG (*N* = 49)		Randomised to ONCABG (*N* = 49)		Overall (*N* = 98)	
	n	%	*n*	%	*n*	%
Drugs on admission						
ACE inhibitors or ARB II	40	82%	32	65%	72	73%
Beta blockers	41	84%	32	65%	73	74%
Calcium antagonists	15	31%	16	33%	31	32%
Statins	45	92%	46	94%	91	93%
Aspirin and/or clopidogrel	49	100%	46	94%	95	97%
Time (days) aspirin/clopidogrel stopped pre operation, median (IQR)	5 (1–7)	–	5 (1–6)	–	5 (1–7)	–

BMI, body mass index; b.p.m., beats per minute; TIA, transient ischaemic attack.
a Cohort minimisation factor.
b One patient with missing data (in the OPCABG group).
c Four patients with missing data who have had a previous MI (three in the OPCABG group, and one in the ONCABG group).
d Two patients had AF/flutter and three patients had heart block (all in the ONCABG group).
e Two patients had a temporary pacemaker and two had a permanent pacemaker (all in the ONCABG group).
f In the OPCABG group: one patient had diet-controlled diabetes, eight were on oral medications and two were insulin controlled. In the ONCABG group: three patients had diet-controlled diabetes, six were on oral medications and four were insulin controlled.
g Urgent patients are defined as those waiting in hospital for surgery.

TABLE 11 Operative characteristics

Operative characteristic	Randomised to OPCABG (*N* = 49)		Randomised to ONCABG (*N* = 49)		Overall (*N* = 98)	
	n	%	*n*	%	*n*	%
Number of grafts						
2	18	37	10	20	28	29
3	24	49	34	69	58	59
4	7	14	5	10	12	12
Use of partial aortic clamp	32	65	43	88	75	77
Yes, median (IQR) number of times	1 (1–2)	–	1 (1–2)	–	1 (1–2)	–
Significant calcification of ascending aorta[a] (> 50%)	4	8	3	6	7	7
Sinus heart rhythm on chest closure[b]	47	96	47	96	94	96
Defibrillation	4	8	4	8	8	8
Tranexamic acid	26	53	27	55	53	54
Yes, median (IQR) (g)	2 (2–2)	–	2 (2–4)	–	2 (2–2)	–
Cell saver set up	38	78	23	47	61	62
Yes, median (IQR) (ml)	170 (0–410)	–	400 (0–680)	–	251 (0–500)	–
IABP	3	6	3	6	6	6
Inotropes (excluding noradrenaline)	10	20	7	14	17	17
Noradrenaline	16	33	12	24	28	29
Vasodilators	12	24	11	22	23	23
Pacing	7	14	13	27	20	20
Red blood cells used	8	16	15	31	23	23
Yes, median (IQR) units	1.5 (1–2.5)	–	2 (1–2)	–	2 (1–2)	–
Plasma used	2	4	0	0	2	2
Platelets used	4	8	5	10	9	9
ONCABG surgery specific details[c]	**Randomised to OPCABG (*N* = 4)**		**Randomised to ONCABG (*N* = 49)**		**Overall (*N* = 53)**	
	n	%	*n*	%	*n*	%
Myocardial protection						
Warm temperature	1	25	14	29	15	28
Blood solution	4	100	47	96	51	96
Antegrade infusion mode[d]	4	100	44	92	48	92
Continuous timing	1	25	4	8	5	9
Cumulative cross-clamp time (minutes), median (IQR)	41 (19.5–77)	–	45 (35–57)	–	44 (35–57)	–
Total bypass time (minutes), median (IQR)	91.5 (60.5–146)	–	71 (62–92)	–	71 (62–95)	–

continued

TABLE 11 Operative characteristics (*continued*)

Graft details	Grafts of patients randomised to OPCABG (*N* = 136)		Grafts of patients randomised to OPCABG (*N* = 142)		Overall (*N* = 278)	
	n	%	*n*	%	*n*	%
Carotid endarterectomy[e]	0	0	1	1	1	0
Proximal						
Aorta	63	46	71	50	134	48
LIMA (in situ)	51	38	44	31	95	34
RIMA (in situ)	4	3	5	4	9	3
Gastroepiploic (in situ)	0	0	2	1	2	1
Saphenous vein (piggyback/skip)	8	6	13	9	21	8
Radial artery (piggyback/skip)	7	5	1	1	8	3
LIMA (piggyback/skip)	3	2	4	3	7	3
RIMA (piggyback/skip)	0	0	1	1	1	0
Arch/great vessels	0	0	1	1	1	0
Conduit[f]						
Saphenous vein	71	52	75	54	146	53
Radial artery	9	7	7	5	16	6
LIMA	46	34	44	31	90	33
RIMA	10	7	6	4	16	6
Cryopreserved	0	0	8	6	8	3
Distal						
Left anterior descending artery	47	35	50	35	97	35
Diagonal 1	17	13	11	8	28	10
Diagonal 2	1	1	3	2	4	1
Obtuse marginal 1	33	24	31	22	64	23
Obtuse marginal 2	8	6	6	4	14	5
Posterolateral circumflex	4	3	4	3	8	3
Main right coronary artery	4	3	5	4	9	3
Posterior descending artery/ posterior interventricular	21	15	31	22	52	19
Posteroventricle	1	1	1	1	2	1

LIMA, left internal mammary artery; RIMA, right internal mammary artery.

a Four were defined clinically in the OPCABG group and two in the ONCABG group. Defined on investigation for the remaining patient (ONCABG group).

b Two patients in the OPCABG group and one in the ONCABG group had AF/flutter. One patient in the ONCABG group had heart block.

c Only relevant for (1) patients randomised to ONCABG who did not convert to OPCABG and (2) patients randomised to OPCABG who converted to ONCABG.

d One patient with missing data (ONCABG group).

e For the graft with coronary endarterectomy: proximal = aorta, conduit = saphenous vein, distal = posterior descending artery/posterior inter ventricular.

f Two grafts with missing data (ONCABG group).

Primary outcome

In both the OPCABG and ONCABG groups, 6 out of 49 (12%) patients experienced the primary outcome in the first 30 days (*Table 12*). The estimated treatment effect, adjusted for age, sex, operative priority and surgeon, was OR = 1.07 (95% CI 0.27 to 4.14; $p = 0.93$).

The most commonly occurring component of the primary outcome was MI (occurring in six patients) and the rarest were death and sternal wound dehiscence (experienced by one patient each). All but one of the constituent events occurred prior to discharge from hospital following cardiac surgery.

Secondary outcomes

Quality of life

Quality-of-life data are presented in *Table 13*. For both angina classifications there is no evidence of any statistically significant differences between the groups in comparing any angina versus no angina (Rose angina class: OR = 1.89, 95% CI 0.54 to 6.61; $p = 0.30$; CCS angina class: OR = 0.79, 95% CI 0.23 to 2.65; $p = 0.70$).

The results presented in *Table 13* combine the results over the three versions of the EQ-5D questionnaire. EQ-5D data split by questionnaire type (three-level, five-level with five descriptors, five-level with three descriptors) are given in *Appendix 2*, *Tables 21* and *22*. The single summary index score was generated by applying the social tariff to patients' responses to the standard three-level version of the EQ-5D ($n = 29$ patients). A tariff to convert responses on the five-level version of the EQ-5D to a single index value is currently under development.

TABLE 12 Primary outcome to day 30

Component of the primary outcome	Randomised to OPCABG (*N* = 49)		Randomised to ONCABG (*N* = 49)		OR (95% CI)	*p*-value
	n	%	*n*	%		
At any time						
Primary outcome	6	12	6	12	1.07 (0.27 to 4.14)	0.93
Death	0	0	1	2		
New-onset renal failure[a]	2	4	1	2		
MI	3	6	3	6		
Stroke	2	4	1	2		
Prolonged ventilation[b]	1	2	2	4		
Sternal wound dehiscence[c]	0	0	1	2		
Pre hospital discharge						
Primary outcome	5	10	6	12		
Death	0	0	1	2		
New-onset renal failure	2	4	1	2		
MI	3	6	3	6		
Stroke	1	2	1	2		
Prolonged ventilation	1	2	2	4		
Sternal wound dehiscence	0	0	1	2		
Post hospital discharge						
Primary outcome	1	2	0	0		
Death	0	0	0	0		
New-onset renal failure	0	0	0	0		
MI	0	0	0	0		
Stroke	1	2	0	0		
Sternal wound dehiscence	0	0	0	0		

a Highest creatinine values: for three patients with new onset renal failure: ONCABG group 367 µmol/l; OPCABG group 320 µmol/l and 440 µmol/l. There were 23 patients with postoperative creatinine > 200 µmol/l and/or > 1.4 times baseline creatinine who did not require RRT (14 in the ONCABG group and nine in the OPCABG group).
b Includes two patients (in the ONCABG group) ventilated for hospital-acquired pneumonia.
c Further intervention was required (V.A.C. dressing).
Patients experiencing components of the primary outcome outside of the 30-day postoperative time window:
Two patients died prior to surgery (one in the ONCABG group and one in the OPCABG group). See *Adverse events and postoperative complications* for further details. One patient had a MI prior to surgery (in the ONCABG group). Three patients died more than 30 days after surgery (one in the ONCABG group and two in the OPCABG group). See *Adverse events and postoperative complications* for further details. One patient had a stroke more than 30 days after surgery (in the ONCABG group).
Patients experiencing multiple primary outcome events:
One patient (in the OPCABG group) had renal failure and MI. One patient (in the OPCABG group) had MI and prolonged ventilation. One patient (in the ONCABG group) had renal failure, a stroke, prolonged ventilation and died.

TABLE 13 Quality of life before and 6–8 weeks after surgery

	Preoperative				4–8 weeks postoperative					
	Randomised to OPCABG (*N* = 48)		Randomised to ONCABG (*N* = 48)		Randomised to OPCABG (*N* = 46)		Randomised to ONCABG (*N* = 45)			
Quality-of-life measure	*n*	%	*n*	%	*n*	%	*n*	%	Effect (95% CI)	*p*-value
Rose and CCS angina class										
Rose angina[a]										
No angina	21	44	14	29	35	76	37	82	OR 1.89 (0.54 to 6.61)[b]	0.30
Grade I	11	23	18	38	6	13	5	11		
Grade II	16	33	16	33	5	11	3	7		
CCS class[c]										
Asymptomatic	10	21	9	19	37	84	34	81	OR 0.79 (0.23 to 2.65)[b]	0.70
Grade I	11	23	6	13	2	5	3	7		
Grade II	15	31	18	38	4	9	5	12		
Grade III	9	19	10	21	0	0	0	0		
Grade IV	3	6	5	10	1	2	0	0		
EQ-5D categorical responses[d]										
Mobility										
No problems walking about	26	54	21	44	31	67	26	58		
Slight problems walking about	5	10	2	4	3	7	3	7		
Some problems walking about	16	33	20	42	12	26	14	31		
A lot of problems walking about	0	0	4	8	0	0	1	2		
Confined to bed	1	2	1	2	0	0	1	2		

continued

TABLE 13 Quality of life before and 6–8 weeks after surgery (*continued*)

	Preoperative				4–8 weeks postoperative					
	Randomised to OPCABG (*N* = 48)		Randomised to ONCABG (*N* = 48)		Randomised to OPCABG (*N* = 46)		Randomised to ONCABG (*N* = 45)			
Quality-of-life measure	*n*	%	*n*	%	*n*	%	*n*	%	Effect (95% CI)	*p*-value
Self-care										
No problems with self-care	44	92	40	83	43	93	41	91		
Slight problems washing or dressing	0	0	1	2	2	4	1	2		
Some problems washing or dressing	3	6	6	13	1	2	3	7		
A lot of problems washing or dressing	1	2	0	0	0	0	0	0		
Unable to wash or dress	0	0	1	2	0	0	0	0		
Usual activities[e]										
No problems with usual activities	23	49	20	42	26	57	17	38		
Slight problems with usual activities	5	11	3	6	5	11	8	18		
Some problems with usual activities	16	34	20	42	14	30	19	42		
A lot of problems with usual activities	0	0	0	0	1	2	0	0		
Unable to perform usual activities	3	6	5	10	0	0	1	2		
Pain/discomfort[e]										
No pain or discomfort	20	43	21	44	26	57	23	51		
Slight pain or discomfort	10	21	5	10	7	15	10	22		
Moderate pain or discomfort	15	32	18	38	13	28	11	24		
A lot of pain or discomfort	1	2	0	0	0	0	0	0		
Extreme pain or discomfort	1	2	4	8	0	0	1	2		

Quality-of-life measure	Preoperative				4–8 weeks postoperative				Effect (95% CI)	*p*-value
	Randomised to OPCABG (*N* = 48)		Randomised to ONCABG (*N* = 48)		Randomised to OPCABG (*N* = 46)		Randomised to ONCABG (*N* = 45)			
	n	%	*n*	%	*n*	%	*n*	%		
Anxiety/depression[f]										
Not anxious or depressed	31	65	28	60	38	83	33	77		
Slightly anxious or depressed	7	15	6	13	3	7	2	5		
Moderately anxious or depressed	7	15	9	19	5	11	6	14		
Very anxious or depressed	0	0	0	0	0	0	1	2		
Extremely anxious or depressed	3	6	4	9	0	0	1	2		
EQ-5D single summary index and visual analogue scale[g]										
Single summary index[h]										
Median (IQR)	0.69 (0.69–0.78)	–	0.73 (0.51–0.84)	–	0.81 (0.73–1.00)	–	0.71 (0.69–1.00)	–		
Mean (SD)	0.666 (0.295)	–	0.653 (0.278)	–	0.829 (0.123)	–	0.748 (0.260)			
Visual analogue scale[e]										
Mean (SD)	68.6 (15.9)	–	65.9 (17.0)	–	76.5 (13.6)	–	70.8 (15.2)	–	MD 4.92 (–0.94 to 10.8)[i]	0.11
CROQ[g]										
Core total[j]										
Median (IQR)	51.4 (47.4–55.0)	–	48.8 (44.4–54.4)	–	52.0 (48.1–53.9)	–	51.5 (45.4–53.4)	–	MD 1.10 (–0.97 to 3.17)[i]	0.30
Symptoms[j]										
Median (IQR)	74.1 (60.4–86.9)	–	68.5 (54.2–85.7)	–	94.6 (89.9–100)	–	92.9 (85.7–98.2)	–		
Physical functioning										
Median (IQR)	71.9 (46.9–87.5)	–	50.0 (25.0–81.3)	–	75.0 (62.5–93.8)	–	68.8 (50.0–81.3)	–		

continued

TABLE 13 Quality of life before and 6–8 weeks after surgery (*continued*)

	Preoperative				4–8 weeks postoperative					
	Randomised to OPCABG (*N* = 48)		Randomised to ONCABG (*N* = 48)		Randomised to OPCABG (*N* = 46)		Randomised to ONCABG (*N* = 45)			
Quality-of-life measure	*n*	%	*n*	%	*n*	%	*n*	%	Effect (95% CI)	*p*-value
Cognitive functioning[j]										
Median (IQR)	80.0 (60.0–96.7)	–	86.7 (53.3–96.7)	–	93.3 (73.3–100)	–	90.0 (70.0–100)	–		
Psychosocial functioning[j]										
Median (IQR)	66.6 (58.9–86.6)	–	62.5 (47.3–84.8)	–	83.9 (75.0–91.1)	–	85.7 (71.0–91.1)	–		
Satisfaction[k]										
Median (IQR)					86.4 (75.8–100)	–	83.3 (69.4–91.7)	–		
AEs										
Median (IQR)					89.8 (79.5–93.2)	–	84.1 (79.5–90.9)	–		

a Eight patients preoperatively (two in the OPCABG group and six in the ONCABG group) and two patients at 4–8 weeks postoperative (one in the OPCABG group and one in the ONCABG group) have inconsistent data across questions. They have answered 'No' to question 1 'Do you ever have any pain or discomfort in your chest?' but 'Yes' to either question 2 'When you walk at an ordinary pace on the level does this produce the pain?' and/or question 3 'When you walk uphill or hurry does this produce the pain?'.
b OR is from a mixed effects logistic regression model (xtmelogit in Stata) comparing any angina (Grade I or higher) with no angina. Preoperative angina level, age, sex and operative priority are included as fixed effects and operating surgeon as a random effect.
c Five patients with missing postoperative data (two in the OPCABG group and three in the ONCABG group).
d For EQ-5D data split by questionnaire type (three-level, five-level with five descriptors, five-level with three descriptors) see *Appendix 2*, *Tables 21* and *22*.
e One patient with missing preoperative data (in the OPCABG group).
f One patient with missing preoperative data (in the ONCABG group), two patients with missing postoperative data (in the ONCABG group).
g For all EQ-5D and CROQ scales, higher scores indicate better QoL.
h Single summary index scores are only available for patients who completed the three-response version of the questionnaire. Therefore, the following numbers of patients are included in the analysis: preoperative – 13 in the OPCABG group and 16 in the ONCABG group; 4–8 weeks postoperative – 14 in the OPCABG group and 15 in the ONCBAG group. Owing to the small numbers of patients a treatment effect could not be reliably estimated.
i Treatment effect is from a mixed effects regression model (xtmixed in Stata) modelling preoperative and postoperative scores jointly to avoid the necessity to exclude patients with missing preoperative values. Age, sex and operative priority are included as fixed effects and operating surgeon and patient as random effects.
j One patient with missing postoperative data (in the ONCABG group).
k Six patients with missing postoperative data (four in the OPCABG group and two in the ONCABG group).
Data were collected for seven patients 1 year postoperatively, for details see *Appendix 2*, *Table 24*.

In general, for each of the five categorical response EQ-5D questions, slightly more patients in the OPCABG group than in the ONCABG group were classified as having no problems/symptoms both preoperatively and postoperatively; however, no formal statistical comparisons were made and the numbers of patients are low. The single summary index scores for the subset of patients completing the standard three-level version of the EQ-5D were similar at baseline, while postoperatively, the difference in the mean score between the groups was on average 0.081 (95% CI −0.076 to 0.237) higher in the ONCABG group. Similarly, on average, patients in the OPCABG group scored slightly higher on the EQ-5D visual analogue scale. However, a formal treatment comparison of postoperative scores adjusting for preoperative scores was not statistically significant (MD = 4.92, 95% CI −0.94 to 10.8; $p = 0.11$).

The CROQ QoL data also suggest that, on average, patients in the OPCABG score slightly higher both preoperatively and postoperatively, albeit with no statistically significant postoperative treatment differences (core total MD = 1.10, 95% CI −0.97 to 3.17; $p = 0.30$).

A small number of QoL data were collected at 1-year follow-up (see *Appendix 2*, *Table 24*).

Resource use

Resource-use data are summarised in *Table 14*. On average, patients randomised to ONCABG spent 0.22 of an hour (approximately 13 minutes) longer in surgery than patients randomised to OPCABG. Time on ventilation after surgery, measured from the time the operation ended to the time the patient was extubated, was longer for patients in the ONCABG group (median 7.1 vs. 5.7 hours). On average, patients randomised to ONCABG also spent longer in the CICU (median 27.7 vs. 26.0 hours), although this difference was not statistically significant (*Figure 5*). Of those admitted to HDU, the stay was, on average, 37.3 hours (1.6 days) longer in the ONCABG group. In total, six patients were not admitted to a ward; one (in the ONCABG group) had died postoperatively but prior to hospital discharge. On average, of the patients admitted to a ward, length of stay was again longer in the ONCABG group. After surgery, patients randomised to ONCABG spent longer in hospital than patients randomised to OPCABG (median 8 vs. 7 days, *Figure 6*).

TABLE 14 Resource use in the period from surgery to 6–8 weeks after surgery

Resource	Randomised to OPCABG (*N* = 49) *n*	%	Randomised to ONCABG (*N* = 49) *n*	%	Effect (95% CI)[a]
Intraoperative					
Duration of surgery (hours)[b]					
Median (IQR)	3.2 (2.7–3.9)	–	3.4 (3.0–4.2)	–	
Mean (SD)	3.39 (1.18)	–	3.61 (0.86)	–	MD −0.22 (−0.601 to 0.209)
Postoperative					
Red blood cells used	25	51	25	51	
If yes, median (IQR) units	1.0 (1.0–2.0)	–	2.0 (2.0–4.0)	–	
Plasma used	7	14	3	6	
Platelets used	9	18	5	10	
Any haemostatic agents used	16	33	17	35	
Tranexamic acid	10	20	11	22	
Activated factor VII	0	0	0	0	
Other haemostatic agent	6	12	8	16	
Duration of ventilation (hours)[c,d]					
Median (IQR)	5.7 (4.9–11.3)	–	7.1 (4.9–14.3)	–	
Mean (SD)	12.0 (23.2)	–	17.5 (36.4)	–	MD −5.48 (−18.13 to 6.36)
CICU stay[c,e]					
Median hours (IQR)	26.0 (21.3–65.1)	–	27.7 (20.7–66.5)	–	HR 1.15 (0.69 to 1.91)
Mean hours (SD)	45.9 (49.4)	–	55.1 (58.8)	–	MD −9.20 (−30.2 to 11.7)
Mean days (SD)	1.91 (2.06)	–	2.29 (2.45)	–	MD −0.38 (−1.26 to 0.48)
Admitted to HDU	29	59	27	55	
HDU stay[c,f]					
Median hours (IQR)	41.0 (25.8–72.0)	–	48.8 (29.0–100)	–	
Mean hours (SD)	57.95 (52.03)	–	95.23 (145.07)	–	MD −37.28 (−99.2 to 8.86)
Mean days (SD)	2.41 (2.17)	–	3.97 (6.04)	–	MD −1.55 (−4.36 to 0.38)
Admitted to ward	48	98	44	90	
Ward stay[f]					
Median hours (IQR)	98.0 (70.9–139)	–	94.8 (72.5–143)	–	
Mean hours (SD)	110.0 (56.37)	–	136.7 (126.9)	–	MD −26.7 (−68.5 to 15.1)
Mean days (SD)	4.58(2.35)	–	5.69 (5.29)	–	MD −1.11 (−2.97 to 0.47)

TABLE 14 Resource use in the period from surgery to 6–8 weeks after surgery (*continued*)

Resource	Randomised to OPCABG (*N* = 49) *n*	%	Randomised to ONCABG (*N* = 49) *n*	%	Effect (95% CI)[a]
Hospital stay[g]					
Median days (IQR)	7 (6–9)	–	8 (6–10)	–	HR 1.26 (0.81 to 1.95)
Mean days (SD)	8.49 (4.98)	–	10.12 (7.39)	–	MD −1.63 (−4.03 to 0.83)
Reoperation[h]	0	0	4	8	MD −0.082 (−0.159 to −0.005)
Other unplanned procedure[i]	3	8	0	0	MD 0.079 (−0.007 to 0.165)
Medications at discharge					
ACE inhibitors/ARB II	26	53	22	45	
Beta blockers	38	78	35	71	
Calcium antagonists	5	10	0	0	
Statins	45	92	47	96	
Aspirin/clopidogrel	47	96	47	96	
Medications at 4–8 weeks					
ACE inhibitors/ARB II[j]	24	50	26	55	
Beta blockers[j]	35	73	34	72	
Calcium antagonists[j]	7	15	2	4	
Statins[j]	42	88	43	91	
Aspirin/clopidogrel[j]	46	96	42	89	

a Confidence intervals for MDs are bootstrapped. HRs are from Cox proportional hazards models, with age and sex included as fixed effects, operative priority as a fixed effect (duration of CICU stay) or a time-dependent covariate (duration of hospital stay) and a shared frailty term for operating surgeon.
b The large SD in the OPCABG group was due to the presence of outliers.
c The median and mean values differ because the distributions are highly skewed.
d Initial ventilation time only, excluding any further periods of ventilation. Four patients were re-intubated: one patient was re-intubated for 9.6 hours duration and one patient was re-intubated for 521 hours duration (OPCABG group); one patient was re-intubated for 52.5 hours duration and one patient was re-intubated twice, firstly for 58 hours then for 67.4 hours (ONCABG group).
e Initial CICU admission only, excluding any further periods of readmission to CICU. Three patients were readmitted to CICU: one patient was readmitted for 27 days (in the OPCABG group) and two patients were readmitted for 2 days each (both in the ONCABG group). The time to discharge was treated as a censored observation for one patient (in the ONCABG group) who died in CICU (length of stay = 253 hours).
f Subset of patients admitted to HDU/ward. One patient was readmitted to HDU for 1 day, one patient for 3 days and one patient for 4 days (all in the ONCABG group). Two patients were readmitted to the ward for 4 days each (both in the ONCABG group).
g Estimated from operation date and hospital discharge date. The mean values for postoperative total inpatient stay for each group calculated using these dates are slightly greater than equivalent mean values generated by adding the individual CICU, HDU and ward components (based upon hours). The difference between the two groups, however, is similar regardless of the calculation approach.
h Data on duration or reason for reoperation were not collected.
i Data missing for 22 patients, as this question was not included on early versions of the CRFs.
j Three patients with missing data (one in the OPCABG group and two in the ONCABG group). Note that these are patients who did not attend the 4- to 8-week visit.

The three unplanned procedures in the OPCABG arm were (1) ligation of right lung bulla, (2) supra pubic catheter and (3) mitral valve repair and left arterial maze, and left appendage axis.

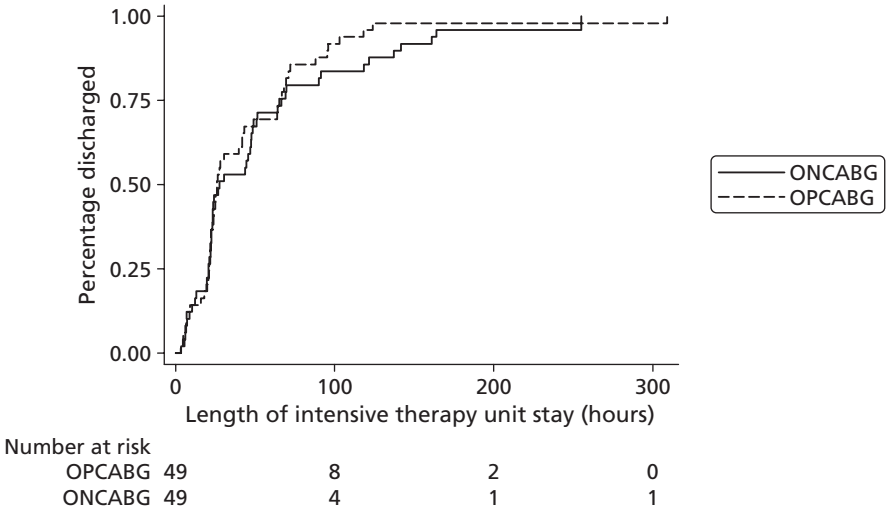

FIGURE 5 Duration of CICU stay.

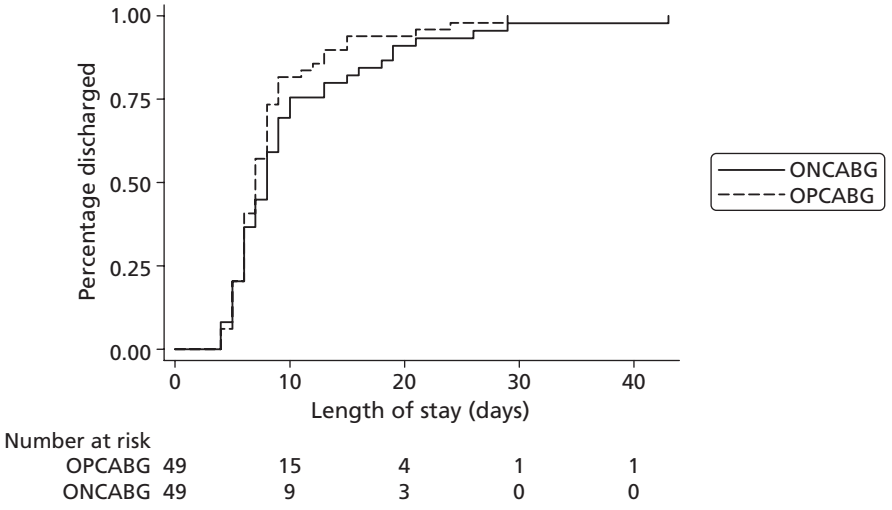

FIGURE 6 Duration of postoperative hospital stay.

Adverse events and postoperative complications

Expected adverse events

There were 74 expected AEs (i.e. listed in the study protocol as expected prior to discharge after cardiac surgery) (*Table 15*). Slightly fewer events occurred in patients who received OPCABG: 32 events in 27 out of 46 (59%) patients, compared with 42 events in 27 out of 54 (50%) patients who received ONCABG. Eight of these events were deemed to meet the criteria of a SAE: one event in a patient who received OPCABG and seven events occurring in six patients who received ONCABG. The most common expected AE was AF and the most common expected SAEs were respiratory infection and AF. There were eight instances of wound infections in patients who received ONCABG and three in patients who received OPCABG. There were no cases of coronary angiography, PCI or repeat CABG, or the need for a LV assist device (LVAD). No patient experienced acute respiratory distress syndrome, deep-vein thrombosis, pulmonary embolism, heparin-induced thrombocytopenia or a transient ischaemic attack (TIA).

TABLE 15 Expected AEs and SAEs

	Received OPCABG ($n = 46$)				Received ONCABG ($n = 54$)				Overall ($n = 100$)			
AE	**AE**	**%**	**SAE[a]**	**%**	**AE**	**%**	**SAE[a]**	**%**	**AE**	**%**	**SAE[a]**	**%**
Total number of events	***32***		***1***		***42***		***7***		***74***		***8***	
Patients with one or more events	***27***	***59***	***1***	***2***	***27***	***50***	***6***	***11***	***54***	***54***	***7***	***7***
Reoperated	0	0	0	0	4	7	1	2	4	4	1	1
Use of IABP	2	4	0	0	3	6	1	2	5	5	1	1
Respiratory infection	8	17	0	0	9	17	3	6	17	17	3	3
Tracheostomy	1	2	0	0	1	2	0	0	2	2	0	0
AF	16	35	1	2	16	30	1	2	32	32	2	2
Superficial wound infection: chest	1	2	0	0	4	7	0	0	5	5	0	0
Superficial wound infection: leg	2	4	0	0	4	7	1	2	6	6	1	1
Superficial wound infection: arm	0	0	0	0	0	0	0	0	0	0	0	0
Gastrointestinal complication	2	4	0	0	1	2	0	0	3	3	0	0

a Serious AEs are a subset of AEs.

Unexpected adverse events

Unexpected AEs (i.e. not listed in the study protocol or occurred after discharge from hospital) are given in *Table 16*. Again, slightly fewer events occurred in patients who received OPCABG: 12 events occurred in 11 patients (24%) versus 20 events in 16 patients (30%) who received ONCABG. The most common events were post-discharge wound infections. A summary of unexpected SAEs is given in *Table 17*. There were 37 unexpected SAEs, with slightly fewer in the patients who received OPCABG (12 vs. 25). Nine patients (20%) who received OPCABG and 15 patients (28%) who received ONCABG experienced one or more unexpected SAEs. Most unexpected SAEs occurred post discharge, and the most common reason for classifying as an event as serious was prolonging an ongoing hospitalisation/causing hospitalisation. Five post-discharge events were classified as possibly related to the method of surgery (two events in the OPCABG group, both breathing difficulties/shortness of breath, and three in the ONCABG group: stroke, sternal wound reopening and death following hospital admission) and one event was classified as probably related to the method of surgery (in the ONCABG group: shortness of breath and palpitations). Owing to the reduction in the follow-up period of the trial, seven of the events reported in *Table 17* (two in the OPCABG group and five in the ONCABG group) took place after the patient's 4- to 8-week follow-up appointment.

Thirty-three out of 46 patients (72%) who received OPCABG, 39 out of 54 patients (72%) who received ONCABG and 72 out of the total 100 patients (72%) experienced either the primary outcome or any AE. Similarly, 13 out of 46 patients (28%) who received OPCABG, 19 out of 54 patients (35%) who received ONCABG and 32 out of the total 100 patients experienced either the primary outcome or any SAE.

TABLE 16 Unexpected AEs

AE	Received OPCABG (*N* = 46) *n*	%	Received ONCABG (*N* = 54) *n*	%	Overall (*N* = 100) *n*	%
Total number of events	***12***		***20***		***32***	
Patients with one or more events	***11***	***24***	***16***	***30***	***27***	***27***
Events pre-hospital discharge						
Cardioverted for atrial flutter	0		1		1	
Coffee ground vomit	0		1		1	
CPAP for bibasal collapse	0		1		1	
Diarrhoea	0		1		1	
Dual chamber ICD implant – planned prior to intervention	0		1		1	
Left pleural effusion: ICD inserted and 500 ml drained	0		1		1	
Pleural effusion: right side	0		1		1	
Renal impairment (acute) (creatinine raised 273 max.)	1		0		1	
Required blood transfusions for haemophilia	0		1		1	
Urinary retention: failed trial without catheter. Commenced on tamsulosin – successful trial without catheter pre discharge	1		0		1	
UTI	1		1		2	
VT	1		0		1	
Wheezing	0		1		1	
Events post hospital discharge						
Attended accident and emergency with shortness of breath, underwent chest radiography and was diagnosed with fluid on the lung. Possible reoccurrence of pleural effusion. Prescribed diuretics and sent home that day	0		1		1	
Respiratory infection	1		3		4	
Superficial wound infection: chest	1		0		1	
Superficial wound infection: leg	6		5		11	
Radiograph taken for a suspected chest infection	0		1		1	

CPAP, continous positive airway pressure; ICD, implantable cardioverter defribrillator; max., maximum; UTI, urinary tract infection.

TABLE 17 Unexpected SAEs

AE		Received OPCABG (*N* = 46) *n*	%	Received ONCABG (*N* = 54) *n*	%	Overall (*N* = 100) *n*	%
Total number of events		***12***		***25***		***37***	
Patients with one or more events		***9***	***20***	***15***	***28***	***24***	***24***
Description of events							
Pre operative							
Death		1		1		2	
Other events	Emergency admission prior to surgery	0		1		1	
	MI	0		1		1	
Post operative but pre discharge							
Death		0		1		1	
Cardiac events	Reintubation and mechanical ventilation	1		0		1	
	Ventilator-associated pneumonia: heart failure	0		1		1	
	Acute coronary syndrome and pulmonary oedema	0		1		1	
Other events	Critical illness neuropathy	0		1		1	
	Diarrhoea/vomiting	0		1		1	
Post discharge							
Death		2		1		3	
Cardiac events	AF	1		0		1	
	Heart failure secondary to AF	0		1		1	
	Shortness of breath/difficulty in breathing	3		2		5	
Pulmonary events	Fluid on lungs	0		1		1	
	Pulmonary embolism	0		1		1	
	Pulmonary oedema	1		0		1	
Infectious events	Chest infection	0		1		1	
	Wound infection	0		1		1	
	Cellulitis	0		2		2	
	Hospital-acquired pneumonia	0		1		1	
	Clostridium difficile infection	0		1		1	

continued

TABLE 17 Unexpected SAEs (*continued*)

AE		Received OPCABG (*N* = 46)		Received ONCABG (*N* = 54)		Overall (*N* = 100)	
		n	%	*n*	%	*n*	%
Other events	Stroke	2		1		3	
	Anaemia and hypotension	1		0		1	
	Fall due to hypotension	0		1		1	
	Diarrhoea/vomiting	0		2		2	
	Sternal wound reopening: failure to heal	0		1		1	
Timing of events	Pre surgery	1		3		4	
	Post surgery but pre discharge	1		5		6	
	Post discharge	10		17		27	
Maximum intensity	Mild	0		2		2	
	Moderate	5		8		13	
	Severe	7		15		22	
Reason event classified as SAE	Resulted in death	3		3		6	
	Is/was life-threatening	2		5		7	
	Resulted in persistence of significant disability/incapacity	4		7		11	
	Prolonged ongoing hospitalisation/caused hospitalisation	9		20		29	
	Other	0		2		2	
Relatedness to the method of surgery	Not related	6		10		16	
	Unlikely to be related	4		11		15	
	Possibly related	2		3		5	
	Probably related	0		1		1	

Seven events (two in the OPCABG group and five in the ONCABG group) took place after the patient's 4- to 8-week follow-up appointment. At the trial's inception, the period of reporting SAEs was from consent to 1-year follow-up; however, when the trial was terminated, this was changed to the period from consent to the 4- to 8-week follow-up visit. The events were:

- OPCABG group: death, shortness of breath.
- ONCABG group: fall due to hypotension, death following hospital admission with chest pain, relapse of *C. difficile* virus, sternal wound reopening, hospital readmission for diarrhoea.

Chapter 4 Discussion

Main findings: study conduct

The main findings of the CRISP trial are that expertise-based randomisation is challenging to implement and make work in a tertiary surgical setting. For a range of logistical reasons, the trial failed to recruit in time and to target, and the proposal to extend the primary outcome to include (1) reoperation for bleeding, (2) low cardiac output, (3) new onset of atrial arrhythmia and (4) AKI, and thereby reduce the study size, was not accepted by the funder. The trial was closed prematurely on the grounds of futility and also because of the perceived overlap between CRISP and the Canadian-led CORONARY trial.

Some of the challenges faced in CRISP were due to the context and nature of the service provision in the UK. Cardiac surgery is a tertiary service. As a consequence, patients are referred from a large geographical area and a significant proportion of referrals are urgent inpatients waiting in neighbouring 'feeder' hospitals for a suitable surgical slot to become available. The information provided at referral was often limited, making the assessment of eligibility for the trial by a research nurse or co-ordinator difficult. CRISP was marketed as a trial in high-risk patients. It was therefore important that only patients likely to be eligible were contacted, to avoid undue stress to patients at lower risk of complications.

Optimising the recruitment pathway was difficult, and the challenges varied according to how the local service was organised. Elective patients were usually seen at least once before surgery in an outpatient referral and/or preoperative assessment clinic. These contacts provided opportunities for the local research team to engage with potential participants, discuss the trial and seek consent, but often patients were unwilling to take part because they either wished to stay with the surgeon they met at the first appointment or wanted the surgeon to decide which type of surgery was best for them. Frequently, the need for surgery was not discussed until this first appointment so contacting a patient in advance of this was not considered appropriate. Urgent patients presented a different challenge. In the centres with a policy of transferring patients to the cardiac centre 2 or 3 days before surgery, the recruitment window was adequate and expertise-based randomisation was achievable, provided experts in both ONCABG and OPCABG were available to carry out the surgery. In centres where the policy was to transfer the patient as close to surgery as possible, recruitment and expertise-based randomisation was severely hampered. The CLRN was not long established when CRISP was set up and support from CLRN research nurses working at 'feeder' hospitals to facilitate recruitment was not forthcoming. This may not be the case now. Research governance issues were also a limiting factor, the concept of the research passport was not working well at that time and the need to identify local principal investigators at hospitals where the study was not taking place and in a speciality that was not theirs proved impossible.

Some of these issues were relevant to the context and setting in which CRISP was based only, but others were not. The availability of an expert surgeon to carry out the operation within a time scale that does not breach local and national targets for treatment applies to any surgical trial using expertise-based randomisation. The allocation of patients to surgeons through a system of named referrals, or via a generic pool, and the willingness or otherwise of surgeons to work together and 'share' their patients is a challenge and potential barrier to recruitment into any trial using expertise-based randomisation. The majority of surgeons continue to work autonomously, but this is gradually changing with the appointment of a clinical director or a chief of service; however, this is by no means widespread, particularly in the UK. When a patient is referred directly to an individual surgeon, that surgeon becomes responsible for that patient. Surgeons are often reluctant to transfer the patient to another surgeon, especially after meeting the patient and the 'doctor–patient bond' has formed. In addition, there continues to be a strongly held belief that the length of a surgeon's waiting list reflects his or her surgical ability. Similarly, understanding

the recruitment pathway and optimising when and how to introduce the trial to patients to ensure that surgeon preferences do not influence patient decisions is relevant to all surgical trials.

Many of these barriers to recruitment have been encountered previously. Ross *et al.*,[58] in 1999, identified time constraints, lack of staff and training, worry about the impact on the doctor–patient relationship, concern for patients, loss of professional autonomy, difficulty with the consent procedure and lack of rewards and recognition as the key clinical-based barriers, while, for patients, the main barriers were the additional demands of the trial, patient preferences, worry caused by uncertainty and concerns about information and consent. A survey from 2011 of centres recruiting to three trials in head and neck surgery, all of which were significantly delayed and behind target, identified patient and surgeon preferences, insufficient time in the NHS clinic, lack of research nurse support, insufficient funding for excess treatment costs and delays in the approval process as the key barriers.[59] Complex recruitment pathways involving staff across different specialties/centres have also hindered recruitment in other trials.[60]

In addition, for a trial such as CRISP to recruit successfully in the UK health-care setting, there has to be an agreement when the research is funded that a centre as a whole will participate in the study. The surgical autonomy needs to be broken down and the structure of the NHS, with consultants responsible for their own patients, is a stumbling block that is not limited to expertise-based recruitment. Surgeons need to work together and there need to be improved links between those responsible for service delivery and for the research. In the UK, the NHS is under huge pressure to deliver services and treatment to target, while at the same time reducing costs. Expertise-based recruitment, with a limited number of surgical experts, will almost inevitably lead to longer waiting times for some patients. For it to be implemented successfully in a surgical trial, the service providers and the health-care commissioners need to be committed to the research and be prepared to allow some flexibility in the targets in order for the research to succeed. Similarly, research needs to be considered an integral part of the service provision of a hospital; strategies for reducing hospital-based costs often impact on research. For example, patients are increasingly spending less time in hospital before their surgery and so the opportunities for recruitment are restricted. This was a particular problem for high-risk urgent in-hospital transfers (ideal candidates for the CRISP trial) as these patients will not have attended the cardiac centre previously and so there were no opportunities for earlier recruitment. Similarly, there needs to be a greater flexibility in the implementation of the research governance framework in NHS hospitals and within the CLRN. The need for local principal investigators at 'feeder' hospitals and the unwillingness of CLRN nurses at these hospitals to facilitate recruitment caused particular frustration.

Main findings: study results

The CRISP trial did not find statistically significant differences between the OPCABG and ONCABG groups owing to the limited power (< 2% of the target number of patients was recruited). However, the question that the trial set out to address remains important. The Cochrane review, published in 2012,[34] acknowledged that mainly patients with low risk of postoperative complications were enrolled in the 86 trials reviewed and patients with three-vessel coronary disease and impaired LV function were under-represented.

The two largest trials to compare ONCABG and OPCABG, the ROOBY[37] and the CORONARY[40] trials, have been published since the CRISP trial began. The ROOBY trial, which contributed 2203 patients to the Cochrane review, has been severely criticised. The operative experience of the surgeons in the OPCABG group was substantially less than that of the ONCABG surgeons (median of 50 patients per surgeon), which was reflected in a high conversion rate from OPCABG to ONCABG (12%), a significant proportion of patients receiving fewer grafts than planned (18% OPCABG vs. 11% ONCABG),[37] significantly lower patency rates (arterial conduits: 85.8% vs. 91.4% and saphenous vein grafts: 72.7% vs. 80.4%) at 1 year and fewer patients with effective revascularisation (50.1% vs. 63.9%) with OPCABG compared with ONCABG.[61] The trial also recruited predominantly low-risk patients.

The CORONARY trial, the largest trial to date, recruited a higher proportion of higher-risk patients than the ROOBY trial, although < 20% of participants had a EuroSCORE of > 5.[40] This compares with 74% of patients recruited to CRISP. The participating surgeons were also more experienced than those recruited to the ROOBY trial: all surgeons were required to have > 2 years' experience and have completed > 100 procedures involving their preferred technique. Trainees were not allowed to be the primary surgeon for any procedure. This experience threshold was consistent with that used in CRISP.

The Cochrane meta-analysis has been updated to include the results from the CORONARY and CRISP trials. The results, for all-cause mortality, MI, stroke and renal failure are summarised in *Table 18*. The RR of death and MI reduced from 1.24 (95% CI 1.01 to 1.53) to 1.18 (95% CI 0.98 to 1.40) and from 1.00 (95% CI 0.79 to 1.26) to 0.96 (95% CI 0.82 to 1.12) respectively, while the RR of a stroke and a renal complication increased from 0.76 (95% CI 0.54 to 1.06) to 0.80 (95% CI 0.61 to 1.06) and from 0.86 (95% CI 0.62 to 1.20) to 0.92 (95% CI 0.70 to 1.21), respectively.

The Cochrane review identified three trials in high-risk patients: the BBS trial, which recruited 341 patients with a EuroSCORE of ≥ 5 and triple-vessel disease;[38,62] a trial by Carrier and colleagues, which recruited 65 patients with at least three of the following criteria: age > 65 years, high blood pressure, diabetes, creatinine > 133 mol/l, LV ejection fraction < 45%, chronic pulmonary disease, unstable angina, congestive heart failure, repeat CABG, anaemia and carotid atherosclerosis;[41] and a study in 128 patients with a ST-segment elevation MI.[42] The data from these trials, plus CRISP, have been combined in meta-analyses, the results of which are shown in *Figures 7–10*. Part (a) of each figure is restricted to early outcomes (30 days or hospital discharge) and part (b) includes outcomes across the full follow-up period of each study. The BBS trial and the trial in patients with a ST-segment elevation MI reported cardiac-related mortality outcomes to 3 years, while CRISP and the trial by Carrier *et al.*[41] reported outcomes to 30 days only. It was not possible to include the CORONARY trial results in these meta-analyses and the data were not reported for the individual components of the trial's composite outcome for the subgroup of high-risk patients. In contrast to the Cochrane review, these analyses suggest a lower risk of death with OPCABG in the early postoperative period (RR 0.46, 95% CI 0.20 to 1.04; $p = 0.06$) and a comparable risk overall (RR 0.90, 95% CI 0.32 to 2.58; $p = 0.85$). The risk of an MI was also reduced in the early postoperative period (RR 0.59, 95% CI 0.33 to 1.06; $p = 0.077$). No differences in the risk of a stroke or of renal complications were found.

The BBS and CORONARY trials both reported the results of a composite primary outcome at 30 days in high-risk patients and the composites varied across studies. The BBS trial[38] used death, MI, cardiac arrest, low cardiac output, stroke and coronary reintervention, while the CORONARY trial[40] used death, MI, stroke and new renal failure requiring dialysis. These compare with the CRISP composite of death, new renal

TABLE 18 Updated meta-analysis: Cochrane review plus CORONARY and CRISP trials

	Randomised to OPCABG		Randomised to ONCABG			
Outcome	*n*	%	*n*	%	RR (95% CI)	*p*-value
Death[a]	249/7604	3.3	220/7570	2.9	1.18 (0.98 to 1.40)	0.077
MI[b]	301/6710	4.5	311/6687	4.7	0.96 (0.82 to 1.12)	0.60
Stroke[c]	86/6951	1.2	112/6943	1.6	0.80 (0.61 to 1.06)	0.13
Renal complication[d]	90/4835	1.9	97/4821	2.0	0.92 (0.70 to 1.21)	0.55

df, degrees of freedom.
a $\chi^2 = 24.77$ (df = 31); $p = 0.78$; $I^2 = 0\%$; $\tau^2 = 0.0000$.
b $\chi^2 = 25.50$ (df = 32); $p = 0.79$; $I^2 = 0\%$; $\tau^2 = 0.0000$.
c $\chi^2 = 17.86$ (df = 26); $p = 0.88$; $I^2 = 0\%$; $\tau^2 = 0.0000$.
d $\chi^2 = 4.89$ (df = 13); $p = 0.98$; $I^2 = 0\%$; $\tau^2 = 0.0000$.

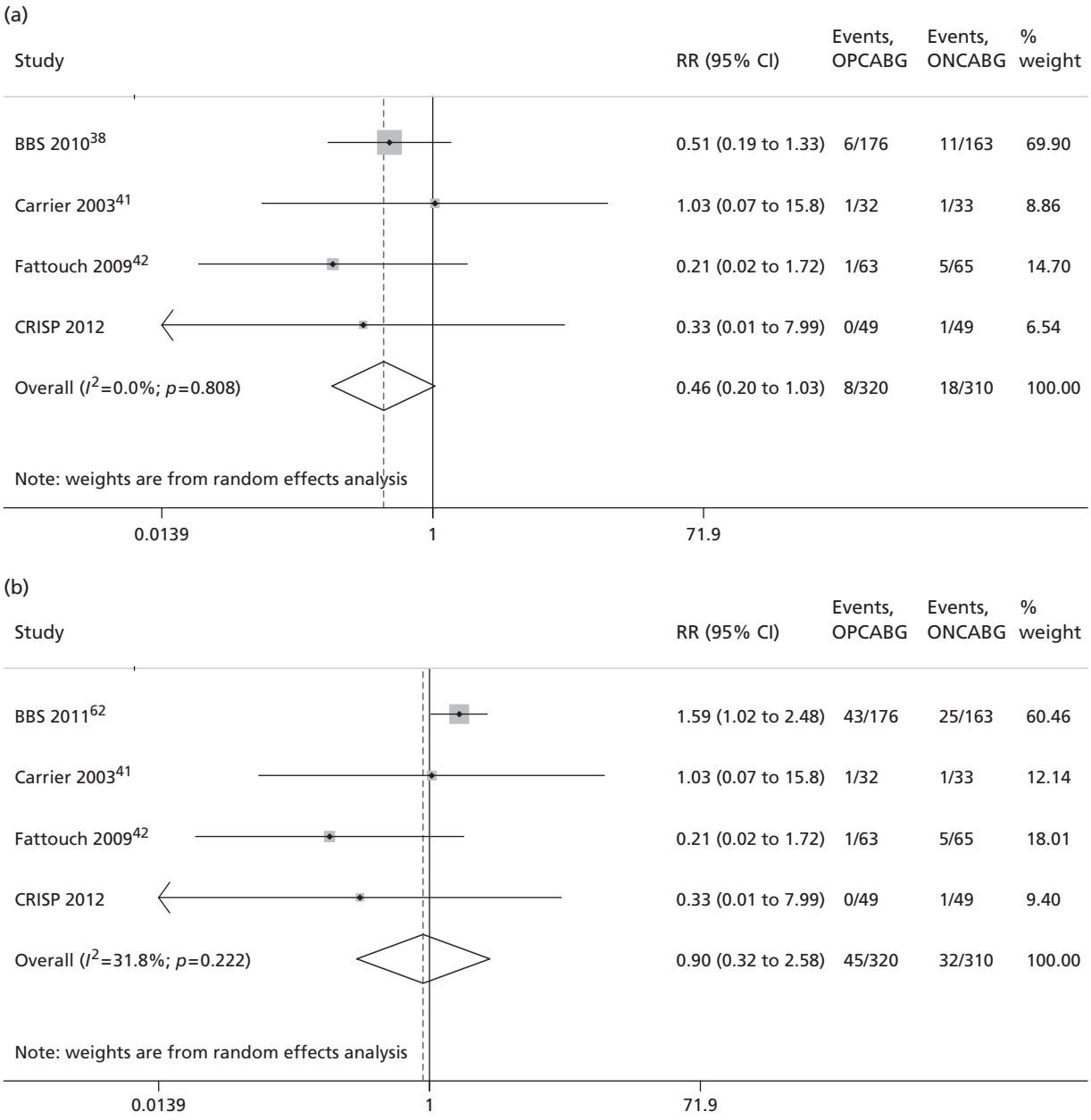

FIGURE 7 Meta-analysis of trials in high-risk patients. a, Death up to day 30/hospital discharge; and b, death up to 3 years.

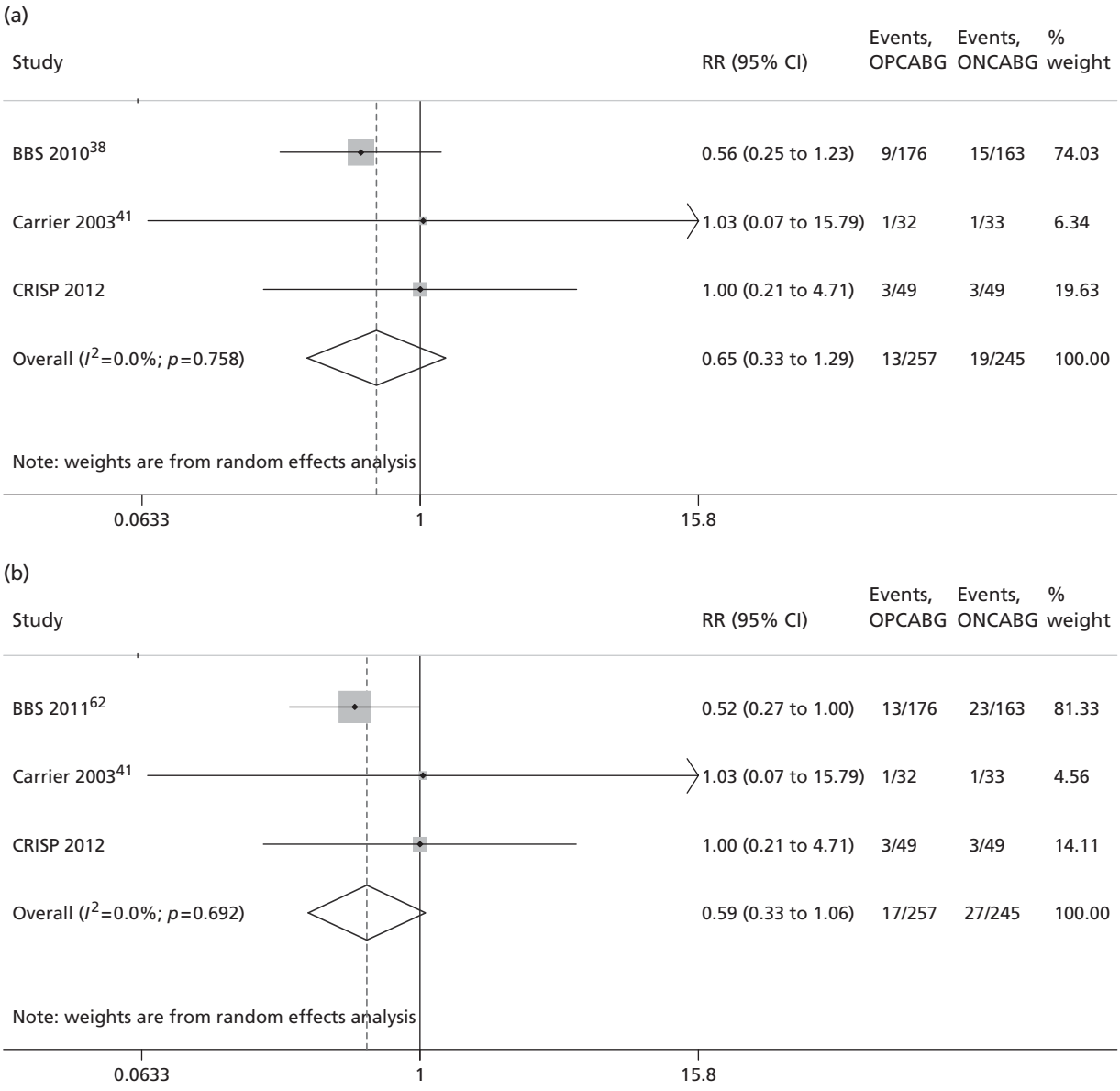

FIGURE 8 Meta-analysis of trials in high-risk patients. a, MI up to day 30/hospital discharge; and b, MI up to 3 years.

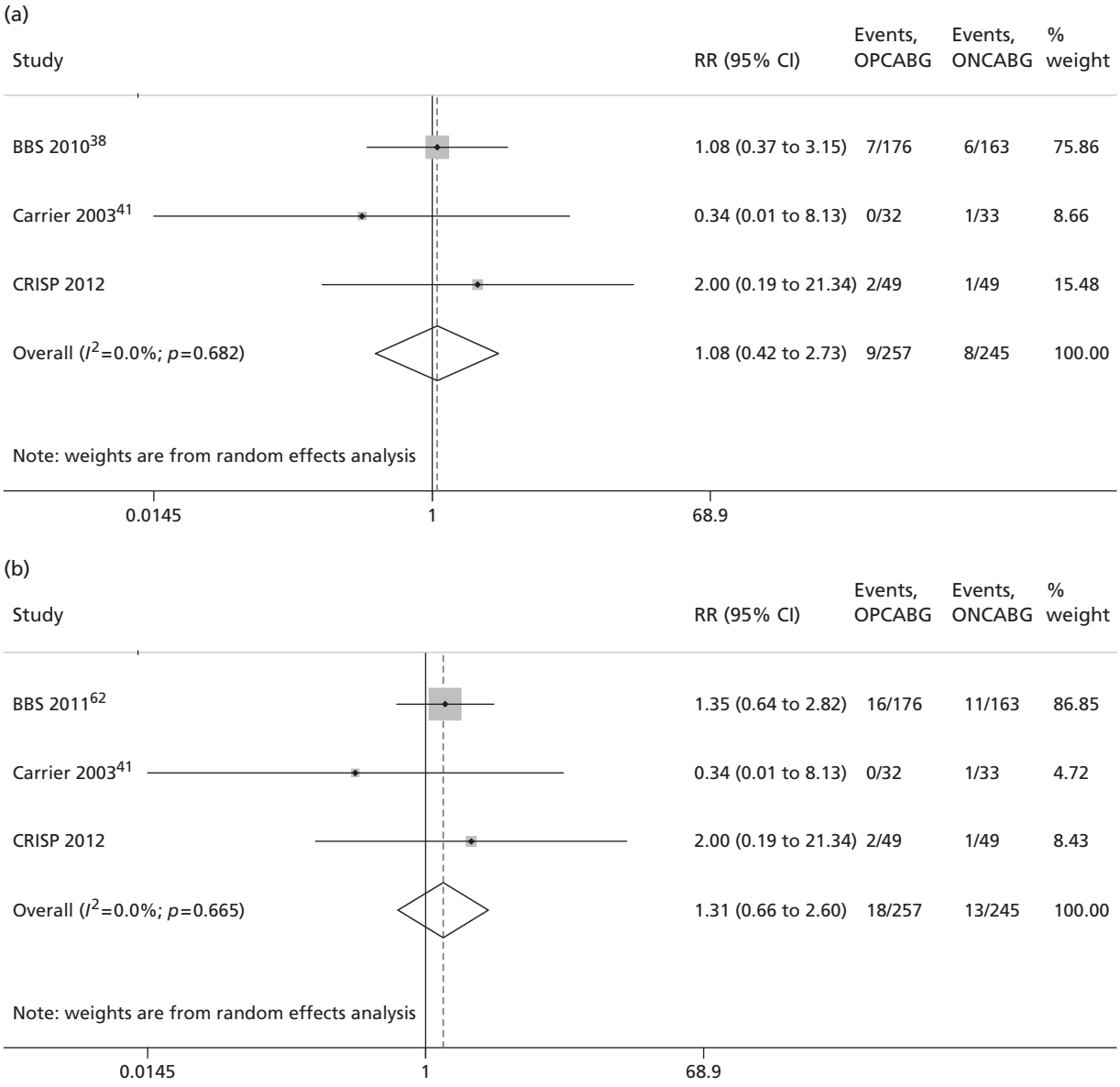

FIGURE 9 Meta-analysis of trials in high-risk patients. a, Stroke up to day 30/hospital discharge; and b, stroke up to 3 years.

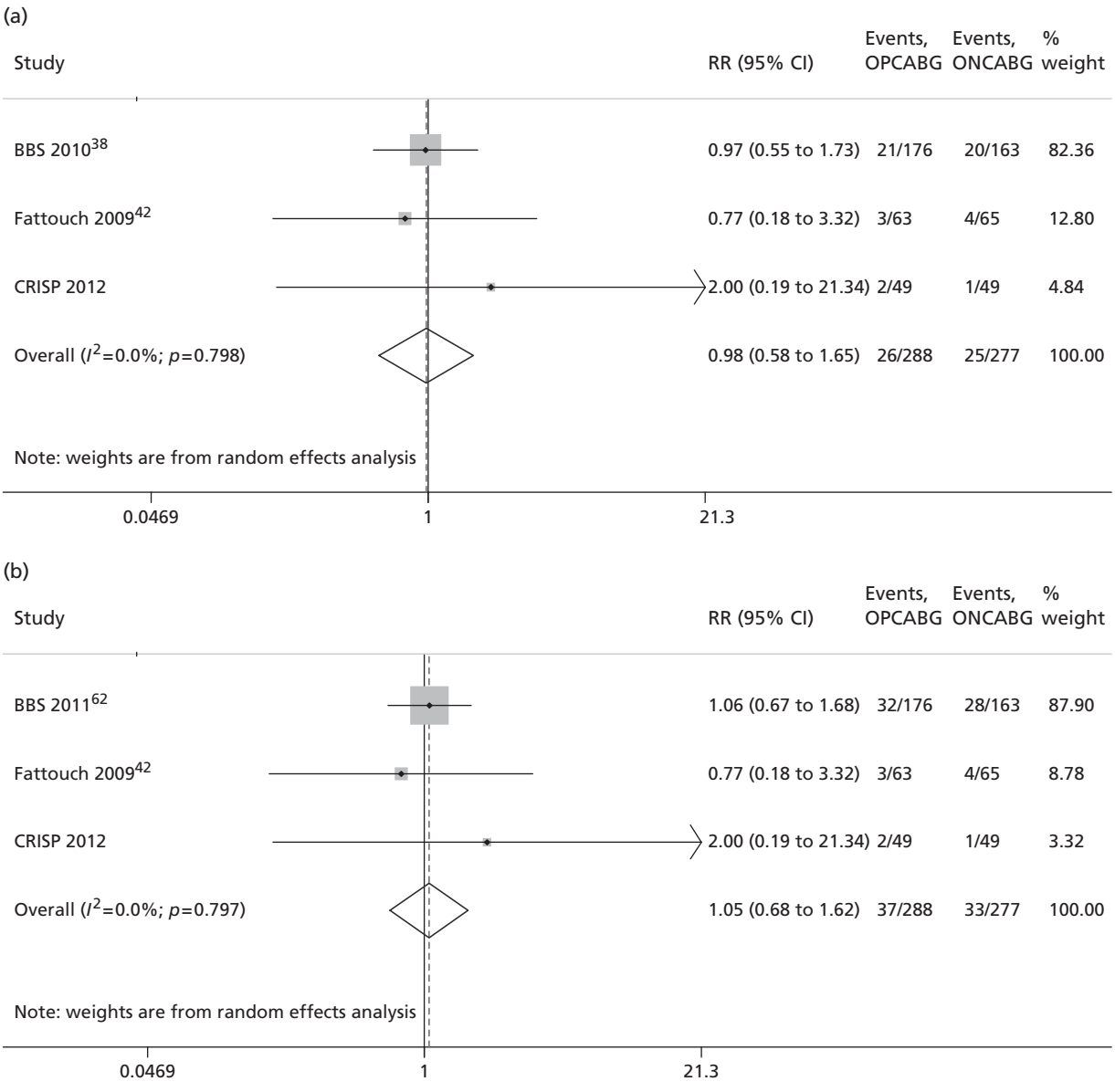

FIGURE 10 Meta-analysis of trials in high-risk patients. a, Renal complications up to day 30/hospital discharge; and b, renal complications up to 3 years.

failure, MI, stroke, prolonged ventilation and sternal wound dehiscence. The composites from these studies were combined in a meta-analysis and the results are summarised in *Table 19*. As anticipated, the pooled estimate reflects the estimate from the large CORONARY trial, but with a narrower CI.

One possible reason for the lack of compelling evidence of a difference between OPCABG and ONCABG in the recent trials is that over time techniques in ONCABG have improved. Different methods of cardioplegia and body temperature cooling have been introduced to reduce myocardial injury and systemic inflammatory response during surgery and a miniaturised CPB circuit has been developed that is associated with a non-significantly reduced risk of adverse outcomes.[63] There may also have been ill-defined temporal improvements in care across both techniques.

Strengths and limitations

Despite the failure of CRISP to recruit to target, the options to improve recruitment were thoroughly tested. There was a strongly held view that the expertise-based randomisation was the key barrier to successful recruitment, but, when we attempted to change to a within-surgeon allocation, many of the OPCABG experts were no longer willing to participate. A survey of orthopaedic surgeons similarly found a strong preference for expertise-based randomisation.[64] We believe that expertise-based randomisation is the only way to evaluate established surgical procedures where there are strongly held preferences but collective equipoise. Furthermore, it avoids the problem of differential expertise bias,[65] can protect against crossover as a result of unfamiliarity or less experience with one surgical method and allows for greater surgeon participation. In addition, an expertise-based design provides the participant with the assurance that the surgery will be carried out by a surgeon who has both the appropriate expertise and is comfortable carrying out the procedure. Expertise-based randomisation has been used successfully in other areas, for example in studies comparing coronary angioplasty and CABG[66–69] and in orthopaedic surgery.[69] However, we have to recognise that it may not be feasible in a tertiary referral setting, when the referral information to determine patient eligibility is often inadequate, surgeon availability is limited and there is an imbalance in the numbers of surgical experts at a centre.

The trial was methodologically strong; the risk of bias was minimised through concealed allocation and objective definitions for the primary end points. There was a blinded review of the blood results and preoperative and postoperative ECGs of all patients and a postoperative MI defined on consensus of the adjudicators. The database used to collect the data was robust and included extensive within-CRF and cross-CRF validation. The screening data were incomplete for most centres, as indicated by the wide variation in the proportion of screened patients recruited, and this is a weakness that was recognised by the TSC.

TABLE 19 Meta-analysis of composite outcomes at day 30 in high-risk patients

Study	*n*	Treatment effect (95% CI)[a]	*p*-value
BBS	341	RR 0.83 (0.52 to 1.34)	
CORONARY	828	HR 0.85 (0.58 to 1.25)	
CRISP	98	OR 1.07 (0.27 to 4.14)	
Overall[b]	1257	RR 0.85 (0.64 to 1.14)	0.28

df, degrees of freedom.
a Ratio OPCABG to ONCABG.
b $\chi^2 = 0.12$ (df = 2); $p = 0.94$; $I^2 = 0\%$; $\tau^2 = 0.0000$.

Despite the poor recruitment, the CRISP patients reflect the population the trial was designed to study. Using data from the Bristol cardiac surgery database, we compared the characteristics of the CRISP patients with 3364 eligible isolated CABG patients with a EuroSCORE of ≥ 5 who had undergone an operation between April 1997 and August 2012 in Bristol. The cohorts were of similar age (median 77 vs. 74 years) and sex mix (23% vs. 28% female) and comorbidities occurred with similar frequency (diabetes 24% vs. 26%, previous MI 70% vs. 68%, previous stroke 8% vs. 6%, median EuroSCORE was 6 in both cohorts). In addition, similar proportions had triple-vessel disease (77% vs. 73%) and > 50% disease in left main stem (33% vs. 30%). However, there was a lower proportion of patients with poor ejection fraction (5% vs. 11%) and the proportion of patients requiring surgery urgently was lower in the CRISP study (45% vs. 66%), which is reflective of the recruitment difficulties.

The final study size is a clear weakness: the study has low power to detect significant differences between the groups and the value of the trial data is their contribution to meta-analyses. However, the approach to the analysis of the data was strong. An analysis plan was prepared in advance of any comparative analyses of the study data and the number of statistical tests carried out was restricted. Formal statistical comparisons of treatment effects were only carried out if > 10 patients in total experienced the outcome (see *Appendix 5*), to minimise the probability of a type 1 error.

We chose to use an additive EuroSCORE of ≥ 5 as a marker of 'high risk'. All scoring systems have their limitations and this score is strongly influenced by age (one point for every 5 years from 60 years onwards) and less by a participant's comorbidity. As a consequence, CRISP recruited more elderly patients than the CORONARY trial (median age 77 vs. 68 years, respectively) and many fewer diabetic patients (24% vs. 47%, respectively), although, in both trials, only 5% of patients had poor LV function. The question of which treatment option is most effective, ONCABG or OPCABG, remains an important question in the large group of patients with poor LV function that cannot be answered by either trial.

Lessons for the future

If we were setting up the CRISP trial now there are many things that we would do differently. First, we would design the trial in two phases, with a feasibility phase followed by a main trial phase. This design is being used in other surgical areas and is an attractive option for funders of difficult-to-do trials.

Second, we would include a qualitative research element, which would involve researchers interviewing the research teams at the study centres in order to gain a full understanding of the recruitment pathway, barriers to recruitment (including a willingness or otherwise to work together and share patients) and the extent of the equipoise. Through feedback and training, the study team (including the surgeons) would be taught how to present the trial in an unbiased way to minimise the number who decline to take part. The strength of the bond formed between surgeon and patient at that first referral would also be explored through interviews with patients who did and did not agree to take part. This approach has been used very successfully in the POTECT trial of surgery versus radiotherapy versus medical management in men with localised prostate cancer.[70] A total of 1500 men were recruited to a trial that many strongly believed would never succeed. Failure to meet the recruitment target is a common problem[71] and qualitative methods have been recommended as the most effective for identifying and overcoming barriers to clinician recruitment activity and increasing recruitment.[72]

Third, we would focus recruitment equally towards UK and overseas centres from the start. Many of the barriers to recruitment experienced in the UK may not be such a problem overseas. Although the centre in India was actively participating for only a short period before CRISP closed, it recruited six patients in 3 weeks, which was more than was achieved in any UK centre. The CORONARY trial, which successfully recruited 4752 patients at 79 centres, recruited only a small number of patients from the UK (227 patients, < 5%). The biggest contributors were India and China (1307 and 781 patients, respectively).

Future research

The answer to the question of whether OPCABG offers an additional benefit over ONCABG in a high-risk population is unclear. The trial evidence in high-risk patients suggests the outcomes are similar, although the collective evidence across all trials suggests the risk of death is higher with OPCABG (RR 1.18; $p = 0.077$). Possible reasons for this are fewer grafts, a greater need for subsequent revascularisation and worse patency. Despite recruiting more than 15,000 patients into trials of OPCABG versus ONCABG, the views of members of the surgical community are polarised. A qualitative evaluation of the reasons behind the views held by the advocates of the two techniques, and in particular what evidence would need to be presented in order to change individual practice, is an area for future research.

One possible explanation for the polarisation is the belief that 'it's in the surgeon's hands'. If the surgeons are true 'experts' then one might anticipate no difference in outcomes between the two methods. Surgeons that use both techniques, albeit one perhaps slightly more frequently than the other, are likely to be less committed to OPCABG than surgeons who use OPCABG exclusively, and this may be reflected in the results. One way to test this hypothesis would be an individual patient data meta-analysis of the trial data, classifying patients according to the characteristics/experience of the surgeon.

Chapter 5 Conclusion

We firmly believe there is still a role for expertise-based randomisation to evaluate established treatments in which there are strong practitioner preferences and both treatments are used. The CRISP trial was not successful for a range of logistical reasons. Nonetheless, the experience gained will be of value for the design and conduct of future trials, so that some of the pitfalls experienced in CRISP can be avoided.

Acknowledgements

The CRISP investigators thank the following, without whose help the study would not have happened:

- the CRISP trial participants
- the CRISP TSC and DMSC members (see *Appendix 6* for details)
- staff at the Bristol Clinical Trials and Evaluation Unit who helped with the set-up and running of the trial: Lucy Dreyer, Jon Evans, Neil Smith, Verity Waine
- research nurse teams at the participating centres
- Professor Raimondo Ascione, Chiara Bucciarelli-Ducci and Elisa Mcalindon for the masked independent evaluation of the blood results and ECGs of CRISP participants
- Carol Wallis, trial administrator, Oxford, for providing a vital link between the Bristol Clinical Trials and Evaluation Unit and the Sponsor's office.

Contribution of authors

- **Dr Chris A Rogers** designed the study with Professors DP Taggart, DG Altman, GD Angelini, A Gray and BC Reeves. She led the team at the Bristol Clinical Trials and Evaluation Unit, which led and managed the trial, and oversaw the analyses and their interpretation. She drafted the report with Miss K Pike.
- **Miss Katie Pike** advised on the design of the CRFs and the trial database. She wrote the statistical analysis plan and carried out the statistical analyses under the guidance of Dr Rogers. She drafted the report with Dr Rogers.
- **Dr Helen Campbell** contributed to the design of the resources use components of the CRFs and analysed some resource use data. She designed the five-level versions of the EQ-5D questionnaires and analysed the EQ-5D data.
- **Professor Barnaby C Reeves** designed the study with Professors DP Taggart, DG Altman, GD Angelini, A Gray and Dr Rogers. He helped to draft the discussion of the trial.
- **Professor Gianni D Angelini** designed the study with Professors DP Taggart, DG Altman, A Gray, BC Reeves and Dr Rogers. He actively promoted the trial amongst his clinical colleagues, particularly those based in European centres. He reviewed a draft of the report.
- **Professor Alastair Gray** designed the study with Professors DP Taggart, DG Altman, GD Angelini, and BC Reeves and Dr Rogers and led the health economic analyses. He reviewed a draft of the report.
- **Professor Doug G Altman** designed the study with Professors DP Taggart, GD Angelini, A Gray, BC Reeves and Dr Rogers. He advised on the use of expertise-based randomisation.
- **Dr Helen Miller** was a trial manager at Bristol Clinical Trials and Evaluation Unit. She liaised with sites about the protocol and queries, carried out visits to sites and facilitated the closure of the trial.
- **Miss Sian Wells** was a trial manager at Bristol Clinical Trials and Evaluation Unit. She designed the trial CRFs and database, liaised with sites about the protocol and queries, and carried out visits to sites.
- **Professor David P Taggart** designed the study with Professors DG Altman, GD Angelini, A Gray, BC Reeves and Dr Rogers. He was chief investigator and the principal applicant in the effort to secure funding. He actively promoted the trial amongst his clinical colleagues. He reviewed a draft of the report.

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Appendix 1 CRISP study centres and principal investigators

UK Centres

Centre	Hospital trust	Principal investigator	Status at study closure
Basildon	Basildon and Thurrock University Hospitals NHS Foundation Trust	Andrew Ritchie	Recruited
Blackpool	Blackpool Teaching Hospitals NHS Foundation Trust	Augustus Tang	Recruited
Bristol	University Hospitals Bristol NHS Foundation Trust	Professor Gianni Angelini	Recruited
King's College	King's College Hospital NHS Foundation Trust	Jatin Desai	Recruited
Oxford	Oxford University Hospitals NHS Trust	Professor David Taggart	Recruited
Papworth	Papworth Hospital NHS Foundation Trust	Max Codiposti	Recruited
Sheffield	Sheffield Teaching Hospitals NHS Foundation Trust	Norman Briffa	Recruited
Wolverhampton	Royal Wolverhampton Hospitals NHS Trust	Patrick Yiu	Recruited
Liverpool	Liverpool Heart and Chest Hospital Hospitals NHS Foundation Trust	Brian Fabri	Withdrew
Brighton	Brighton and Sussex University Hospitals NHS Trust	Uday Trivedi	Participating but no recruitment
University College	University College London Hospitals NHS Foundation Trust	Shyam Kolvekar	Participating but no recruitment
Nottingham	Nottingham University Hospital NHS Trust	David Richens	Participating but no recruitment
Middlesbrough	South Tees Hospitals NHS Foundation Trust	Enoch Akowuah	Approvals in place, but not started
Cardiff	University Hospital of Wales, Cardiff and Vale University Health Board	Dheeraj Mehta	Seeking approvals
Edinburgh	Royal Infirmary of Edinburgh, NHS Lothian	Vipin Zamvar	Seeking approvals

Non-UK Centres

Country	Centre	Principal investigator	Status at study closure
India	RTIICS, Kalkota	Kunal Sarkar	Recruited
Brazil	Pernambuco	Fernando Moraes	Seeking approvals
Brazil	Federal University of Sao Paulo	Walter Gomes	Seeking approvals
Brazil	Florianopolis, Santa Catarina	Sergio Almeida	Seeking approvals
Canada	McGill University Health Centre, Montreal	Patrick Ergina	Seeking approvals
Germany	Universität Leipzig	Friedrich Mohr	Seeking approvals
Germany	Herz- und Gefäßzentrum, Bad Bevensen	Gerhard Wimmer-Greinecker	Seeking approvals
Germany	Herz- und Diabeteszentrum NRW, Bad Oeynhausen	Jochen Borgermann	Seeking approvals
Italy	Pasquinucci, Massa Carrara	Mattia Glauber	Seeking approvals
Italy	University of Insubria, Varese	Andrea Sala	Seeking approvals
Italy	Sacco Hospital, Milan	Carlo Antona	Seeking approvals

Appendix 2 Additional data tables

Withdrawals

TABLE 20 Details of withdrawals

Allocation	Time of withdrawal	Time from randomisation to withdrawal (days)	Consent withdrawn by	Reason for withdrawal	Received surgery
ONCABG	Pre surgery	0	Patient	No reason given	No
ONCABG	Pre surgery	21	Clinician	Surgery no longer required, patient and surgeon agreed medical treatment other than surgery	No
ONCABG	Pre surgery	31	Clinician	Not willing for data to be used	No
OPCABG	Pre surgery	1	Clinician	Decided to treat medically	No
OPCABG	Pre surgery	2	Clinician	Patient no longer being considered for surgery as not symptomatic	No
OPCABG	Pre surgery	4	Patient	Patient withdrew without knowing allocation, wanted to be operated on by the surgeon met in clinic	Yes[a]
OPCABG	Pre surgery	50	Clinician	Not willing for data to be used	No

a The patient was happy for data collection and follow-up to continue; therefore, this patient remained in the analysis cohort.

The European Quality of Life-5 Dimensions responses

TABLE 21 Preoperative EQ-5D responses by type of questionnaire

		Three-level EQ-5D		Five-level with five descriptors EQ-5D		Five-level with three descriptors EQ-5D	
Domain	Levels	Randomised to OPCABG (*n* = 14)	Randomised to ONCABG (*n* = 16)	Randomised to OPCABG (*n* = 18)	Randomised to ONCABG (*n* = 13)	Randomised to OPCABG (*n* = 16)	Randomised to ONCABG (*n* = 19)
Mobility	No problems walking about	7	8	10	3	9	10
	Slight problems walking about	–	–	5	1	0	1
	Some problems walking about	7	8	2	5	7	7
	A lot of problems walking about	–	–	0	4	0	0
	Confined to bed	0	0	1	0	0	1
Self-care	No problems with self-care	12	13	17	11	15	16
	Slight problems washing or dressing	–	–	0	0	0	1
	Some problems washing or dressing	2	3	0	2	1	1
	A lot of problems washing or dressing	–	–	1	0	0	0
	Unable to wash or dress	0	0	0	0	0	1
Usual activities[a]	No problems with usual activities	5	7	10	6	8	7
	Slight problems with usual activities	–	–	4	2	1	1
	Some problems with usual activities	8	7	3	5	5	8
	A lot of problems with usual activities	–	–	0	0	0	0
	Unable to perform usual activities	0	2	1	0	2	3

TABLE 21 Preoperative EQ-5D responses by type of questionnaire (*continued*)

		Three-level EQ-5D		Five-level with five descriptors EQ-5D		Five-level with three descriptors EQ-5D	
Domain	Levels	Randomised to OPCABG (*n* = 14)	Randomised to ONCABG (*n* = 16)	Randomised to OPCABG (*n* = 18)	Randomised to ONCABG (*n* = 13)	Randomised to OPCABG (*n* = 16)	Randomised to ONCABG (*n* = 19)
Pain/ discomfort[b]	No pain or discomfort	5	7	5	4	10	10
	Slight pain or discomfort	–	–	9	4	1	1
	Moderate pain or discomfort	8	7	4	4	3	7
	A lot of pain or discomfort	–	–	0	0	1	0
	Extreme pain or discomfort	1	2	0	1	0	1
Anxiety/ depression[c]	Not anxious or depressed	9	10	11	5	11	13
	Slightly anxious or depressed	–	–	6	6	1	0
	Moderately anxious or depressed	3	6	1	1	3	2
	Very anxious or depressed	–	–	0	0	0	0
	Extremely anxious or depressed	2	0	0	1	1	3

a One patient with missing data (three-level: in the OPCABG group).
b One patient with missing data (five-level with three descriptors: in the OPCABG group).
c One patient with missing data (five-level with three descriptors: in the ONCABG group).
Missing data: two patients did not attempt to complete the EQ-5D (three-level: one in the OPCABG group; five-level with five descriptors: one in the ONCABG group).

TABLE 22 Four- to 8-week postoperative EQ-5D responses by type of questionnaire

		Three-level EQ-5D		Five-level (5 descriptors) EQ-5D		Five-level (3 descriptors) EQ-5D	
Domain	Levels	Randomised to OPCABG (*n* = 14)	Randomised to ONCABG (*n* = 15)	Randomised to OPCABG (*n* = 17)	Randomised to ONCABG (*n* = 12)	Randomised to OPCABG (*n* = 15)	Randomised to ONCABG (*n* = 18)
Mobility	No problems walking about	8	6	12	7	11	13
	Slight problems walking about	–	–	3	2	0	1
	Some problems walking about	6	9	2	1	4	4
	A lot of problems walking about	–	–	0	1	0	0
	Confined to bed	0	0	0	1	0	0
Self-care	No problems with self-care	14	13	15	11	14	17
	Slight problems washing or dressing	–	–	2	0	0	1
	Some problems washing or dressing	0	2	0	1	1	0
	A lot of problems washing or dressing	–	–	0	0	0	0
	Unable to wash or dress	0	0	0	0	0	0
Usual activities	No problems with usual activities	9	6	13	4	4	7
	Slight problems with usual activities	–	–	2	5	3	3
	Some problems with usual activities	5	8	1	3	8	8
	A lot of problems with usual activities	–	–	1	0	0	0
	Unable to perform usual activities	0	1	0	0	0	0
Pain/ discomfort	No pain or discomfort	7	9	12	4	7	10
	Slight pain or discomfort	–	–	4	8	3	2
	Moderate pain or discomfort	7	5	1	0	5	6

TABLE 22 Four- to 8-week postoperative EQ-5D responses by type of questionnaire (*continued*)

Domain	Levels	Three-level EQ-5D		Five-level (5 descriptors) EQ-5D		Five-level (3 descriptors) EQ-5D	
		Randomised to OPCABG (*n* = 14)	Randomised to ONCABG (*n* = 15)	Randomised to OPCABG (*n* = 17)	Randomised to ONCABG (*n* = 12)	Randomised to OPCABG (*n* = 15)	Randomised to ONCABG (*n* = 18)
	A lot of pain or discomfort	–	–	0	0	0	0
	Extreme pain or discomfort	0	1	0	0	0	0
Anxiety/ depression[a]	Not anxious or depressed	12	12	13	9	13	12
	Slightly anxious or depressed	–	–	3	1	0	1
	Moderately anxious or depressed	2	3	1	1	2	2
	Very anxious or depressed	–	–	0	0	0	1
	Extremely anxious or depressed	0	0	0	1	0	0

a Two patients with missing data (five-level with three descriptors: in the ONCABG group).

Missing data: seven patients did not attempt to complete the EQ-5D (three-level: one in the OPCABG group and one in the ONCABG group; five-level with five descriptors: one in the OPCABG group and two in the ONCABG group; five-level with three descriptors: one in the OPCABG group and one in the ONCABG group).

TABLE 23 EQ-5D visual analogue scale responses by type of questionnaire

Questionnaire	Preoperative		4–8 weeks postoperative		
	Randomised to OPCABG	Randomised to ONCABG	Randomised to OPCABG	Randomised to ONCABG	MD (95% CI)
Three-level EQ-5D					
n	13	16	14	15	
Mean (SD)	68 (15)	62 (17)	76 (16)	66 (16)	10 (–2 to 22)
Five-level (five descriptor) EQ-5D					
n	18	13	17	12	
Mean (SD)	69 (17)	71 (15)	77 (16)	74 (12)	3 (–7 to 14)
Five-level (three descriptor) EQ-5D					
n	16	19	15	18	
Mean (SD)	69 (16)	66 (18)	76 (10)	73 (16)	3 (–6 to 13)

TABLE 24 Quality-of-life responses at 1-year follow-up

Quality-of-life measure	Randomised to OPCABG (*n* = 5)	Randomised to ONCABG (*n* = 2)
Rose and CCS angina class		
Rose angina		
No angina	4	0
Grade I	1	1
Grade II	0	1
CCS class		
Asymptomatic	5	1
Grade I	0	0
Grade II	0	1
Grade III	0	0
Grade IV	0	0
EQ-5D categorical responses		
Mobility		
No problems walking about	3	1
Slight problems walking about	0	0
Some problems walking about	1	1
A lot of problems walking about	1	0
Confined to bed	0	0
Self-care		
No problems with self-care	4	2
Slight problems washing or dressing	0	0
Some problems washing or dressing	1	0
A lot of problems washing or dressing	0	0
Unable to wash or dress	0	0
Usual activities		
No problems with usual activities	3	1
Slight problems with usual activities	0	0
Some problems with usual activities	2	1
A lot of problems with usual activities	0	0
Unable to perform usual activities	0	0
Pain/discomfort		
No pain or discomfort	2	1
Slight pain or discomfort	0	0
Moderate pain or discomfort	2	1
A lot of pain or discomfort	0	0
Extreme pain or discomfort	1	0

TABLE 24 Quality-of-life responses at 1-year follow-up (*continued*)

Quality-of-life measure	Randomised to OPCABG (*n* = 5)	Randomised to ONCABG (*n* = 2)
Anxiety/depression		
Not anxious or depressed	4	2
Slightly anxious or depressed	0	0
Moderately anxious or depressed	1	0
Very anxious or depressed	0	0
Extremely anxious or depressed	0	0

Continuous data:
EQ-5D single summary index data were collected for five patients, responses were: OPCABG group –0.02, 0.8, 1 and 1; ONCABG group 0.69.
EQ-5D visual analogue scale data were collected for six patients, responses were: OPCABG group 35, 74, 75 and 75; ONCABG group 70 and 70.
CROQ core total scores were calculated for seven patients, responses were: OPCABG group 42.4, 52.6, 54.7, 55.2 and 55.9; ONCABG group: 34.5 and 54.1.

Appendix 3 CRISP protocol

Coronary artery grafting in High RISk patients randomised to Off Pump or On Pump Surgery

The 

Trial

MREC reference number: 08/MRE00/58

MRC reference number: G0700469/81685

Details of Sponsor

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1. Background

1.1. *Coronary artery bypass grafting (CABG) is the best therapy for severe coronary disease (CAD)*

Despite advances in medical therapy and percutaneous coronary interventions (PCI) there is good evidence that CABG offers superior survival and freedom from repeat intervention in patients with multivessel CAD [1-5]. For example, in the recently published New York State registry of almost 60,000 patients, after risk stratification for cardiac and non-cardiac comorbidity, there was a significant reduction in mortality (absolute difference of 5%) and a seven fold reduction in the need for repeat interventions at three years in patients undergoing CABG rather than PCI using stents [2]. Predictions that drug eluting stents will significantly reduce the need for CABG are premature because, although these stents reduce the incidence of restenosis compared to bare metal stents, three large meta-analyses have shown that they do not improve survival or reduce the incidence of subsequent myocardial infarction [6-8]. There are two reasons why CABG is likely to remain a superior treatment to PCI over the longer term: (i) CABG protects whole zones of proximal myocardium (as the graft is placed to the mid coronary vessel beyond all proximal disease) [9]; (ii) PCI frequently results in incomplete revascularization which adversely affects survival proportional to the incompleteness of revascularization [10]. Currently around half a million patients worldwide undergo CABG each year. There is a real possibility that these numbers will increase with a growing elderly population and an increasing epidemic of diabetes and obesity which all predispose to the development of CAD and an increasing realisation that PCI may merely delay definitive treatment.

1.2. *CABG performed with ('on-pump) or without ('off-pump') cardiopulmonary bypass (CPB)*

Conventional CABG uses cardiopulmonary bypass (CPB) ('on-pump') to support the circulation while the heart is temporarily stopped. CPB causes a systemic inflammatory response syndrome, which leads to multi-organ dysfunction and, although mild and reversible in most, it can contribute to mortality and overt morbidity, particularly in higher-risk patients [11-19]. Evidence from randomized trials (RCTs)*, in low-risk populations,* shows that OPCABG (off-pump) is at least as safe as ONCABG (on-pump) in terms of mortality and that it reduces several aspects of morbidity but may lead to a higher need for subsequent re-intervention [11-14].

However, the exclusion of *high-risk pa*tients from these RCTs is of key importance because there are consistent findings from large observational studies that OPCABG appears to reduce mortality and

morbidity in such patients [15-19]. These studies, summarized in **Table 1**, have used propensity scoring and/or logistic regression to take account of different baseline characteristics in the OPCABG and ONCABG groups but are still prone to all the limitations of non-randomized studies.

Even so only around 15%-20% of all CABG in Europe and the USA are performed as OPCABG because of concerns that it may result both in fewer grafts and in lower graft patency. The Prague-4 RCT of 400 patients in a single centre reported similar 30-day clinical outcomes but a reduction in one year saphenous vein graft patency (49% vs 59%) in the OPCABG group [20]. In contrast, in the Surgical Management of Arterial Revascularization Therapies (SMART) trial, a single-centre, single-surgeon RCT of 197 patients, Puskas et al reported one year angiographic graft patencies of 94% for OPCABG (mean of 3.2 grafts) and 96% for ONCABG (mean of 3.4 grafts) [21]. In the BHACAS studies [22], two single-surgeon RCTs of 401 patients in total, seven year follow-up has shown graft patency of 86.2% and 85.4% respectively.

CRISP is proposed to test the hypothesis that OPCABG reduces mortality and morbidity in high-risk patients without causing a higher risk of re-intervention.

Table 1 Five observational studies of OPCABG vs. ONCABG in propensity matched higher risk patients reporting reduced mortality with OPCABG

O/E= Observed/expected ratio for death

Ref	Effect measure	Numbers		Mortality		OPCABG risk reduction in mortality	p
		ONCABG	OPCABG	ONCABG	OPCABG		
15	O/E ratio for death	106,423	11,717	1.02	0.81	20%	0.001
16	O/E ratio for death	10,631	1,929	1.25	0.61	49%	0.001
17	Bayes risk based mortality	5,163	2,223	2.9%	1.4%	52%	0.001
18	30 day death with additive EuroSCORE >6	510	510	5.9%	3.1%	47%	0.04
19	Mortality in 422 very high risk	211	211	11%	4%	64%	<0.05

1.3. *Past Research*

There have been six meta-analyses and two consensus statements [13,14] addressing the issue of OPCABG vs. ONCABG. The key summary points of the four largest meta-analyses and consensus statements, which differed little in their conclusions, are reproduced in italics below. (It should be noted that these papers report, in effect, analyses of the same primary data from RCTs.) Two earlier meta-analyses (Parolari A et al Ann Thorac Surg 2003; 76: 37-40 and Reston TJ et al 2003; 76: 1510-15), with fewer patients (listed in several publications) were statistically less rigorous and are excluded.

- META-ANALYSIS 1. Cheng DC et al 2005 [11].

Summary: *Meta-analysis of 37 RCTs (3369 patients) of OPCABG vs ONCABG. No significant differences were found for 30-day mortality (OR 1.02 95% CI 0.58 to 1.80), myocardial infarction (OR 0.77 95% CI 0.48 to 1.26), stroke (OR 0.68 95% CI 0.33 to 1.40), renal dysfunction (OR 0.58 95% CI 0.25 to 1.33), intra-aortic balloon pump, wound infection, rethoracotomy, or reintervention. However, OPBCABG significantly decreased atrial fibrillation, transfusion, inotrope requirements, respiratory infections, ventilation time, intensive care unit stay, and hospital stay. Patency and neurocognitive function results were inconclusive. In-hospital and 1-yr direct costs were higher for ONCABG. Therefore, this meta-analysis demonstrates that mortality, stroke, myocardial infarction, and renal failure were not statistically significantly reduced in OPCABG; however, selected short-term and mid-term clinical and resource outcomes were improved compared with ONCABG.*

- META-ANALYSIS 2. Wijeysundera DN, et al 2005 [12].

Summary: *A meta-analysis of 37 RCTs (3449 patients) and 22 risk-adjusted (logistic regression or propensity-score) observational studies (293,617 patients). In RCTs, OPCAB was associated with reduced atrial fibrillation and trends toward reduced 30-day mortality (OR 0.91 95% CI 0.45 to 1.83), stroke (OR 0.52; 95% CI 0.25 to 1.05), and myocardial infarction (OR 0.79; 95% CI 0.50 to 1.25). Observational studies showed OPCAB to be associated with reduced 30-day mortality (OR 0.72; 95% CI 0.66 to 0.78), stroke (OR 0.62; 95% CI 0.55 to 0.69), infarction (OR 0.66; 95% CI 0.50 to 0.88), and atrial fibrillation (OR 0.78; 95% CI 0.74 to 0.82). At one to two years, OPCAB was associated with trends toward reduced mortality, but also increased repeat revascularization (RCT: OR 1.75, 95% CI 0.78 to 3.94; Observational: OR 1.35, 95% CI 0.76 to 2.39). CONCLUSIONS: RCTs did not find, aside from atrial fibrillation, the statistically significant reductions in short-term mortality and morbidity demonstrated by observational studies. These discrepancies might be due to differing patient-selection and study methodology. Future studies must focus on improving research methodology, recruiting high-risk patients, and collecting long-term data.*

- META-ANALYSIS 3. Sedrakyan et al 2006 [42].

Summary: *A meta-analysis of 41 RCTs (3996 patients) of OPCABG vs. ONCABG. No statistically significant differences were found for mortality (RR 0.96 95% CI 0.58 to 1.60), myocardial infarction (RR 0.80 95% CI 0.54 to 1.19), renal failure (RR 0.61 95% CI 0.26 to 1.45), reintervention (RR 1.90 95% CI 0.92 to 3.90) or recurrence of angina. However, OPBCABG significantly decreased atrial fibrillation (RR 0.70 95% CI 0.57 to 0.84), stroke (RR 0.52 95% CI 0.37 to 0.74) and wound infection.*

- META-ANALYSIS 4. Moller CH, et al 2008 [43].

Summary: *A meta-analysis of 66 RCTs (5537 patients) of OPCABG vs. ONCABG. No significant differences were found for mortality (RR 0.98 95% CI 0.66 to 1.44), myocardial infarction (RR 0.95 95% CI 0.65 to 1.37), repeat revascularisation (RR 1.34 95% CI 0.83 to 2.18) or stroke (RR 0.62 95% CI 0.32 to 1.19). However, OPBCABG significantly decreased atrial fibrillation (RR 0.69 95% CI 0.57 to 0.83). RECOMMENDATION: To increase the strength of evidence in which method to prefer consecutive high risk patients should be recruited into large RCTs with longer term follow-up and blinded outcome assessment.*

- AMERICAN HEART ASSOCIATION SCIENTIFIC STATEMENT: Selke FW et al [13].

One of the most hotly debated and polarizing issues in cardiac surgery has been whether coronary artery bypass grafting (CABG) without the use of cardiopulmonary bypass or cardioplegia (off-pump CABG, or OPCAB) is superior to that performed with the heart-lung machine and the heart chemically arrested (standard CABG). Various clinical trials are reviewed comparing the 2 surgical strategies, including several large retrospective analyses, meta-analyses, and the randomized trials that address different aspects of standard CABG and OPCAB. Although definitive conclusions about the relative merits of standard CABG and OPCAB are difficult to reach from these varied randomized and nonrandomized studies, several generalizations may be possible. Nevertheless, there appear to be trends in most studies. These trends include less blood loss and need for transfusion after OPCAB, less myocardial enzyme release after OPCAB up to 24 hours, less early neurocognitive dysfunction after OPCAB, and less renal insufficiency after OPCAB. Fewer grafts tend to be performed with OPCAB than with standard CABG. Length of hospital stay, mortality rate, and long-term neurological function and cardiac outcome appear to be similar in the 2 groups. To answer definitively the remaining questions of whether either strategy is superior and in which patients, a large-scale prospective randomized trial is required".

- RECOMMENDATIONS OF THE NATIONAL HEART, LUNG, AND BLOOD INSTITUTE WORKING GROUP ON FUTURE DIRECTION IN CARDIAC SURGERY. OFF-PUMP CORONARY ARTERY BYPASS. [14]

Although cardiopulmonary bypass may reduce the technical difficulty of performing CABG surgery, it also contributes to the risk of specific complications, such as perfusion-related embolization, hypoperfusion, generalized inflammatory response, and anaemia. Consequently, a number of surgeons perform OPCAB, in which cardiopulmonary bypass is avoided, in an effort to avoid perfusion-related complications. Definitive data establishing the superiority of one technique over the other are lacking. Retrospective reviews of large databases suggest that OPCAB is associated with a decrease in risk-

adjusted mortality and morbidity. Smaller prospective, randomized clinical trials comparing OPCAB with pump-based CABG have produced varying results, even when only graft patency is examined. Such conflicting information has led to adoption of OPCAB in a haphazard manner that poorly serves the large patient population with coronary artery disease. Currently, fewer than 25% of coronary revascularizations are performed without cardiopulmonary bypass, and this percentage of OPCAB procedures has not increased over the last 3 years. A large multi-centre, randomized clinical trial comparing OPCAB and CABG is needed to resolve uncertainty regarding their relative benefits.

2. Aims and objectives

Although both meta-analyses of RCTs showed clinically important effect sizes (similar to those in the observational studies) they were underpowered for statistical significance. The total number of patients in RCTs is around 50% fewer than the number we propose to recruit to the CRISP trial. CRISP will also have the advantage of recruiting higher risk patients (see below).

Currently there are only two other RCTs, one in the USA [23] and the other in Canada [24]:

(1) A USA Veterans Affairs RCT [*Outcomes Following Myocardial Revascularization: on and Off Cardiopulmonary Bypass (ROOBY)* [http://clinicaltrials.gov/ct/show/NCT00032630] which commenced in April 2002 and recruited 2203 patients by April 2008. The trial results were published in the New England Journal of Medicine in November 2009 [25]. The study had two primary null hypotheses: (i) there will be no difference in composite clinical outcome (30 day death or major morbidity); (ii) there will be no difference in one year mortality and/or acute myocardial infarction and/or a subsequent revascularization procedure. All patients having isolated CABG as an elective or urgent procedure were eligible for this trial, but the majority of patients recruited were low-risk. Many of the off-pump surgeons were inexperienced (median of 50 operations) and, on average, each surgeon contributed 7 cases/year. Major morbidity/mortality at 30-days was similar in the two trial arms (7% off-pump vs. 5.6% on-pump, relative risk 1.26 (0.91 to 1.74), p=0.19).

(2) The Canadian led CORONARY (CABG Off or On Pump Revascularization Study) trial [http://clinicaltrials.gov/ct2/show/NCT00463294], which commenced in November 2006 plans to recruit 4700 patients by May 2014. The primary end point is to determine if OPCABG reduces major clinical vascular end-points (death, stroke, MI and renal failure and need for repeat revascularization) at 30-days and over 5-years. A secondary end-point is to assess total costs and resource use over the same time frames. To be eligible for this trial patients are required to have at least one of age≥70 years, peripheral vascular disease, cerebrovascular disease, renal insufficiency or age>60 years with one of diabetes, urgent in-patient, left ventricular ejection fraction<35%, current or recent smoker. Some, but not all, of these factors are included in the additive EuroSCORE. The additive EuroSCORE increases with age (1 point per 5 years from age 60); the other risk factors contribute 2 or 3 points each.

While the Canadian trial is important, without enrolling predominantly higher risk patients it is unlikely to detect differences in important clinical end-points, as has been seen for the ROOBY trial [25].

The CRISP Trial is proposed to test the hypothesis that OPCABG reduces mortality and morbidity in high-risk patients without a higher risk of re-intervention. It is an international, multi-centre, open RCT of ***OPCABG*** versus ***ONCABG*** in patients with an additive EuroSCORE ≥5. The primary outcome is a composite of 30 day death or major morbidity: renal failure, myocardial Infarction, stroke, prolonged ventilation, sternal wound infection with dehiscence requiring reoperation. Patients will be followed-up for a minimum of 1-year.

3. Plan of Investigation

3.1. *Study design*

An international multi-centre open randomised controlled trial of isolated off-pump CABG (OPCABG) versus on-pump CABG (ONCABG) in high risk patients with an additive EuroSCORE ≥5.

The trial coordinating centre is the Clinical Trials and Evaluation Unit of the Bristol Heart Institute. The University of Oxford is the sponsor for the trial. The trial will be conducted in accordance with the principles of the Helsinki Declaration and the European Union Directive 2001/20/EC on clinical trials.

3.2. *Trial interventions*

Trial patients will be randomised to

a) CABG without cardiopulmonary bypass, i.e. off-pump CABG (OPCABG) on the beating heart, via a median sternotomy incision

or

b) CABG with cardiopulmonary bypass i.e. on-pump CABG (ONCABG) on a chemically arrested heart, via a median sternotomy incision

3.3. *Study population*

Patients having isolated CABG surgery will be eligible if they satisfy the following criteria:

Inclusion criteria

- Additive EuroSCORE ≥5.

  Patients with an additive EuroSCORE of 5 or more are at higher risk of mortality and morbidity. They will usually be patients with one or more of the following risk factors (percentages in brackets are the approximate prevalence in Bristol and Oxford combined in the period 1999 to 2006, 2595 patients with an additive EuroSCORE ≥5)

- Age >65 (87%), >70 (70%), >75 (37%), >80 (8%) [1 additive EuroSCORE point per 5 years from age 60]
- Poor left ventricular function (15.0% with ejection fraction <30%) [3 additive EuroSCORE points]
- Impaired renal function (3.7% with creatinine > 200 µmol/L) [2 additive EuroSCORE points]
- History of previous stroke (11.2%) [2 additive EuroSCORE points]
- Redo operation (previous sternotomy) (7.2%) [3 additive EuroSCORE points]
- Chronic obstructive pulmonary disease (10.3%) [1 additive EuroSCORE point]

- Non-emergency surgery
- Operation to be carried out via a median sternotomy
- Written informed patient consent

Exclusion criteria

- Additive EuroSCORE <5
- Emergency operation (immediate revascularisation for haemodynamic instability)
- Concomitant cardiac procedure with CABG
- Operation to be carried out via an incision other than a median sternotomy (e.g. anterolateral left thoracotomy)
- Known contraindication to ONCABG or OPCABG (e.g. calcified aorta, calcified coronaries, small target vessels)

3.4. *Randomisation*

Patients will be randomly assigned in a 1:1 ratio. The randomisation will be stratified by centre and cohort minimisation will be used to minimise imbalance of key prognostic factors (age, gender, urgency of operation, poor LV function, impaired renal function, previous stroke, redo CABG, significant pulmonary disease) across the OPCABG and ONCABG groups.

The preferred method of randomisation will be to an **experienced off-pump surgeon** or to an **experienced on-pump surgeon**, i.e. "expertise-based" as extensively reviewed in reference [26]. Individual surgeons, because of their training and experience, are generally more proficient in a particular

technique, and so are likely to use primarily a single surgical approach. This could compromise the validity of a conventional RCT as the surgical expertise may be skewed toward the technique which is best established, most widely used or easiest to perform; a conventional RCT also has limited applicability since, by design, only surgeons experienced in OPCABG can take part. Surgical procedures which require a "learning curve" are clearly disadvantaged as a minimum number of cases need to be performed and considerable experience is needed before a surgeon feels at ease with both techniques. Unless participating surgeons have expertise in both procedures, there is also a potential for differential crossover in the two arms of the trial (i.e. more crossovers in one direction than the other). OPCABG, compared to ONCABG, is less frequently performed, technically more demanding, and may have a more prolonged "learning curve". Previous conventional RCTs have been criticised for recruiting "inexperienced" OPCABG surgeons, resulting in poor OPCABG results with an excess of graft occlusion recruiting OPCABG devotees, and not the best ONCABG surgeons [27]. Expertise-based randomisation will avoid these problems.

If expertise-based randomisation is not feasible then stratified within-surgeon randomisation will be used. This will only be used when, after detailed discussion with the research team, it is agreed that expertise-based randomisation is not possible. Centres and surgeons planning to use within-surgeon randomisation will require approval from the trial steering committee.

After obtaining written informed consent, randomisation will be carried out using an internet-based system (e.g. Sealed Envelope Ltd) to guarantee concealment of allocation. Designated site staff will log on to a dedicated website (password-protected). Only after key patient identifiers and information about eligibility criteria have been entered will the system divulge the treatment allocation.

If a patient is unexpectedly rescheduled, he/she will retain his/her study numbers and randomised allocation, i.e. the rescheduled operation will need to be carried out by a surgeon participating in CRISP who prefers to operate using the allocated method of surgery (centres using expertise-based randomisation) or by a surgeon participating in CRISP who is operating using both methods (within-surgeon randomisation).

3.5. *Surgical procedure*

The anaesthetic technique and method of myocardial protection used should be in accordance with established local protocols. As there is a consistent 30-day mortality of around 2% for CABG across most

UK centres this suggests that minor differences in anaesthetic technique and methods of myocardial protection do not have a major influence on peri-operative mortality. Surgical details will be recorded in the case report form (CRF). The only requirement is that the centre/surgeon follows the randomisation allocation. Should it prove necessary to convert from OPCABG to ONCABG during the operation, this will be recorded in the CRF.

3.6. *Surgeon eligibility*

Surgeons at participating centres using the preferred method of expertise-based randomisation will be eligible to join CRISP if they have a stated preference for either off-pump or on-pump CABG and been approved the trial steering committee as being sufficiently experienced in their preferred technique (i.e. at least 100 operations). When operating on CRISP patients, surgeons will perform only the procedure in which they have expertise. This will minimise the learning curve and reduce any potential for a subconscious bias associated with performing extra grafts or ordering extra tests, as surgeons will perform only the procedure which they usually perform for patients requiring isolated CABG. Also, the risk of crossover is decreased as the level of surgical expertise for both techniques is relatively high.

Surgeons at participating centres where the trial steering committee has approved the use of within-surgeon based randomisation the surgeons concerned will be required to provide evidence that they have expertise in both techniques (at least 100 operations carried out using each method) and that they use both techniques with similar frequency.

3.7. *Patient recruitment*

Potential trial participants will be identified from out-patient clinic lists (elective patients) and in-patient waiting lists (urgent patients). All potential participants will be sent/given a patient Information Sheet describing CRISP and will be seen by a research nurse/trial coordinator who will answer questions, confirm the patient's eligibility and take written informed consent. Most patients will have at least 48 hours to consider whether to participate or not.

Consenting patients will then be randomised and the research nurse/trial coordinator will liaise with the consultant surgeon and hospital staff responsible for organising operating schedules to arrange the surgery. The randomisation will take place as close as possible to the operation.

Details of all patients approached for the trial and reason(s) for non-participation (e.g. reason for being ineligible, patient or clinician preference or patient refusal) will be documented.

3.8. *Duration of treatment period*

The duration of treatment period is the time from randomisation to the end of the operation.

3.9. *Frequency and duration of follow up*

Participants will be followed during their index hospital admission and will be assessed at hospital discharge and at the routine follow-up visit, scheduled between 4 and 8 weeks after discharge.

3.10. *Definition of end of the trial*

The end of the trial for an individual patient is when they have completed the 4-8 week assessment. The end of the trial as a whole is when the last patient recruited has completed the 4-8 week assessment.

3.11. *Primary and secondary endpoints*

Primary outcome

The primary outcome is a composite endpoint of death or serious morbidity (**CRISPSw).**

While the mortality from CABG is around 2%, 10-15% of CABG patients suffer clinically significant morbidity that prolongs and complicates post-operative recovery and which is estimated to consume around 40% of all hospital resources related to cardiac surgery [28,29]. While mortality after CABG reflects disease-specific variables such as recent myocardial infarction or low ejection fraction, morbidity reflects, at least in part, comorbid illness such as peripheral vascular disease, renal impairment and chronic pulmonary disease [28,29]. Also, while CPB adversely affects all organs at a sub-clinical level, clinical morbidity is dominated particularly by haematological, cerebral, respiratory, myocardial and renal dysfunction. It is of particular relevance that the elderly are most susceptible to the adverse sequelae of CPB because the age of patients undergoing cardiac surgery is rapidly increasing. Furthermore, as all evidence suggests that OPCABG has a similar direction of effect for all components of the composite end point, and that the composite end point is not obviously dominated by any one component (death

contributes most, see sample size below), this avoids some of the common pitfalls in using a composite outcome.

The components of the composite endpoint (**CRISPSw)** are defined as follows:

- Death after **C**ardiac surgery within 30-days (i.e. ≤ 30-days) of the operation from any cause. Deaths after 30-days but during the index hospitalisation (i.e. the hospital admission for surgery) will recorded but will not be included in the 30-day composite outcome.

- New onset **R**enal failure, defined by:

- A postoperative creatinine value of >200µmol/L AND a percentage increase from the preoperative creatinine of ≥40%.

  AND

- The need for renal replacement therapy (e.g. dialysis or haemofiltration)

  within 30-days (i.e. ≤ 30-days) of the operation. Renal failure after 30-days but still during the index hospitalisation will be recorded, but will not be included in the 30-day composite outcome. Dialysis or haemofiltration during cardiopulmonary bypass only will NOT constitute a requirement for renal replacement therapy. Any patient who received renal replacement therapy in the month prior to surgery will not be eligible for this endpoint. Creatinine will be measured in all patients preoperatively and at day 2. Creatinine will also be recorded if new onset renal failure is indicated.

- Myocardial **I**nfarction (MI). On day 5 all patients will have an ECG and blood samples taken for the assessment of cardiac markers (Troponin T or Troponin I where possible, only if these tests are not available should CK-MB be used). There is some flexibility in the timing of samples; they can be taken between days 4 and 6, depending on local routine care. If a suspected MI occurs at any other time up to one year post surgery, a blood sample must be taken (Troponin T or Troponin I, or/and CK-MB) and an ECG must be preformed. MI following surgery will be identified by a troponin I >0.5 µg/L or troponin T >0.2 µg/L and new pathologic Q waves with documented new wall motion abnormalities other than in the septum or CK-MB ≥ 10 ULN (non-Q MI) or from ECG changes consistent with infarction (new significant Q waves ≥0.04cm or a reduction in R waves of >25%, in at

least two contiguous leads). If the blood results do not indicate an MI (i.e. troponin I ≤0.5 µg/L and troponin T ≤0.2 µg/L) but the ECG suggests an MI has occurred the results will be adjudicated by an independent committee masked to the randomised allocation. In such instances the ECG results will be requested by study team. For this reason copies of all ECGs must be kept until the end of the study.

- **S**troke defined as a new acute focal neurological deficit thought to be of vascular origin with signs or symptoms lasting longer than 24 hours and confirmed by a neurologist. Imaging will be encouraged to further delineate between an ischemic or hemorrhagic event.

- **P**rolonged ventilation ≥ 96 hours during the index hospital admission for surgery. Any periods of reintubation following the initial extubation will be recorded but will not be included in the calculation of the index ventilation time.

- **S**ternal **w**ound dehiscence requiring non-pharmacological intervention (e.g. vac dressing or re-operation) within 30-days (i.e. ≤ 30-days) of the operation. Sternal wound dehiscence after 30-days will be recorded but will not be included in the 30-day composite outcome.

Secondary outcomes

Secondary outcome measures are:

- Duration of intensive care unit stay during index hospital admission, excluding any periods where the patient is returned to the intensive care unit after initial discharge to the ward or high dependency unit (periods where the patient is returned to the intensive care unit will be documented separately).

- Duration of hospital stay during index hospital admission. For urgent hospitalised patients, the waiting time outside the cardiac surgery unit will be excluded; the time will be calculated from the date of operation.

- Resource utilisation (hospital resources during index admission).

- Quality of life assessment at 4-8 weeks using the Rose Angina Questionnaire (short), Canadian Cardiovascular Society Angina (CCS) class, EuroQol EQ-5D and for UK patients only, the Coronary Revascularisation Outcome Questionnaire (CROQ) [30].

- Cost-effectiveness (within-trial cost per CRISPSw event averted, extrapolated cost per life-year gained and per quality-adjusted life year gained).

EQ-5D

Patients recruited at UK centres will be randomised to receive either the standard EQ-5D which has 5 questions each with three possible responses or an extended version that has the same 5 questions but with 5 response options for each rather than three [31]. As a sub-study of CRISP, this will provide data to compare patient responses using the two scoring systems in patients undergoing coronary surgery which will complement previous studies in the general population and in patients with cancer [32,33].

3.12. *Measures taken to avoid bias*

The trial will be analysed on an intention-to-treat basis, i.e. outcomes will be analysed according to the treatment allocation, irrespective of future management and events, and every effort will be made to include all randomised patients. Follow-up for the primary 30-day outcome should be complete for all patients.

The primary composite outcome will be tracked through prospective data collection from randomisation until 30-days. To minimise the possibility of outcome events occurring after randomisation and before CABG, operations will be performed as close to randomisation as possible. The time from randomisation to surgery will be recorded and compared for both groups.

Participants will not be informed of their allocation and the external signs of surgery will be similar for both groups.

It is not possible to blind the surgeon or those involved in the post-operative care of the patient. However, at the majority of centres post-operative care follows strict protocols which are not ONCABG or OPCABG specific. The primary 30-day composite outcome will be based on objective outcomes of death or major morbidity (as described above). Clinical outcome measures will not be assessed by a

Clinical Events Adjudication Committee. Adjudication has not been shown to improve the ability to determine treatment effects [34]. Participating centres will be required to submit data promptly for all randomised patients. Detailed scrutiny of the submitted data will be carried out centrally by the data coordinating centre and suspect or missing items will be queried.

3.13. *Data collection*

Purpose-designed case report forms (CRFs) will be used to record data at each stage of a patient's journey through the trial. The key data collection points are summarised in **Table 2**. Primary and secondary outcomes up to 30 days will be collected by the local investigators. Questionnaires will be completed before surgery and at the 30 day follow-up visit.

Table 2 Key data collection points

	Pre-surgery	Day of surgery	Day 2	Day 5	Discharge	4 to 8 weeks post - discharge	
Eligibility (incl. additive EuroSCORE)	✓						
Written consent	✓						
Randomised allocation	✓						
Demographics and past medical history	✓						
Bloods for Creatinine	✓		✓				
Bloods for Troponin				✓*			
ECG				✓*			
Operative details		✓					
Clinical outcomes					✓	✓	
Quality of life questionnaires	✓					✓	
Resource use data					✓		

* can be taken between days 4 - 6, or at discharge if <4 days

The research nurse/trial coordinator at each centre will be responsible for "tracking" each patient during their hospital stay and for ensuring all tests are carried out and blood samples are taken at the designated time. Blood samples for measuring ischemic injury/creatinine will be taken through *in situ* venous/arterial lines. The research nurse/trial coordinator will be responsible for the secure storage of samples until they are analysed in the laboratory. Blood and other test results will be linked with the other data by a unique anonymised identifier (patient trial number). The research nurse/trial coordinator will also be responsible for collecting data on events between discharge and 30-days, at the routine follow-up visit, 4 to 8 weeks after discharge (most patients are discharged between 5 and 7 days after surgery, only a very small number will remain in hospital beyond 30-days).

Each centre will be provided with a protocol, study manual, questionnaires and patient CRFs. Specific adverse event forms for death, myocardial infarction, major bleed, cerebrovascular accident, revascularisation and other serious adverse events (i.e. other events that require or prolong hospitalisation) will be provided. Centres will be required to complete these adverse event forms and send them to the CTEU within 72 hours of their knowledge of the event.

Completed CRFs will either be sent to a dedicated secure fax at the central trial coordinating centre or entered directly via into the trial database via a password protected web-based interface.

3.14. *Sample size calculation*

The meta-analyses and observational studies of OPCABG versus ONCABG (Table 1) suggest that a relative risk of about 0.7 for the primary outcome (**CRISPSw**) is plausible, especially given that benefits are hypothesised to be higher for high risk patients.

Data collected for the National Adult Cardiac Surgical database show that the risk of **CRISPSw** in patients with a pre-operative additive EuroSCORE ≥5 is about 10%-15% [35]. Data from the Bristol and Oxford cardiac databases show that around 9% of patients with an additive EuroSCORE ≥5 had one or more of these outcomes (**Table 3**). The dataset included 2595 patients with an additive EuroSCORE ≥5, of whom 573 had an additive EuroSCORE of 8 or more (22%).

Table 3 Combined event frequencies (%) in Bristol and Oxford

	Additive EuroSCORE ≥5 (n=2595)			Additive EuroSCORE ≥8 (n=573)		
Surgery	TOTAL	Off-pump	On-pump	TOTAL	Off-pump	On-pump
C	4.7	4.0	5.2	10.3	8.6	11.3
CS	5.6	4.6	6.2	12.2	10.5	13.2
CIS	7.5	7.6	7.4	14.8	15.3	14.6
CRIS	8.5	8.6	8. 5	17.3	17.7	17.0
CRISP	8.8	8.9	8.6	17. 5	17.7	17.3
$CRISPS_W$	9.3	9.5	9.2	17.8	18.2	17.6

C=death after cardiac surgery; S=stroke; I=myocardial infarction; R=renal failure; P=prolonged ventilation ≥96 hours; Sw=re-operation for sternal wound infection

For sample size calculations, the event rate pooled over the two centres has been used as the reference. **Table 4** shows sample sizes required for different power parameters. It illustrates the sample sizes necessary to detect a 30% reduction in different composite outcomes, with 80%, 85% and 90% power at a 5% level of significance. The table also shows the influence on the sample size needed of the number of participating surgeons (between 80 and 120) and the intraclass correlation coefficient (ICC of 0.001 and 0.005).

The sample size is based on the assumption that our preferred method of randomisation (i.e. expertise based randomisation, with patients randomised to either a surgeon who prefers ONCABG or a surgeon who prefers OPCABG), will be used. All patients randomised to a given surgeon will have their operations using the same technique and cannot be regarded as independent of each other. The "standard" sample size calculation must be modified to reflect this non-independence, or clustering effect [36], using the ICC. Data from Bristol and Oxford accrued since April 1999 were used to estimate plausible values for the ICC.

Table 4 Sample size estimates for a 30% risk reduction (figures are for the total sample size)

Additive EuroSCORE ≥ 5; allocation ratio 1:1; statistical significance = 5%

ICC	0.005	0.005	0.005	0.001	0.001	0.001	0.005	0.005	0.005	0.001	0.001	0.001
Surgeons	120	120	120	120	120	120	80	80	80	80	80	80
Power	80%	85%	90%	80%	85%	90%	80%	85%	90%	80%	85%	90%
Outcome												
C	8584	10270	12828	6684	7660	9014	10452	13080	17566	6874	7914	9358
CS	6820	8092	9942	5574	6382	7488	7966	9728	12550	5708	6552	7728
CIS	4604	5366	6476	3996	4566	5344	5088	6048	7498	4062	4654	5468
CRIS	3926	4560	5484	3480	3976	4648	4282	5062	6200	3534	4042	4742
CRISP	3796	4412	5306	3380	3858	4510	4124	4860	5958	3426	3918	4596
$CRISPS_W$	3514	4064	4870	3148	3590	4196	3790	4448	**5418**	3188	3646	4274

We propose to recruit 5418 patients to provide the best balance between power, feasibility, etc. This means the trial will have 90% power of detecting a risk reduction of 30% in the primary outcome in patients with an additive EuroSCORE of ≥5 (assuming 80 surgeons and ICC= 0.005).

In the last 5 years 30% of Bristol patients had an additive EuroSCORE of ≥5.

3.15. *Planned recruitment rate*

We estimate that 30% of 25,000 annual CABG patients in the UK have an additive EuroSCORE ≥5 [35] i.e. 7500 eligible procedures are carried out annually. We plan to recruit 20% into CRISP over 2 years (i.e. 3000 patients; 1500 per year) in 20 UK centres. We intend to recruit the remaining patients from centres outside the UK that carry out at least 500 high risk OPCABG per annum.

A typical UK centre such as Oxford or Bristol might expect around 200 to 300 eligible patients per year and be able to recruit >40% (as per BHACAS2 [22]), i.e. 80 to 120 per year. Assuming 90 patients per year in 40 centres, over 2 years, the trial would achieve 7200 patients.

3.16. *Participating centres*

We plan to recruit 40 centres (20 from the UK and 20 international, many of whom are already part of the MRC/BHF ART trial) [37]. Details of the centres who have indicated that they are willing to join CRISP are listed in **Appendix 2**.

Each centre will be paid a sum per-patient to help support a study co-ordinator. Study site co-ordinators will be responsible for screening patients (and recording the data on a screening log), enrolling patients into the trial, providing a contact point for patients, liaising with CTEU, completing CRFs, recording adverse events, ensuring data are sent to CTEU and that all data queries are resolved.

3.17. *Investigators' responsibilities*

Investigators will be required to ensure that Local Ethics Committee and research governance approvals have been obtained (or equivalent authorities in non-UK centres) as well as Agreements signed off by their Institution prior to the start of the study. Investigators will be required to ensure compliance to the protocol and study manual and with completion of the CRFs. Investigators will be required to allow access to study documentation or source data on request for monitoring visits and audits performed by the Sponsor or CTEU or any regulatory authorities.

3.18. *Training*

Pre-study training visit

Before the study commences each centre will receive a training visit by the CTEU. These visits will ensure that personnel at each site (including principal investigators, co-investigators and the study site co-ordinator) fully understand the protocol, CRFs and the practical procedures for the study.

Monitoring visits

Routine monitoring visits to each centre by the data coordinating centre are not planned. However, the completeness and consistency of the data will be monitored centrally on an ongoing basis and queries fed back to centres. It has been suggested that on-site monitoring is an inefficient way to identify errors most likely to compromise patient safety or bias study results [38]. Central monitoring of submitted data is

more likely to lead to tangible benefits,[38] is less costly and represents a more efficient use of trial personnel.

3.19. *Compliance with the allocated treatment*

As the intervention is the operation, compliance is likely to be 100%, except for technical surgical reasons. In the BHACAS trials 2/401 (0.5%) participants were converted from OPCABG to ONCABG [22], similar to overall rates of <1% reported by experienced OPCABG surgeons [39].

3.20. *Likely rate of loss to follow-up*

We anticipate 100% follow-up for the primary outcome at 30 days. Bristol achieves 85% follow-up from routine long-term monitoring for all cardiac surgery patients and would expect 100% for survival and >98% follow-up via the Office of National Statistics and NHS population register. The Canadian registry, which is minimally funded and makes no special effort to chase follow-up achieves a follow-up rate of 98% at 1-year.

3.21. *Statistical analysis*

Analyses will be carried out on the basis of intention to treat. The primary analysis will report on the proportion of patients experiencing the composite outcome of death or major morbidity (CRISPSw) up to 30 days in OPCABG and ONCABG groups. The feasibility of adjusting for the factors included in the cohort minimisation using logistic regression, with surgeons modelled as random effects will be explored but it is possible that the effects may not estimated reliably.

Secondary analyses will compare other secondary outcomes, in OPCABG and ONCABG groups. Again the feasibility of adjusting for the factors included in the cohort minimisation will be examined.

For the “time to event” outcomes, Cox regression will be the preferred method of analysis. The validity of the assumption of proportional hazards will be tested and, if this assumption is violated, a Cox model with a time-dependent covariate (the interaction term between the treatment and the survival time) will be used. This type of model will allow the difference between OPCABG and ONCABG to be estimated within discrete time periods, to describe further the difference in outcome due to the treatment group. Participants who die prior to discharge will be censored at their last follow-up date.

Quality of life outcomes will be compared using a mixed regression model to account for the non-independence between repeated scores. The pre and post surgery scores will be modelled jointly to avoid the need to exclude or impute values for cases with missing preoperative scores.

All statistical analyses and trial reports will conform to the CONSORT guidelines.[40]

3.22. *Subgroup analyses*

No subgroup analyses are planned.

3.23. *Frequency of analyses*

Analyses will be performed for the primary and short-term secondary outcomes at 30 days after the operation.. The Data Monitoring and Safety Committee will advise on the frequency of interim analyses and stopping rules.

3.24. *Economic issues*

Given the large number of CABG procedures currently performed in the UK and worldwide, and the fact that the sickest 10%-15% of CABG patients consume 40% of resources [28,29], economic issues are important. Previous studies have limitations: one UK study reported costs for 200 patients [41], one Dutch study reported 1-year cost-effectiveness for 139 patients [42] and one USA study reported 1-year costs for 200 patients [21]. CRISP therefore offers an ideal opportunity to perform a much more informative and reliable cost analysis and cost-effectiveness analysis of the potential of OPCABG to reduce costs. The primary economic evaluation will be performed from the perspective of the UK NHS, but resource use and quality of life data will be collected from all participating centres, to facilitate subsequent economic evaluation in and by each participating country. The UK health economics team will collaborate with health economists in other countries to undertake such analyses, and make outcome and resource use data and the extrapolation model available for use. For the UK evaluation, we propose (subject to heterogeneity tests) to use the full power of the international study to inform the estimated difference in effectiveness and resource use between therapies, and the impact of each intervention and complications on quality of life, but will use UK specific unit costs when estimating incremental cost-effectiveness.

Resource use information will be collected from all centres on resources used during the hospital stay; time in operating theatre, total blood and coagulant product use, time in cardiac recovery unit, days on ward; treatment of complications (e.g. return to theatre); drugs prescribed at hospital discharge; use of cardiac rehabilitation.

Information on subsequent in-patient episodes (including interventions and duration) on outpatient visits and diagnostic procedures, and on GP and practice nurse consultations, will be obtained using a short postal questionnaire sent to each trial patient 12 months after intervention. This will also contain a simple checklist of specified medications (aspirin, statins, ace-inhibitors, beta-blockers, calcium channel antagonists), and a simple question on current employment status. This postal questionnaire is being used successfully in the MRC/BHF Arterial Revascularisation Trial, including foreign language versions.

Participating centres will record and report subsequent re-hospitalisations and revascularisations of trial patients. Overall analysis will be performed from the health care system perspective, with data on employment status at 12 months also being reported.

Unit costs from UK centres and from national sources will be used to obtain a cost per patient. Missing data will be handled via multiple imputation.

In line with the primary outcome of the trial, the economic analysis will use within-trial CRISPSw events as a single composite outcome measure. In addition, lifetime life-years gained and quality adjusted life-years gained will be estimated, using an extrapolation model. This will be a Markov-type state transition model, with transition probabilities to fatal and non-fatal CRISPSw events based on within-trial data, and deaths from other causes based on life-table data. Quality adjustment will be performed using the EQ-5D, available in all required language versions.

The first cost-effectiveness result to be estimated will be the within-trial UK incremental cost per CRISPSw event averted. This will allow detailed within-trial information on costs and quality of life to be reported. Second, using the extrapolation model, plus results from the EQ-5D annual questionnaires, the lifetime incremental cost per life year gained and per quality adjusted life year gained will be calculated. All resource use, cost, outcome and cost-effectiveness information will be reported as the mean per patient in each arm of the trial and the mean difference, with appropriate measures of variance. Cost-effectiveness acceptability curves and net benefit statistics will also be reported.

The results of this trial will be used

- To inform if OPCABG offers more benefit than harm, compared to ONCABG, in high risk patients.
- To help resolve resource use questions

Demonstration of survival and clinical (reduced morbidity) benefits of OPCABG would have major implications for individual patients and economic implications for health services.

4. Trial management

4.1. *Day-to-day management*

The Clinical Trials and Evaluation Unit (CTEU), Bristol University, Bristol, UK is the coordinating centre for this study and is primarily responsible for the development of the trial protocol, organisation of the study, development of the randomisation scheme, the study database, data internal consistency checks, data analysis and coordination of the centres. The Bristol CTEU is a UK Clinical Research Collaboration registered Trials Unit.

All local investigators are experienced cardiac surgeons (more than 2 years of experience) and experts in on-pump or off-pump CABG (more than 100 cases). The statistical analysis will be under the supervision of Dr Chris Rogers and Professor Doug Altman, who have overseen the analyses of several major trials and large registries.

The principal investigator, Professor David Taggart, and the research team, along with the study trial manager, they will form the operations committee, which will be responsible for the day-to-day management of the study.

4.2. *Steering Committee and Data Monitoring and Safety Committee*

The steering committee will meet at least annually and is responsible for all major decisions in the trial. Membership of the Trial Steering Committee has been established. The membership includes a patient representative.

An independent Data Monitoring and Safety Committee (DMSC) has been established.

5. Safety reporting

Serious and other adverse events will be recorded and reported in accordance with the International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines and the Sponsor's Research Related Adverse Event Reporting Policy. Serious adverse events will be reported from the point of consent, up until the time that the 4-8 week post-surgery assessment has been completed, the patient has withdrawn, or the patient is found to be 'lost to follow-up'.

ONCAG and OPCAB are similar surgical methods so expected adverse events are likely to be the same. In cardiac surgery, post-operative transient complications are not unexpected and are not infrequent prior to discharge. The research team will only notify fatal and 'unexpected' non-fatal serious adverse events to the Trial Sponsor (University of Oxford) (as per Figure 1 overleaf). Unexpected events are those not listed in the trial protocol or on the CRFs.

The following pre-discharge serious adverse events are 'expected':

MI, including:

- New Q's waves ≥0.04cm in at least 2 contiguous leads
- Reduction in R waves >25% in at least 2 leads
- Raised Troponin I or Troponin T (or CK-MB)

Coronary angiography

PCI

Redo CABG

Reoperation, e.g for:

- Bleeding
- Tamponade

Use of IABP

Use of LVAD

Prolonged Ventilation >96 hours

Respiratory Infection

Tracheostomy

ARDs

Artial Fibrilation requiring drug therapy

Sternal wound dehiscence, requiring:

- Vac dressing
- Formal surgical reconstruction

Superficial wound infection

- Chest
- Leg
- Arm

Deep vein thrombosis

Pulmonary embolism

Heparin induced thrombocytopenia (comfirmed by immunoassay)

Renal failure requiring dialysis or haemofiltration

GI complications, including

- Peptic ulcer/GI bleed/perforation
- Pancreatic (amylase >1500iu)

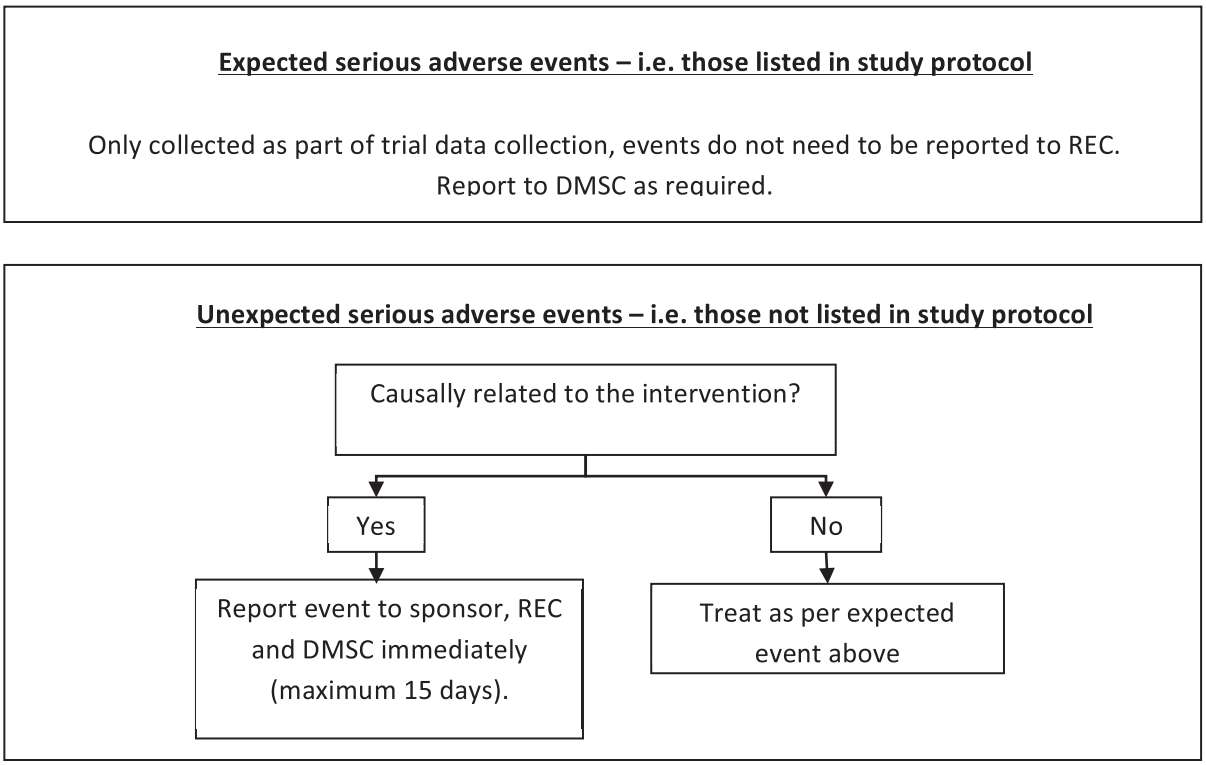
- Other (e.g. laparotomy, obstruction)

Neurological complications, including

- Stroke
- TIA

Data on these serious adverse events collected during the trial will be regularly reported to the trial DMSC.

Figure 1 **Serious adverse event reporting flow chart for non-CTIMP studies**



6. Ethical approval, research governance and indemnity

6.1. *Ethical review*

Ethics review of the protocol for the trial will be carried out by a UK NHS Research Ethics Committee (REC) and other bodies with similar roles/authority for centres outside the UK.

The existence of collective equipoise about the main research question is evident as only around 20% of operations in the UK [30] and USA [15] are OPCABG and allocation of patients to either technique is on the basis of a surgeon using predominantly one or other technique. Our expertise-based design is designed to allow surgeons with different preferences to be included. There is a 'demand' for OPCABG; anecdotally, some patients have a preference for it and seek out surgeons who use it, presumably because of information implying that it is 'better'.

6.2. *Research governance*

This study will be conducted in accordance with:

- The Medicine for Human Use (Clinical Trial) Regulations 2004
- International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines
- Research Governance Framework for Health and Social Care

Local Research and Development (R&D) approval in the UK requires that the trial be conducted in compliance with the Research Governance Framework. The trial will also comply with requirements in countries outside the UK.

6.3. *Risks and anticipated benefits*

Potential benefits to participants:

- They will be operated on by a team led by a consultant 'skilled' in their preferred technique.

- They will be followed and monitored more thoroughly in the trial than with 'usual care' (at least in the UK and other countries with publicly-funded health services), which should mean that any complications are detected and treated early.

Potential harms to participants:

- The possibility of randomisation to an inferior treatment (a possible harm of participating in any trial)

- Possible side effects of the techniques. However, the 'reasonableness' of asking participants to accept randomisation is evident from current use of both techniques. Despite consensus statements about the short term benefits of OPCABG, most surgeons do not use it, presumably because of uncertainty about longer term outcomes and whether the existing evidence applies to their practice (on-pump surgeons were excluded from previous trials).

Possible adverse effects of each technique:

- On-pump: potentially higher risks of (a) thromboembolic complications, e.g. stroke or MI, (b) atrial fibrillation; (c) transfusion; (d) respiratory infection; (e) longer ICU and hospital stay [11].

- Off-pump: risk of conversion to on-pump (about 1%), with increased complications [34]; potentially higher risks of (a) incomplete revascularisation, (b) less good distal anastomoses and (c) cardiac-related events and recurrence of symptoms in the long term.

The proven benefits of OPCABG (in the hands of surgeons who prefer it) are finely balanced against the potential longer term harms, compared to ONCABG. This balance justifies informing patients of the potential benefits and harms and inviting them to participate; patients who strongly prefer one or other technique will be able to choose to have their operation by that technique and will not be included in the trial.

Benefits to society:

Whatever the results, the trial will benefit society because the findings will resolve the existing uncertainty about the effectiveness and cost-effectiveness of the two techniques in high risk patients, i.e. the CABG patients in whom mortality and morbidity is highest.

6.4. *Informing potential trial participants of possible benefits and known risks*

For UK centres, information about possible benefits and risks of participation will be described in a Patient Information Sheet given/sent to patients when they are approached to take part. This information sheet will be part of our application to a UK NHS REC. International centres will need to obtain approval from their RECs (or equivalent) and may need to adapt the UK materials accordingly.

6.5. *Obtaining informed consent from participants*

All participants will be required to give written informed consent. This process, including the information about the trial given to patients in advance of recruitment, will be described in our application to a UK NHS REC for ethical approval; similar information will be provided to other ethics review bodies. All patients will receive information about the trial at least 24 hours before being asked to give informed consent.

6.6. *Monitoring and audit*

The study will be monitored and audited in accordance with the Sponsor's policy, which is consistent with the Research Governance Framework and the Medicines for Human Use (Clinical Trials) Regulations 2004. All study related documents will be made available on request for monitoring and audit by the University or the Ethics Committee.

The trial coordinating centre will carry out regular audit of compliance of centres with GCP and data collection procedures.

6.7. *Data protection*

Data will be collected and retained in accordance with the UK Data Protection Act 1998 and will comply with any data protection requirements applicable in countries outside the UK.

6.8. *Data storage and sharing*

Data storage

We will propose to the UK NHS REC that we retain all trial documentation in a secure location during the conduct of the study and for 5 years after the end of the trial, when all patient identifiable paper records will be destroyed by confidential means. In compliance with the MRC Policy on Data Preservation, we will also propose that the fully anonymised dataset, a separate secure electronic 'key' with a unique patient identifier, and relevant 'meta'-data about the trial be retained in electronic form indefinitely because of the potential for the raw data to be used subsequently for secondary research.

Data sharing

Data will not be made available for sharing until after publication of the main results of the trial. Thereafter, anonymised individual patient data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the MRC Policy on Data Preservation and Sharing regarding scientific quality, ethical requirements and value for money. We propose that a minimum requirement with respect to scientific quality should be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research, e.g. a protocol for a Cochrane systematic review. The second file containing patient identifiers would be made available for record linkage or a similar purpose, subject to confirmation that the secondary research protocol has been approved by a UK REC or other similar, approved ethics review body.

6.9. *Indemnity*

Oxford University operates a Clinical Trials protection scheme, which operates in respect of the University's legal liabilities arising as Sponsor. Furthermore, the standard provisions of the NHS indemnity scheme will operate in respect of the provision of clinical treatment. Other applicable local arrangements for those collaborating centres beyond the UK will be arranged.

7. Dissemination of findings

It is not anticipated that the trial will lead to commercially exploitable findings. The findings will be disseminated by usual academic channels, i.e. presentation at international meetings, as well as by peer-reviewed publications and through patient organisations, a public web-site and newsletters to patients, where available. Trial centres will be kept informed of the trial progress though regular newsletters.

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9. Amendments to protocol

Amendment number	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
1	2	21 July 2008	3	10 July 2009	SAE section updated	22 July 2009
2	3	10 July 2009	4	10 October 2009	Clarification of blood tests for cardiac markers, inclusion of Troponin T.	14 October 2009
3	4	10 October 2009	5	15 January 2010	Update of published evidence Change to inclusion criteria and to definition of new-onset renal failure Addition of creatinine at day 2 Survival to 3 months and CCS class at 1 year added as secondary outcomes	15 February 2010
4 (Amendment to REC number 5)	5	15 January 2010	6	07 April 2011	Removal of 12 month follow-up. Update to analysis plan and CRISP study centres	05 May 2011

Appendix 4 CRISP case report forms and database validation

Example of database validation

Records with Validation Issues

Exc	Patient	Form	Field	Message	Excl Reason
✖	BHI9999	D1	Date of first HDU admission	HDU admission date and time must be after operation end	

First 1 Last

CRISP case report forms

CRISP
ASSESSMENT OF PATIENT ELIGIBILITY
A1

Patient Name _____ ONLY ENTER NAME IF CONSENTED _____ Crisp Patient ID: ☐☐☐☐☐☐☐

1 PATIENT URGENCY tick one

Elective (patient waiting at home) ☐ Inpatient/urgent (patient waiting in hospital) ☐

2 PATIENT INFORMATION SHEET

Has the patient received the patient information sheet? Yes ☐ No ☐ *If **YES** please record how given, date given, and type/version*

Faxed to ward ☐ Posted to home address ☐ Given in person ☐ Date sent ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)

Version v. ☐ Type WS (within-surgeon) ☐ EB (expertise based) ☐

3 EUROSCORE Please calculate the Euroscore for the patient according to the instructions (Form A1)

1. Age (please circle age group)

*Age	≤59	60-64	65-69	70-74	75-79	80-84	85-89	90-94	≥95
Score	0	1	2	3	4	5	6	7	8

Add score here →

2. Sex
Male ☐ Add 0 Female ☐ Add 1 →

3. Chronic pulmonary disease
Yes ☐ Add 1 No ☐ Add 0 →

4. Extracardiac arteriopathy
Yes ☐ Add 2 No ☐ Add 0 →

5. Neurological dysfunction
Yes ☐ Add 2 No ☐ Add 0 →

6. Previous cardiac surgery (pericardium open)
Yes ☐ Add 3 No ☐ Add 0 →

7. Serum creatinine >200µmol/L pre-op
Yes ☐ Add 2 No ☐ Add 0 →

8. Active endocarditis (still on antibiotics)
Yes ☐ Add 3 No ☐ Add 0 →

9. Critical preoperative state
Yes ☐ Add 3 No ☐ Add 0 →

10. Unstable angina
Yes ☐ Add 2 No ☐ Add 0 →

11. LV function
Good >50% ☐ Add 0 Mod/LVEF 30-50% ☐ Add 1
Poor/LVEF <30% ☐ Add 3 →

12. Pulmonary hypertension (systolic PA >60 mmHg)
Yes ☐ Add 2 No ☐ Add 0 →

13. Recent Myocardial Infarct (<90days)
Yes ☐ Add 2 No ☐ Add 0 →

Total score ☐

4 ELIGIBILITY PRIOR TO CONSENT

Euroscore ≥5? Yes ☐ No ☐
Non-emergency operation? Yes ☐ No ☐
Planned median sternotomy? Yes ☐ No ☐
Planned concomitant cardiac/valve procedure? Excluding Endarterectomy & Ablation Yes ☐ No ☐
Known contraindications to on or off-pump surgery? Yes ☐ No ☐

☐ ***IF ANY OF THE SHADED BOXES ARE TICKED THIS PATIENT IS NOT ELIGIBLE*** → ***Inform patient of ineligibility. Send form to DMC & update screening log***

6 CONSENT

Has the patient been approached? Yes ☐ No ☐
If **No**, reason _____
Has the patient given written consent? Yes ☐ No ☐
If **No**, reason _____

If **consented**, date copy given to patient ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)
Consent form in patient notes? Yes ☐ No ☐

If no consent given - stop here and send form (A1) to DMC & update screening log

Name of person completing form* (capitals): _____
Signature of person completing form: _____ Date (dd/mm/yyyy) ☐☐ ☐☐ ☐☐☐☐

Name of person entering data*: _____ Date data entered: ___ / ___ / _____ CRISP CRF v5.0 OCT 2010

* Names must appear on the site delegation signature log

CRISP

CRISP – INSTRUCTION FORM 1

Euroscore for **Euro**pean **S**ystem for **C**ardiac **O**perative **R**isk **E**valuation

To calculate the EUROSCORE assign the participant a score for each of the questions listed. Note that 'male' or 'No' = 0. Record individual question scores and the total in the boxes provided on the patient assessment for trial eligibility case report form (A).

Patient-related factors		Definition	Score
1.	**Age***	Per 5 years or part thereof ≥60 years	**1**
2.	**Sex**	Female	**1**
3.	**Chronic pulmonary disease**	Long-term use of bronchodilators or steroids for lung disease	**Yes=1**
4.	**Extracardiac arteriopathy**	Any one or more of the following: claudication, carotid occlusion or >50% stenosis, previous or planned intervention on the abdominal aorta, limb arteries or carotids	**Yes=2**
5.	**Neurological dysfunction**	Disease severely affecting ambulation or day-to-day functioning	**Yes=2**
6.	**Previous cardiac surgery**	Requiring opening of pericardium	**Yes=3**
7.	**Serum creatinine**	>200 µmol/L pre-operatively	**Yes=2**
8.	**Active endocarditis**	Patient still under antibiotic treatment for endocarditis at the time of surgery	**Yes=3**
9.	**Critical preoperative state**	Any one or more of the following: ventricular tachycardia or fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before arrival in the anaesthetic room, preoperative inotropic support, intraaortic balloon counter pulsation or preoperative acute renal failure (anuria or oliguria <10 mL/hour)	**Yes=3**
Patient-related factors		**Definition**	**Score**
10.	**Unstable angina**	Rest angina requiring i.v. Nitrates until arrival in the anaesthetic room	**Yes=2**
11.	**LV dysfunction**	Moderate or LVEF 30-50%	**Yes=1**
	LV dysfunction	Poor or LVEF <30	**Yes=3**
12.	**Recent myocardial infarct**	<90 days	**Yes=2**
13.	**Pulmonary hypertension**	Systolic PA pressure >60 mmHg	**Yes=2**
EuroSCORE			**Total**

*Age	≤59	60-64	65-69	70-74	75-79	80-84	85-89	90-94	≥95
Score	0	1	2	3	4	5	6	7	8

CRISP CRF v5.0 OCT 2010

CRISP
ASSESSMENT OF PATIENT ELIGIBILITY

A2

Patient Name _____ **Crisp Patient ID:** ☐☐☐☐☐☐☐

7 PATIENT DETAILS *Alternatively place patient addressograph here*

First Name _____

Surname _____

Address _____

_____

_____

Postcode ☐☐☐☐ ☐☐☐

Patient telephone number _____

Hospital number _____

NHS number ☐☐☐ ☐☐☐ ☐☐☐☐

8 GP DETAILS

Family physician/GP _____

Address _____

_____

_____

Postcode ☐☐☐☐ ☐☐☐

Date GP letter sent ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)

9 CONTACT

Can answer machine messages be left? *Yes* ☐ *No* ☐

Email address (optional) _____

Would the patient like to receive a summary of results at the end of the trial? *Yes* ☐ *No* ☐

10 RANDOMISATION Please log-in to randomisation website: **www.sealedenvelope.com/crisp/**

Date of birth ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)

Gender *Male* ☐ *Female* ☐

Urgency of operation *Elective* ☐ *Urgent* ☐

LV function (Poor LVEF<30%) *Yes* ☐ *No* ☐

Serum creatinine >200µmol/L pre-op *Yes* ☐ *No* ☐

Previous sternotomy *Yes* ☐ *No* ☐

Pulmonary hypertension *Yes* ☐ *No* ☐

Previous stroke *Yes* ☐ *No* ☐

Randomisation *Within surgeon* ☐ *Expertise based* ☐

Date randomised ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)

Allocated treatment ***On-Pump*** ☐ ***Off-Pump*** ☐

Randomisation number ☐☐☐☐☐

Pre op questionnaires completed *Yes* ☐ *No* ☐

Name of person completing form* (capitals): _____

Signature of person completing form: _____ Date (dd/mm/yyyy) ☐☐ ☐☐ ☐☐☐☐

Name of person entering data*: _____ Date data entered: ___ / ___ / _____ CRISP CRF v5.0 OCT 2010

* Names must appear on the site delegation signature log

CRISP PREOPERATIVE DETAILS

B1

Patient Name _____ **Crisp Patient ID:** ☐☐☐☐☐☐☐

1 PRE-OPERATIVE ASSESSMENT

Date of admission ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)

Anthropometrics

Height ☐☐☐ cm Weight ☐☐☐.☐ kg

Blood pressure (*Left arm*) ☐☐☐ Systolic ☐☐☐ Diastolic

Heart rate ☐☐☐ bpm

Blood

Haemoglobin ☐☐.☐ g/dl

Creatinine ☐☐☐☐ µmol/L

Cardiovascular disease

>50% disease in left main stem Yes ☐ No ☐

Coronary disease number of vessels Single ☐ Double ☐ Triple ☐

NYHA class (tick one only)

I ☐ No symptoms and no limitations in ordinary physical activity

II ☐ Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.

III ☐ Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.

IV ☐ Severe limitations. Experiences symptoms even while at rest.

Angina class (CCS) (tick one only) ☐ Asymptomatic

I ☐ Angina with strenuous/prolonged exertion. Ordinary activity such as walking does not cause angina

II ☐ Slight limitation of activity. Events such as rapid walking or climbing stairs, emotional stress cause angina

III ☐ Marked limitation of activity. Walking or climbing stairs in normal conditions at normal pace cause angina.

IV ☐ Inability to carry out any physical activity without discomfort, angina symptoms may be present at rest.

2 MEDICAL HISTORY

Smoker Yes ☐ Ex > 1 month ☐ No ☐

Hypertension requiring treatment Yes ☐ No ☐

Diabetes Diet ☐ Oral ☐ Insulin ☐ No ☐

Previous myocardial infarction (MI) Yes ☐ No ☐

If Yes, give date of last MI ☐☐ ☐☐☐☐

Previous cardiac surgery Yes ☐ No ☐

Previous percutaneous coronary intervention (PCI) Yes ☐ No ☐

Previous stroke or Transient Ischemic attack Yes ☐ No ☐

Doppler carotid stenosis ≥70% Not known ☐ Yes ☐ No ☐

Haemofiltration/dialysis Yes ☐ No ☐

Peripheral vascular disease Yes ☐ No ☐

Congestive cardiac failure Yes ☐ No ☐

Heart rhythm Sinus ☐ Atrial fib/flutter ☐ Heart block ☐

Pacemaker Permanent ☐ Temporary ☐ No ☐

Other cardiac history? Yes ☐ No ☐

If yes, please specify: _____

_____

_____

_____

3 REGULAR MEDICATIONS

ACE-Inhibitors or ARB II Yes ☐ No ☐

Beta blockers Yes ☐ No ☐

Calcium antagonists Yes ☐ No ☐

Statins Yes ☐ No ☐

Aspirin and/or Clopidogrel Yes ☐ No ☐

If Aspirin or Clopidogrel is regular medication but has been stopped prior to admission, how many days before surgery was it stopped ☐☐

Name of person completing form* (capitals): _____

Signature of person completing form: _____ Date (dd/mm/yyyy) ☐☐ ☐☐ ☐☐☐☐

Name of person entering data*: _____ Date data entered: ___ / ___ / _____ CRISP CRF v5.0 OCT 2010

* Names must appear on the site delegation signature log

CRISP
OPERATION DETAILS

C1

Patient Name _____ **Crisp Patient ID:** ☐☐☐☐☐☐☐

1 DETAILS

Operating surgeon (initials) ☐☐☐

Date of surgery ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)

Emergency operation *Yes* ☐ *No* ☐

Patient allocated to *On-Pump CABG* ☐ *Off-Pump CABG* ☐

Start of operation (24 hr clock) (knife to skin) ☐☐:☐☐

End of operation (24 hr clock) (time patient leaves theatre) ☐☐:☐☐

Any additional unplanned procedures carried out *Yes* ☐ *No* ☐

If yes, specify: _____

2a Complete if allocated to ON-PUMP

Was participant put on-pump with cardioplegic arrest? *Yes* ☐ *No* ☐

*If **yes** please complete section 3 myocardial protection*

*If **no**, please give reason for conversion below & continue to section 4:*

(PLEASE PRINT) _____

2b Complete if allocated to OFF-PUMP

Was operation carried out off-pump? *Yes* ☐ *No* ☐

*If **yes**, please continue to section 4*

*If **no** please complete section 3 myocardial protection **and** give reason for conversion below:*

(PLEASE PRINT) _____

3 MYOCARDIAL PROTECTION (only to be completed if allocated to on-pump, or converted to on-pump)

Temperature ☐ *Warm* ☐ *Cold (inc hot shot)*

Solution ☐ *Blood* ☐ *Crystalloid*

Infusion mode ☐ *Antegrade* ☐ *Retrograde* ☐ *Combined*

Timing ☐ *Continuous* ☐ *Intermittent*

Cumulative cross-clamp time ☐☐☐ min

Total bypass time ☐☐☐ min

4 OPERATIVE DETAILS (to be completed for all patients)

Was a partial aortic clamp used *Yes* ☐ *No* ☐

If Yes, number times clamp applied ☐☐

Significant calcification of ascending aorta (>50% area) *Yes* ☐ *No* ☐

If Yes: *Defined clinically* ☐ *Defined on investigation* ☐

Any arrhythmias on chest closure *Sinus* ☐ *Atrial fib/ flutter* ☐ *Heart block* ☐

Defibrillation *Yes* ☐ *No* ☐

Tranexamic acid *Yes* ☐ *No* ☐

If Yes, dose ☐☐.☐ *g*

Cell saver set up *Yes* ☐ *No* ☐

If yes, volume infused ☐☐☐☐ *ml*
(0ml if no blood returned to patient)

Was an IABP used *Yes* ☐ *No* ☐

Was a LVAD used *Yes* ☐ *No* ☐

Intraoperative inotropes (excluding noradrenaline) *Yes* ☐ *No* ☐

Intraoperative noradrenaline *Yes* ☐ *No* ☐

Intraoperative vasodilators *Yes* ☐ *No* ☐

Intraoperative pacing *Yes* ☐ *No* ☐

Total blood products used intra-operatively

RBC *enter 0 if none* ☐☐☐ units

Plasma (FFP or Cryo) *Yes* ☐ *No* ☐

Platelets *Yes* ☐ *No* ☐

Activated factor VII *Yes* ☐ *No* ☐

Status at end of operation *Dead** ☐ *Alive* ☐ ***complete SAE form***

Name of person completing form* (capitals): _____

Signature of person completing form: _____ Date (dd/mm/yyyy) ☐☐ ☐☐ ☐☐☐☐

Name of person entering data*: _____ Date data entered: ___ / ___ / _____ CRISP CRF v5.0 OCT 2010

* Names must appear on the site delegation signature log

CRISP OPERATION DETAILS

C2

Patient Name _____ **Crisp Patient ID:** ☐☐☐☐☐☐☐

5 DETAILS OF GRAFTS/TARGETS COMPLETED

Total Number of Grafts ☐

To determine the code, identify the location and corresponding code using the appropriate column in the table below. Record in the boxes provided

	Proximal	Conduit	Distal	Coronary Endarterectomy
	Please enter appropriate code in each box for each graft			*Please tick Yes or No for each graft*
Graft I	☐	☐	☐	*Yes* ☐ *No* ☐
Graft II	☐	☐	☐	*Yes* ☐ *No* ☐
Graft III	☐	☐	☐	*Yes* ☐ *No* ☐
Graft IV	☐	☐	☐	*Yes* ☐ *No* ☐
Graft V	☐	☐	☐	*Yes* ☐ *No* ☐

Proximal	Code	**Conduit**	Code	**Distal**	Code
Aorta	1	Saphenous vein	1	Left anterior descending artery (LAD)	1
Left internal mammary artery (LIMA) – in situ	2	Radial artery	2	Diagonal 1 (D1)/Ramus intermedius	2
Right internal mammary artery (RIMA) – in situ	3	LIMA	3	Diagonal 2 (D2)	3
Gastroepiploic (in situ)	4	RIMA	4	Obtuse marginal 1 (OM1)	4
Saphenous vein (Piggyback/skip)	5	Cryopreserved	5	Obtuse marginal 2 (OM2)	5
Radial artery (RA) (Piggyback/skip)	6	Gastroepiploic	6	Postero-lateral (PL) circumflex	6
LIMA (Piggyback/skip)	7			Main right coronary artery (RCA)	7
RIMA (Piggyback/skip)	8			Posterior descending artery (PDA)/Posterior inter ventricular (PIV)	8
Arch/great vessels	9			Postero-Ventricle (PV-RCA)	9

Name of person completing form* (capitals): _____

Signature of person completing form:_____ Date (dd/mm/yyyy) ☐☐ ☐☐ ☐☐☐☐

Name of person entering data*: _____ Date data entered: ___ / ___ / _____ CRISP CRF v5.0 OCT 2010

* Names must appear on the site delegation signature log

CRISP
POST OPERATIVE & DISCHARGE DETAILS

D1

Patient Name _____ **Crisp Patient ID:** ☐☐☐☐☐☐☐

1 BLOODS & ECG

Day 2 Creatinine ☐☐☐☐ µmol/L

Day 5 ECG performed (can be taken between days 4-6) Yes ☐ No ☐

If Yes: Date ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)

New Q waves ≥ 0.04cm **or** a reduction in R waves of >25% in at least two leads Yes ☐ No ☐

If yes, file copy of ECG and a pre-op ECG in CRF folder

Day 5 Cardiac Markers (can be taken between days 4-6)

Blood sample taken (Troponin I or T preferred, or CK-MB) Yes ☐ No ☐

If Yes: Date ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)

Troponin → I or T ☐ → ☐☐☐.☐☐ I =µg/L T=ng/L
Enter letter

OR

CK-MB → ☐☐☐.☐☐ ng/ml

2 BLOOD PRODUCTS RECEIVED POSTOPERATIVELY

Did the patient receive blood products? Yes ☐ No ☐

If yes;

RBC *enter 0 if none* ☐☐☐ units

Plasma (FFP or Cryo) Yes ☐ No ☐

Platelets Yes ☐ No ☐

Chest tube blood loss 12 hours post surgery ☐☐☐☐ ml

Did the patient receive hemostatic agents? Yes ☐ No ☐

If yes;

Tranexamic acid Yes ☐ No ☐

Activated factor VII Yes ☐ No ☐

Other *(specify)* _____ Yes ☐ No ☐

3 EXTUBATION

Date Extubated ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)

Time Extubated (24 hr clock) ☐☐:☐☐

Did patient need Re-Intubation? Yes ☐ No ☐

If Yes, how many times Re-Intubated ☐☐

Date Re-Intubated ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)

Time Re-Intubated (24 hr clock) ☐☐:☐☐

Date Re-Extubated ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)

Time Re-Extubated (24 hr clock) ☐☐:☐☐

If patient was Re-Intubated on more than two occasions, complete CRF Z1 Extra Re-Intubations, entering dates & times

4 WARD MOVEMENTS

Enter time & date the patient is FIRST admitted to each of the wards listed, & date of readmission to the wards if this occurred. Tick NA if none. If patient readmitted more than once, complete CRF Z1 Extra Ward Movements, entering dates & times

	First Admission:			Readmission:		
	24 hours	d d m m y y y y	N/A	d d m m y y y y	N/A
CICU / 1:1* Cardiac Intensive Care Unit	☐☐:☐☐	☐☐ ☐☐ ☐☐☐☐	☐	☐☐ ☐☐ ☐☐☐☐	☐
HDU / 2:1* High Dependency Unit	☐☐:☐☐	☐☐ ☐☐ ☐☐☐☐	☐	☐☐ ☐☐ ☐☐☐☐	☐
Ward / >2:1*	☐☐:☐☐	☐☐ ☐☐ ☐☐☐☐	☐	☐☐ ☐☐ ☐☐☐☐	☐

* Patient : Nurse ratio

Name of person completing form* (capitals): _____

Signature of person completing form: _____ Date (dd/mm/yyyy) ☐☐ ☐☐ ☐☐☐☐

Name of person entering data*: _____ Date data entered: ___ / ___ / _____ CRISP CRF v5.0 OCT 2010

* Names must appear on the site delegation signature log

CRISP
POST OPERATIVE & DISCHARGE

D2

Patient Name _____ **Crisp Patient ID:** ☐☐☐☐☐☐☐

5a DISCHARGE DETAILS FROM CARDIAC WARD

Date of discharge or death ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)

Status at discharge from cardiac surgery ward

Alive ☐ *Continue to 5b*

Dead ☐ *Continue to 6*

5b MEDICATIONS AT DISCHARGE

ACE inhibitors or ARB II	Yes ☐	No ☐
Beta blockers	Yes ☐	No ☐
Calcium antagonists	Yes ☐	No ☐
Statins	Yes ☐	No ☐
Aspirin and/or Clopidogrel	Yes ☐	No ☐

6 PRIMARY POSTOPERATIVE EVENTS at discharge (or up to 30 days postoperatively if discharge delayed)

Death Yes ☐ No ☐ If yes; *Please complete SAE form*

Renal failure requiring dialysis or haemofiltration Yes ☐ No ☐ If yes;

- Date therapy started ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)
- Patient received renal replacement therapy in month prior to surgery Yes ☐ No ☐
- Highest recorded post-operative creatinine, prior to start of dialysis ☐☐☐☐ µmol/L

Myocardial Infarction Yes ☐ No ☐ If yes;

- Date of MI ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)

Defined by:

- ECG → New Q waves ≥ 0.04cm **or** a reduction in R waves of >25% in at least two leads Yes ☐ No ☐ *If yes, file copy of ECG showing changes, along with ECG from before suspected MI*
- Cardiac Enzymes → Troponin → I or T ☐ (Enter letter) ☐☐☐.☐☐ I =µg/L T=ng/L
  OR
  CK-MB ☐☐☐.☐☐ ng/ml

ECG and blood test must both be performed if a MI is suspected

Stroke Yes ☐ No ☐ If yes;

- Date of diagnosis ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)
- Signs or symptoms lasting >24 hours Yes ☐ No ☐
- Symptoms confirmed by neurologist Yes ☐ No ☐
- Confirmed by imaging Yes * ☐ No ☐

* *If yes fax imaging results to DMC*

Prolonged Ventilation >96 hours Yes ☐ No ☐ If yes please give reason;

- Pre-existing poor lung function (<30% normal) Yes ☐ No ☐
- Hospital acquired pneumonia Yes ☐ No ☐

Sternal wound dehiscence Yes ☐ No ☐ If yes;

- Date of diagnosis ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)
- Further intervention required Yes ☐ No ☐

If yes;

- Vac dressing Yes ☐ No ☐
- Formal surgical reconstruction Yes ☐ No ☐

Name of person completing form* (capitals): _____

Signature of person completing form:_____ Date (dd/mm/yyyy) ☐☐ ☐☐ ☐☐☐☐

Name of person entering data*: _____ Date data entered: ___ / ___ / _____ CRISP CRF v5.0 OCT 2010

* Names must appear on the site delegation signature log

CRISP
POST OPERATIVE & DISCHARGE

D3

Patient Name _____ **Crisp Patient ID:** | | | | | | | |

7 POSTOPERATIVE EVENTS at discharge (or up to 30 days postoperatively if discharge delayed)

The following events are 'expected' and therefore do not require an additional SAE form to be completed. However, please tick the 'SAE' box if the event fits any of the following criteria:

i) Increased length of hospital admission,
ii) life threatening,
iii) persistent or significant disability,
iv) caused death

Event	Present		Date of onset (d d m m y y y y)	SAE	
Coronary angiography	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
PCI	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
Redo CABG	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
Re-operated (e.g. for bleeding or tamponade)	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
Use of IABP	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
Use of LVAD	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
Respiratory infection	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
Tracheotomy	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
ARDS	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
Atrial fibrillation requiring drug therapy	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
Superficial wound infection chest	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
Superficial wound infection leg	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
Superficial wound infection arm	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
Deep vein thrombosis	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
Pulmonary embolism	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
Heparin induced thrombocytopenia (HIT) (confirmed by immunoassay)	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
GI complication	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
TIA	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐

Other events (list all other medical events/complications that have occurred since surgery)

i) _____			☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
ii) _____			☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
iii) _____			☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐

If yes to 'other' event being classed as SAE, complete SAE form

Name of person completing form* (capitals): _____

Signature of person completing form: _____ Date (dd/mm/yyyy) ☐☐ ☐☐ ☐☐☐☐

Name of person entering data*: _____ Date data entered: ___ / ___ / _____ CRISP CRF v5.0 OCT 2010

* Names must appear on the site delegation signature log

CRISP
4-8 WEEKS POST OPERATIVE ASSESSMENT

E1

Patient Name _____ **Crisp Patient ID:** ☐☐☐☐☐☐☐

1 FOLLOW-UP APPOINTMENT DETAILS

Date of visit ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)

Status at visit
- Patient attended ☐
- Patient alive but DNA'd ☐
- Dead ☐ *Continue to 3*
- Unknown ☐

2 CURRENT MEDICATIONS

ACE inhibitors or ARB II	Yes ☐	No ☐
Beta blockers	Yes ☐	No ☐
Calcium antagonists	Yes ☐	No ☐
Statins	Yes ☐	No ☐
Aspirin and/or Clopidogrel	Yes ☐	No ☐

3 POST DISCHARGE EVENTS (or events since form D2 completed, if discharge was delayed)

Death Yes ☐ No ☐ If yes; Date of death ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)

Renal failure requiring dialysis or haemofiltration since discharge Yes ☐ No ☐ If yes; Date therapy started ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)

Highest recorded creatinine prior to start of dialysis ☐☐☐☐ µmol/L

Myocardial Infarction Yes ☐ No ☐ If yes; Date of MI ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)

Defined by:

ECG and blood test must both be performed if a MI is suspected

ECG → New Q waves ≥ 0.04cm **or** a reduction in R waves of >25% in at least two leads Yes ☐ No ☐

If yes, file copy of ECG showing changes, along with ECG from before suspected MI

Cardiac Enzymes → Troponin → I or T ☐ (*Enter letter*) → ☐☐☐.☐☐ I =µg/L T=ng/L

OR

CK-MB → ☐☐☐.☐☐ ng/ml

Stroke Yes ☐ No ☐ If yes; Date of diagnosis ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)

Signs or symptoms lasting >24 hours Yes ☐ No ☐

Symptoms confirmed by neurologist Yes ☐ No ☐

Confirmed by imaging Yes ☐ No ☐

If yes fax imaging results to DMC

Sternal wound dehiscence Yes ☐ No ☐ If yes; Date of diagnosis ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)

Further intervention required Yes ☐ No ☐

If yes; Vac dressing Yes ☐ No ☐

Formal surgical reconstruction Yes ☐ No ☐

If Yes ☑ to any of the above 5 events, please complete SAE form

Name of person completing form* (capitals): _____

Signature of person completing form:_____ Date (dd/mm/yyyy) ☐☐ ☐☐ ☐☐☐☐

Name of person entering data*: _____ Date data entered: ___ / ___ / _____ CRISP CRF v5.0 OCT 2010

* Names must appear on the site delegation signature log

CRISP
4-8 WEEKS POST OPERATIVE ASSESSMENT

E2

Patient Name _____ **Crisp Patient ID:** | | | | | | | |

4 POST DISCHARGE EVENTS (or events since form D3 completed, if discharge was delayed)

Please assess presence of each event listed below
An event is classified as an SAE if it fits any of the following criteria:
i) caused/Increased length of hospital admission, iii) persistent or significant disability,
ii) life threatening, iv) caused death

Event	Present		Date of onset (d d m m y y y y)	SAE	
Coronary angiography	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
PCI	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
Redo CABG	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
Re-operated (e.g. for bleeding or tamponade)	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
Use of IABP	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
Use of LVAD	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
Respiratory infection	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
Tracheotomy	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
ARDs	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
Atrial fibrillation requiring drug therapy	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
Superficial wound infection chest	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
Superficial wound infection leg	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
Superficial wound infection arm	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
Deep vein thrombosis	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
Pulmonary embolism	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
Heparin induced thrombocytopenia (HIT) (confirmed by immunoassay)	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
GI complication	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
TIA	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	No ☐
Hospital Admission	Yes ☐	No ☐	☐☐ ☐☐ ☐☐☐☐	Yes ☐	

If Yes ☑ to any of the above events being classified as SAE, please complete SAE form

Name of person completing form* (capitals): _____

Signature of person completing form:_____ Date (dd/mm/yyyy) ☐☐ ☐☐ ☐☐☐☐

Name of person entering data*: _____ Date data entered: ___ / ___ / _____ CRISP CRF v5.0 OCT 2010

* Names must appear on the site delegation signature log

CRISP
4-8 WEEKS POST OPERATIVE ASSESSMENT

E3

Patient Name _____ **Crisp Patient ID:** ☐☐☐☐☐☐☐

5 OTHER POST DISCHARGE EVENTS (or events since form D3 completed, if discharge was delayed)

Have any 'other' medical events or complications occurred since patient was discharged (or since D3 completed) Yes ☐ No ☐

If yes please continue below, if no please continue to 6

Please list below ALL 'other' medical events or complications that have occurred since discharge form
An event is classified as an SAE if it fits any of the following criteria:

i) caused/Increased length of hospital admission,
ii) life threatening,
iii) persistent or significant disability,
iv) caused death

Event (please print in capitals)	**Date of onset** d d m m y y y y	**SAE**
i) _____	☐☐ ☐☐ ☐☐☐☐	Yes ☐ No ☐
ii) _____	☐☐ ☐☐ ☐☐☐☐	Yes ☐ No ☐
iii) _____	☐☐ ☐☐ ☐☐☐☐	Yes ☐ No ☐
iv) _____	☐☐ ☐☐ ☐☐☐☐	Yes ☐ No ☐
v) _____	☐☐ ☐☐ ☐☐☐☐	Yes ☐ No ☐
vi) _____	☐☐ ☐☐ ☐☐☐☐	Yes ☐ No ☐

If Yes ☑ to any of the above events being classified as SAE, please complete SAE form

6 FUTURE FOLLOW-UP DETAILS

Patients will be sent follow-up questionnaires at one year post surgery, please remind patients of this, and stress importance of completing and returning them

Patient reminded of questionnaires at one year post surgery Yes ☐ No ☐

Patient address same as on form A1 Yes ☐ No ☐

If no, please complete new address: _____

_____ Postcode ☐☐☐☐ ☐☐☐

Patient telephone number same as on form A2 Yes ☐ No ☐

If no, please complete new telephone number: _____

Name of person completing form* (capitals): _____

Signature of person completing form:_____ Date (dd/mm/yyyy) ☐☐ ☐☐ ☐☐☐☐

Name of person entering data*: _____ Date data entered: ___ / ___ / _____ CRISP CRF v5.0 OCT 2010

* Names must appear on the site delegation signature log

CRISP
SERIOUS ADVERSE EVENTS

X1

Patient Name _____ **Crisp Patient ID:** ☐☐☐☐☐☐☐

1 SERIOUS ADVERSE EVENTS

Please use one form per event. Fax to Bristol DMC within 24 hours of notification of the event

Brief description of event _____

Time point *please select one* **Prior to surgery** ☐ **Prior to discharge for CABG surgery** ☐ **Post discharge for CABG surgery** ☐

Maximum intensity (up until time of report): *(tick one)*

Mild - Barely noticeable, does not influence functioning; causes no limitations of usual activities. ☐

Moderate - Makes participant uncomfortable, influences functioning; causing some limitations of usual activities. ☐

Severe - Severe discomfort, treatment needed; severe and undesirable, causing inability to carry out usual activities. ☐

Reason event classed as SAE: *(tick all that apply)*

Resulted in death ☐

Is/was life threatening ☐

Resulted in persistent or significant disability/incapacity ☐

Prolonged an ongoing hospitalisation/ resulted in hospitalisation ☐

Other *(specify)* ☐

_____

_____

Is the SAE related to the method of surgery (on or off pump)? *(tick one)* ***(to be completed by PI for centre)***

Not related ☐ Unlikely to be related ☐ Possibly related ☐ Probably related ☐ Definitely related ☐

Signature of Principal Investigator _____ Date ☐☐ ☐☐ ☐☐☐☐

Onset date and time

Date(dd/mm/yyyy) ☐☐ ☐☐ ☐☐☐☐ Time (24h clock) ☐☐:☐☐

Resolution date and time

Date(dd/mm/yyyy) ☐☐ ☐☐ ☐☐☐☐ Time (24h clock) ☐☐:☐☐

Or Ongoing ☐*

Location (e.g. home, GP surgery, hospital (including ward) etc.): _____

Full description of event/reaction, including body site, reported signs and symptoms and method of diagnosis. If died, give cause and PM details where available**:**

_____

_____

Please also record any action taken:

_____

_____

Any other relevant information such as medical history or test results:

_____

_____

Please fax SAE form along with any relevant information, autopsy (PM) report, discharge report etc to Fax no: 00 44 117 342 3288, FAO CRISP Team

*** For 'On-going' SAEs, please fax follow-up reports every 5 days until resolved**

Name of person completing form* (capitals): _____

Signature of person completing form:_____ Date (dd/mm/yyyy) ☐☐ ☐☐ ☐☐☐☐

Name of person entering data*: _____ Date data entered: ___ / ___ / _____ CRISP CRF v5.0 OCT 2010

* Names must appear on the site delegation signature log

CRISP EXIT FORM

Y1

Patient Name _____ **Crisp Patient ID:** ☐☐☐☐☐☐☐

1 EXIT FROM STUDY

Date patient exited from study ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)

Was the decision to withdraw from study pre or post surgery Pre surgery ☐ Post surgery ☐

Decision to exit study

Patient withdrew consent	Yes ☐	No ☐
Clinician's decision	Yes ☐	No ☐

Reason for withdrawal

Surgery no longer required	Yes ☐	No ☐
Type of surgery allocated to	Yes ☐	No ☐
Patient did not give reason	Yes ☐	No ☐
Other *(please specify)*	Yes ☐	No ☐

_____

Is patient willing for study team to continue monitoring from the NHS register	Yes ☐	No ☐
Is patient willing for data already collected to be used	Yes ☐	No ☐
Is patient willing for data collection to continue	Yes ☐	No ☐
Is patient willing for completion of follow-up and questionnaires to continue	Yes ☐	No ☐

If patient is being withdrawn for any clinical reason, e.g. no longer to receive surgery, please give full explanation as to clinical reasoning:

Any further relevant information on the withdrawal:

For further instructions on the EXIT process please refer to the CRISP Manual

Name of person completing form* (capitals): _____

Signature of person completing form:_____ Date (dd/mm/yyyy) ☐☐ ☐☐ ☐☐☐☐

Name of person entering data*: _____ Date data entered: ___ / ___ / _____ CRISP CRF v5.0 OCT 2010

* Names must appear on the site delegation signature log

CRISP
Extra Forms – OPERATIVE DETAILS

Z1

Patient Name _____ **Crisp Patient ID:** | | | | | | | |

1 EXTRA RE-INTUBATIONS

Please use this section of the form to document additional re-intubations. The completed form should be stored next to, and entered/faxed at same time as form D1.

Re-Intubation

1	Date Re-intubated (d d m m y y y y)		Time Re-intubated (24 hr clock)	:
	Date Re-extubated (d d m m y y y y)		Time Re-extubated (24 hr clock)	:
2	Date Re-intubated (d d m m y y y y)		Time Re-intubated (24 hr clock)	:
	Date Re-extubated (d d m m y y y y)		Time Re-extubated (24 hr clock)	:
3	Date Re-intubated (d d m m y y y y)		Time Re-intubated (24 hr clock)	:
	Date Re-extubated (d d m m y y y y)		Time Re-extubated (24 hr clock)	:

2 EXTRA WARD MOVEMENTS

Please use this section of the form to document additional ward movements. The completed form should be stored next to, and entered/faxed at same time as form D1.

	Further readmission 1: (d d m m y y y y)	**Further readmission 2:** (d d m m y y y y)	**Further readmission 3:** (d d m m y y y y)
CICU / 1:1* Cardiac Intensive Care Unit			
HDU / 2:1* High Dependency Unit			
Ward / >2:1*			
Other *specify* _____			

* Patient : Nurse ratio

Name of person completing form* (capitals): _____

Signature of person completing form:_____ Date (dd/mm/yyyy) | | | | | | | | |

Name of person entering data*: _____ Date data entered: ___ / ___ / _____ CRISP CRF v5.0 OCT 2010

* Names must appear on the site delegation signature log

CRISP
Extra Forms – EVENTS/COMPLICATIONS

Z2

Patient Name _____ **Crisp Patient ID:** ☐☐☐☐☐☐☐

1 POSTOPERATIVE EVENTS RECURRANCES

Please use this form to list any additional events/complications that could not be entered onto forms D3 and E3. Use one form for each time point (i.e. D3 and E3) and store next to respective CRF. Enter data at same time as corresponding form.

Time point *please select one* **Discharge** (or at 30 days if discharge delayed), i.e. form **D3** ☐ **4-8 week postoperative** i.e. form **E3** ☐

Myocardial Infarction Yes ☐ No ☐ If yes; Date of MI ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)

Defined by: ECG → New Q waves ≥ 0.04cm **or** a reduction in R waves of >25% in at least two leads Yes ☐ No ☐

ECG and blood test must both be performed if a MI is suspected

If yes, file copy of ECG showing changes, along with ECG from before suspected MI

Cardiac Enzymes → Troponin → I or T ☐ *Enter letter* → ☐☐☐.☐☐ I =µg/L T=ng/L

OR

CK-MB → ☐☐☐.☐☐ ng/ml

Stroke Yes ☐ No ☐ If yes; Date of diagnosis ☐☐ ☐☐ ☐☐☐☐ (d d m m y y y y)

Signs or symptoms lasting >24 hours Yes ☐ No ☐

Symptoms confirmed by neurologist Yes ☐ No ☐

Confirmed by imaging Yes ☐ No ☐

If yes fax imaging results to DMC

An event is classified as an SAE if it fits any of the following criteria:
i) caused/Increased length of hospital admission,
ii) life threatening,
iii) persistent or significant disability,
iv) caused death

Event (please print in capitals)	**Date of onset** (d d m m y y y y)	**SAE**
i) _____	☐☐ ☐☐ ☐☐☐☐	Yes ☐ No ☐
ii) _____	☐☐ ☐☐ ☐☐☐☐	Yes ☐ No ☐
iii) _____	☐☐ ☐☐ ☐☐☐☐	Yes ☐ No ☐
iv) _____	☐☐ ☐☐ ☐☐☐☐	Yes ☐ No ☐
v) _____	☐☐ ☐☐ ☐☐☐☐	Yes ☐ No ☐
vi) _____	☐☐ ☐☐ ☐☐☐☐	Yes ☐ No ☐
vii) _____	☐☐ ☐☐ ☐☐☐☐	Yes ☐ No ☐
viii) _____	☐☐ ☐☐ ☐☐☐☐	Yes ☐ No ☐

If Yes ☑ to any of the above events being classified as SAE, please complete SAE form

Name of person completing form* (capitals): _____

Signature of person completing form:_____ Date (dd/mm/yyyy) ☐☐ ☐☐ ☐☐☐☐

Name of person entering data*: _____ Date data entered: ___ / ___ / _____ CRISP CRF v5.0 OCT 2010

* Names must appear on the site delegation signature log

CRISP
Extra Forms – CHANGE OF PATIENT/GP DETAILS

Z3

Patient Name _____ **Crisp Patient ID:** | | | | | | | |

1 PATIENT DETAILS

Please complete any sections where details have changed

Date new details active from | | | | | | | | | | |
d d m m y y y y

New Address _____ Tel Number _____

_____ Email address _____

_____

Postcode | | | | | | | |

2 GP DETAILS

Date new details active from | | | | | | | | | | |
d d m m y y y y

Family physician/GP _____ Tel Number _____

Address _____

_____

_____

Postcode | | | | | | | |

If using Data Entry: Please enter any changes directly onto the database. Changes can be entered over previous details on forms A1 and A2

If Faxing: Please fax form to DMC

Name of person completing form* (capitals): _____

Signature of person completing form:_____ Date (dd/mm/yyyy) | | | | | | | | |

Name of person entering data*: _____ Date data entered: ___ / ___ / _____ CRISP CRF v5.0 OCT 2010

* Names must appear on the site delegation signature log

Appendix 5 CRISP statistical analysis plan

Coronary artery grafting in High RISk patients randomised to Off Pump or On Pump Surgery

The 

Trial

STATISTICAL ANALYSIS PLAN

List of abbreviations

Acronym	Details
SAP	Statistical analysis plan
RCT	Randomised controlled trial
CABG	Coronary artery bypass
OPCABG	Off-pump CABG
ONCABG	On-pump CABG
RRT	Renal replacement therapy
MI	Myocardial infarction
ECG	Electrocardiogram
CICU	Cardiac intensive care unit
QoL	Quality of life
CCS	Canadian cardiovascular society
CROQ	Coronary revascularisation outcome questionnaire
LV	Left ventricular
ITT	Intention to treat
CRF	Case report form
SD	Standard deviation
IQR	Inter quartile range
OR	Odds ratio
CI	Confidence interval
HR	Hazard ratio
MAR	Missing at random
SAE	Serious adverse event
MD	Mean difference
HDU	High dependency unit

1. INTRODUCTION TO STATISTICAL ANALYSIS PLAN

1.1 Scope

The CRISP trial was prematurely terminated after recruitment of 106 patients. This document details information regarding the statistical analysis of the completed CRISP trial and covers all of the analyses of trial data outlined in the study protocol, with the exception of the health economic analyses. There will also be additional data presented in final reports regarding site-specific recruitment challenges that are not covered in this document.

1.2 Editorial changes

Any changes made to this statistical analysis plan (SAP) after approval must be clearly justified and documented as an amendment at the end of this document.

1.3 SAP document approval

The trial statistician should authorise this document.

2. STUDY OBJECTIVES

CRISP is an international multi-centre open randomised controlled trial (RCT).

Two methods of performing isolated coronary artery bypass (CABG) surgery in high risk patients with an additive EuroSCORE ≥5 are compared: off-pump CABG (OPCABG) on the beating heart and on-pump CABG (ONCABG) on a chemically arrested heart.

The objectives are to compare mortality and morbidity. It is hypothesised that OPCABG reduces mortality and morbidity in high-risk patients without a higher risk of re-intervention.

2.1 Primary outcome

The primary outcome is a composite endpoint of death or serious morbidity **(CRISPSw)** within 30 days of surgery (i.e. ≤30-days). The components are defined as follows:

Death after **C**ardiac surgery from any cause.

New onset **R**enal failure, defined by:

1) A postoperative creatinine value of >200µmol/L, AND
2) A percentage increase from preoperative creatinine of ≥40%, AND

3) The need for renal replacement therapy (RRT), e.g. dialysis/haemofiltration[1]

Creatinine will be measured in all patients preoperatively and at day 2 postoperatively. Creatinine will also be recorded if new onset renal failure is indicated.

Myocardial **I**nfarction (MI), defined by:

1) Elevated Troponin I or T
2) CK-MB ≥ 10 ULN (non-Q MI)
3) Electrocardiogram (ECG) changes consistent with infarction (new significant Q waves ≥0.04cm or a reduction in R waves of >25%, in at least two contiguous leads)

On day 5 all patients will have an ECG and blood samples taken for the assessment of cardiac markers (Troponin T or Troponin I where possible, only if these tests are not available should CK-MB be used).

All Troponin, ECG and CK-MB measurements will be assessed by an independent committee masked to the randomised allocation, who will decide whether an MI has occurred or not.

Stroke defined as new acute focal neurological deficit thought to be of vascular origin with signs or symptoms lasting longer than 24 hours and confirmed by a neurologist.

Prolonged ventilation ≥96 hours during the initial hospital admission for surgery. This does NOT include any periods of re-intubation following the initial extubation.

Sternal **w**ound dehiscence requiring non-pharmacological intervention (e.g. vac dressing or re-operation).

2.2 Secondary outcomes

Secondary outcomes are listed in the study protocol as:

Duration of cardiac intensive care unit (CICU) stay during index hospital admission. This does NOT include any periods where the patient is returned to CICU after initial discharge.

Duration of hospital stay during index hospital admission. This will be calculated as the time from operation to discharge.

Quality of life (QoL) assessment at 4-8 weeks using:

- Rose Angina questionnaire

[1] Dialysis/haemofiltration during cardiopulmonary bypass only will NOT constitute a requirement for RRT. Any patient who received RRT in the month prior to surgery will not be eligible for this endpoint.

- Canadian Cardiovascular Society (CCS) angina class
- EuroQol EQ-5D
- Coronary Revascularisation Outcome Questionnaire (CROQ)

Resource utilisation, determined by hospital resources during index admission.

Cost-effectiveness, determined by within-trial cost per CRISPSw event averted, extrapolated cost per life-year gained and per quality-adjusted life year gained.

The latter two outcomes are not covered by this document as they will be undertaken by the trial health economists.

In addition, patients at centres were randomised to receive either the standard EQ-5D questionnaire, or an extended version. A sub-study was planned to compare patient responses using the two versions. Due to the early termination of the trial this sub-study will be descriptive only.

3. STUDY POPULATION

The study population is all high risk patients (EuroSCORE ≥5) having non-emergency CABG surgery to be carried out via a median sternotomy incision. The original planned number of patients to be randomised and included in the analyses was 5418 patients. The trial was terminated after 106 patients had been randomised. A graph showing recruitment trends over time will be given as well as centre specific recruitment data.

3.1 Randomisation

The preferred method of randomisation is "expertise-based" randomisation, whereby patients are randomly allocated either to an experienced OPCABG surgeon or to an experienced ONCABG surgeon. If expertise-based randomisation is not feasible then within-surgeon randomisation is used.

Randomisation is stratified by centre and cohort-minimisation used to minimise imbalance of key prognostic factors (age, gender, urgency of operation, poor left ventricular (LV) function, impaired renal function, previous stroke, redo CABG, significant pulmonary disease) across the OPCABG and ONCABG groups.

The variables used in the cohort minimisation scheme will be described by treatment group as part of the analysis of demographic data (see later).

3.2 Protocol deviations

We consider five main protocol deviations:

Patient received the alternative treatment to that allocated

Patient did not meet the trial eligibility criteria but was treated in the trial (e.g. patient received additional procedures other than just CABG alone, patient had emergency surgery, EuroSCORE <5)

The surgeon was not on the trial's list of surgeons (split by randomisation type)

Expertise based randomisation was used, but the surgeon was not an expert in the allocated type of surgery

Within surgeon randomisation was used, but the operating surgeon was an expert in ONCABG surgery

It is possible for a patient to be classified as a protocol deviation for more than one reason.

The frequency of each type of protocol deviation will be described by group and full details (along with reasons) of each protocol deviation will be described. This will allow for the identification of any imbalances in protocol deviation by group and by centre.

3.3 Flow of participants

It was originally intended to follow patients up twice after hospital discharge: firstly at their routine outpatients' hospital appointment 4-8 weeks after surgery (data collection on primary outcome, adverse events and QoL); and secondly at one year postoperatively (data collection on QoL, adverse events and resource use). Due to the early termination of the trial the one-year assessment will not happen, therefore the duration of follow-up will be until the patient's 4-8 week assessment.

The study population will be described via a flowchart.

Characteristics of patients who are 1) ineligible and 2) were eligible but did not consent will be described, where possible. This will consist of comparisons of operative priority, total EuroSCORE and EuroSCORE components between these patients and randomised patients.

3.4 Withdrawals

Patients (or clinician's on their behalf) can withdraw from the trial at any time post-randomisation (including prior to their surgery). In some cases patients were happy for data collection to

continue, and therefore such patients will be included in the trial analyses on an intention to treat basis (ITT), see section 3.5. Data on all withdrawals is captured on a specific case report form (CRF), and will be provided in table form (grouped by reason and treatment allocation) and full listings.

3.5 Analysis groups

The analysis population consists of all randomised patients excluding:

- Patients who died prior to surgery
- Patients withdrawn who were unwilling for data collected to be used
- Patients withdrawn prior to surgery as it was decided not to perform surgery

The main trial analyses will be performed on an ITT basis. A secondary analysis will be performed for the primary outcome whereby patients who died prior to surgery are included in the analysis.

3.6 Safety population

The safety population consists of all patients who were randomised and received either intervention. Excluded patients are:

- Patients withdrawn who were unhappy for data collected to be used
- Patients withdrawn prior to surgery as it was decided not to perform surgery

Safety data will be analysed by the treatment received (i.e. not ITT). In addition, safety data for patients who were did not meet the trial eligibility criteria but were treated in the trial will be described.

4. DERIVATIONS

4.1 Primary outcome

Each component of the primary outcome is derived according to:

Component	Derivation: pre-discharge events (CRF D2)	Derivation: post-discharge events (CRF E1)
Death	Status at discharge=Dead AND	Status at visit=Dead AND

Component	Derivation: pre-discharge events (CRF D2)	Derivation: post-discharge events (CRF E1)
	(Date of death – operation date) ≤ 30	(Date of death – operation date) ≤ 30
Renal failure	Renal failure requiring RRT=Yes AND Highest recorded creatinine >200µmol/L AND (Highest record creatinine) / (Pre-op creatinine) ≥ 1.4 AND Patient received RRT in month prior to surgery=No AND (Date therapy started – operation date) ≤ 30	Renal failure requiring RRT=Yes AND Highest recorded creatinine >200µmol/L AND (Highest record creatinine) / (Pre-op creatinine) ≥ 1.4 AND Pre-op haemofiltration/dialysis=No AND (Date therapy started – operation date) ≤ 30
MI	Listings of all components will be provided to clinicians for independent adjudication. Components will be: New Q waves or reduction in R waves (yes/no) from day 5 ECG, along with a copy of the ECG Troponin I or T or CK-MB from day 5 blood sample New Q waves or reduction in R waves (yes/no) from ECG for suspected MI, along with a copy of the ECG Troponin I or T or CK-MB from blood sample for suspected MI The clinician's assessments of whether an MI has happened will be used to	Listings of all components will be provided to two clinicians for independent adjudication. Components will be: New Q waves or reduction in R waves (yes/no) from ECG for suspected MI, along with a copy of the ECG Troponin I or T or CK-MB from blood sample for suspected MI The clinician's assessments of whether an MI has happened will be used to decide whether an MI has occurred, with consensus between clinician's sought.

Component	Derivation: pre-discharge events (CRF D2)	Derivation: post-discharge events (CRF E1)
	decide whether an MI has occurred, with consensus between clinician's sought. Events will only be included in the primary outcome if they occurred within 30 days of operation	Events will only be included in the primary outcome if they occurred within 30 days of operation
Stroke	Stroke=Yes AND Signs or symptoms lasting > 24 hours=Yes AND (Symptoms confirmed by neurologist) or (symptoms confirmed by imaging) = Yes AND (Date of diagnosis – operation date) ≤ 30	Stroke=Yes AND Signs or symptoms lasting > 24 hours=Yes AND (Symptoms confirmed by neurologist) or (symptoms confirmed by imaging) = Yes AND (Date of diagnosis – operation date) ≤ 30
Prolonged ventilation	Prolonged ventilation > 96 hours = Yes	N/A
Sternal wound dehiscence	Sternal wound dehiscence = Yes AND Further intervention required = Yes AND (Date of diagnosis – operation date) ≤ 30	Sternal wound dehiscence = Yes AND Further intervention required = Yes AND (Date of diagnosis – operation date) ≤ 30
Overall primary outcome	If any of the above components=Yes then overall primary outcome=Yes If all of the above components=No (with no missing components) then	If any of the above components=Yes then overall primary outcome=Yes If all of the above components=No (with no missing components) then

Component	Derivation: pre-discharge events (CRF D2)	Derivation: post-discharge events (CRF E1)
	overall primary outcome=No Otherwise overall primary outcome=Missing	overall primary outcome=No Otherwise overall primary outcome=Missing

Note: all events must occur postoperatively.

For each component (with the exception of prolonged ventilation), as well as the overall primary outcome indicator, an overall indicator of the event occurring at any time in the first 30 days post-surgery (pre- or post-discharge) will be created according to the following rules:

- If event=Yes at either time point then overall event indicator=Yes
- If event=No at both time points (with no missing data) then overall event indicator=No
- Otherwise overall event indicator=Missing

4.2 Rose angina

A category of angina is assigned according to the following rules [1]:

- *No angina:* 1) Pain when walking at ordinary pace on level = No, AND 2) Pain when walking uphill or hurrying = No
- *Grade I:* 1) Pain when walking at ordinary pace on level = No, AND 2) Pain when walking uphill or hurrying= Yes or Unable
- *Grade II:* 1) Pain when walking at ordinary pace on level = Yes or Unable

4.3 EQ-5D

For patients who completed type A questionnaires only, a five digit 'state' will be derived from the mobility, self-care, usual activities, pain/discomfort and anxiety/depression scores using the following:

State = 10000*mobility score + 1000*self-care score + 100*usual activities score + 10*pain/discomfort score + anxiety/depression score

Each state will then be assigned a single summary index score according to standard scales. These index scores are numerical and range from -0.59 to 1.00, with a score of 1.00 denoting perfect health.

For all EQ-5D questionnaire types visual analogue scales were collected. Such scores range from 0 to 100 (with higher scores denoting higher QoL) and their analysis will be described in section 5.

4.4 CROQ

Data from the CROQ questionnaires will be used to derived seven QoL scores (core total, symptoms, physical functioning, cognitive functioning, psychosocial, satisfaction and adverse events) [2]. Each score uses the questionnaire items detailed below:

Score	Questions
Core total	1a-e, 2, 4, 5a-h, 6a-d, 7a-k (excluding 7d), 8a-c
Symptoms	1a-e, 2 and 4
Physical functioning	5a-h
Cognitive functioning	8a-c
Psychosocial	6a-d and 7a-k (excluding d)
Satisfaction	11a-c, 12, 13 and 14
Adverse events	10a-k

Notes: a) questions 3, 7d, 9 and 15 are not used in the scoring, b) the satisfaction and adverse events scores are only calculated post-operatively.

Responses to each question are coded 1, 2, 3,…., with a higher score indicating better QoL.

Derivation of core total score:

- Transform each response separately to a standardised z-score (mean 0, standard deviation (SD) 1). Note that this is done prior to the rescaling mentioned in the "Derivation of all other scores" section.
- Sum the standardised scores
- Transform to a t-score (mean 50, SD 10)
- The score is only calculated if at least 50% of the component questions (16 component questions) have been answered

Derivation of all other scores:

- If different questions to be used for a score have different numbers of possible responses, then responses are recalibrated so that all are on the same scale[2]. This is relevant for:
  - Question 2 (recalibrate 6-point to 5-point scale)
  - Question 12 (recalibrate 5-point to 4-point scale)
  - Question 13 (set option 4 to missing then recalibrate remaining 3-points to 4-point scale)
  - Question 14 (recalibrate 3-point to 4-point scale)
- Calculate a raw score by summing the relevant responses
- Examine the number of components that are non-missing:
  - If 50% or more are non-missing: calculate the mean of all responses (i.e. divide the raw sum by the number of non-missing components) and impute this resultant value for any missing components
  - If less than 50% are non-missing: set the raw sum to missing
- Recalculate the raw score by summing all relevant responses again (with appropriate imputed values from the step above)
- Transform the raw score to a score constrained between 0 and 100 using the following:

$$\textit{Transformed score} = \frac{\textit{(raw score – minimum possible raw score)}}{\textit{(range of possible raw scores)}} \times 100$$

[2] E.g. 1) If one question has a 3-point response scale and the remaining questions have 4-point response scales then the question on the 3-point response scale should be re-calibrated (1=1) (2=2.5) (3=4).
2) If one question has a 5-point response scale the remaining questions have 4-point response scales then the question on the 5-point response scale should be re-calibrated (1=1) (2=1.75) (3=2.5) (4=3.25) (5=4).

4.5 Other variables

Details for any other variables which are derived for use in any other figures or tables are given below:

New variable	Rules
Reason for exclusion from trial	If any eligibility criteria not met = Ineligible If all eligibility criteria met but patient not approached = Not approached If all eligibility criteria met, patient approached but did not consent = Did not consent Otherwise = Other
Protocol deviation type 1 – patient didn't receive allocated treatment	If either: 1) treatment group on randomisation system does not match CRF C1, or 2) indicated on CRF C1 that operation wasn't carried out as randomised; then = Yes Otherwise = No
Protocol deviation type 2 – patient ineligible	If either: 1) emergency surgery on CRF C1, 2) patient had additional cardiac procedure on CRF C1 or 3) patient's EuroSCORE<5 on CRF A1; then = Yes Otherwise = No
Protocol deviation type 3 – surgeon not on trial list	If operating surgeon = 'OTH' on CRF C1 then = Yes Otherwise = No
Protocol deviation type 4 – expertise based randomisation used but surgeon's expertise not as allocation	If 1) expertise based randomisation used, and 2) surgeon expertise does not equal treatment group on randomisation system; then = Yes Otherwise = No
Protocol deviation type 5 – within surgeon randomisation used with ONCABG surgeon	If 1) within surgeon randomisation used, and 2) surgeon expertise = ONCABG; then = Yes Otherwise = No
Age	(Operation date – DOB)/365.25
BMI	Weight (kg) / Height $(cm)^2$ * 10,000
Mean arterial pressure	DBP + (SBP-DBP)/3

New variable	Rules
Time between randomisation and surgery (days)	Operation date – randomisation date
Time between surgery and previous MI (months)	(Year of operation – Year of previous MI)*12 + Month of operation – Month of previous MI
Time between randomisation and withdrawal (days)	Withdrawal date – randomisation date
Operative duration (hours)	Operation end – operation start
Duration of ventilation (hours)	(Extubation date + Extubation time – Operation date – Operation end)*24
Duration of re-ventilation period 1 (hours)	(Re-extubation date + Re-extubation time – Re-intubation date – Re-intubation time)*24
Duration of re-ventilation period 2 (hours)	(Further re-extubation date + Further re-extubation time – Further re-intubation date – Further re-intubation time)*24
Discharged from CICU to	If admitted to high dependency unit (HDU) but not ward = HDU If admitted to ward but not HDU = ward If admitted to HDU and ward and HDU admission date prior to ward admission date = HDU If admitted to HDU and ward and ward admission date prior to HDU admission date = ward
CICU length of stay (hours)	(HDU/ward* admission date + HDU/ward* admission time – Operation end date + Operation end time[3])*24 ** HDU or ward is used according to the value of the "CICU discharge to" variable. If admission times are not known midday is used.*
CICU length of stay censoring variable	If patient dies prior to discharge from CICU = Yes Otherwise = No

[3] Operation end date/time is used as the start of the CICU period to ensure time spent in the recovery room is included (this varies between sites, in particular patients in Sheffield have spent up to 8 hours in recovery). For future cost analyses the period can be split into 1) recovery and 2) CICU. This will also include the period in the recovery room for any patients who weren't admitted to CICU but were admitted straight to HDU

New variable	Rules
Length of stay of any CICU readmission (days)	If patient readmitted to CICU prior to first ward admission = (Date of ward admission – Date of CICU readmission) If patient readmitted to CICU after first ward admission = (Date of HDU readmission – Date of CICU readmission) Otherwise = Missing
HDU length of stay (hours)	If patient admitted to ward and not readmitted to other areas = (Ward admission date + Ward admission time – HDU admission date – HDU admission time)*24 If patient not admitted to ward and not readmitted to other areas = (Date of discharge + Time of discharge – HDU admission date – HDU admission time)*24 If patient readmitted to ITU after initial HDU admission = [Minimum(ITU re-admission date + ITU re-admission time, Ward admission date + Ward admission time) – HDU admission date – HDU admission time]*24 *If admission times are not known midday is used.*
Length of stay of any HDU readmission (days)	If patient readmitted to HDU AND readmitted to ward = (Date of ward readmission – date of HDU readmission) If patient readmitted to HDU but not readmitted to ward = (Date of discharge – date of HDU readmission) Otherwise = Missing
Ward length of stay (hours)	If patient not readmitted to other areas after initial ward admission = (Date of discharge + Time of discharge – HDU admission date – HDU admission time)*24 If patient readmitted to ITU/HDU after initial ward admission = (ITU/HDU re-admission date + ITU/HDU re-admission time – Ward admission date – Ward admission time)*24 *If admission times are not known midday is used.*
Length of stay of any ward readmission (days)	If patient readmitted to ward = (Date of discharge – date of ward readmission) Otherwise = Missing

New variable	Rules
Total length of stay (days)	Date of discharge – Date of operation
Total length of stay censoring variable	If patient dies prior to discharge from hospital = Yes Otherwise = No
Change in creatinine (from baseline to day 2 post-op)	Day 2 creatinine – Pre-operative creatinine
Serious adverse event (SAE) maximum intensity	Maximum of intensity variable on initial SAE form and all follow-up SAE forms
SAE relatedness	Maximum (worst case scenario) of relatedness variable on initial SAE form and all follow-up SAE forms
SAE resolution date and time	SAE end date and time on final follow-up SAE form (or initial SAE form if no follow-up forms required)

5. STATISTICAL ANALYSES

5.1 Baseline, intraoperative and postoperative (non trial outcome) characteristics

Baseline (i.e. patient demography and past history), intraoperative and postoperative (excluding primary/secondary outcomes) characteristics will be described by treatment group for patients in the analysis population group.

Continuous variables will be summarised using the mean and SD (or median and inter quartile range (IQR) if the distribution is skewed), and categorical data will be summarised as a number and percentage. Summary statistics are those we expect to use based on a-priori knowledge of the clinical measurements gained from previous trials. However, if distributional assumptions are not valid, changes will be made.

Any imbalances in the characteristics of the patients at the start of the study will be described but statistical tests for baseline imbalance will not be carried out.

5.2 Quantification of treatment effects

5.2.1 Adjustment in models

The intention is to adjust all models for factors included in the cohort minimisation: age, sex (females vs males), operative priority (urgent vs elective), LV function (poor vs moderate/good),

serum creatinine (≤200 vs >200), previous sternotomy (yes vs no), pulmonary hypertension (yes vs no) and previous stroke (yes vs no) as fixed effects, and surgeon as a random effect. However due to the reduced sample size the feasibility of adjustment will be explored, but it is possible that the effects may not be estimated reliably. Occasionally values of these variables differ between the study database and the randomisation system as they have been entered incorrectly into the randomisation system, in this case the values from the study database will be used.

For continuous outcomes that are measured preoperatively as well as postoperatively (EQ-5D and CROQ); preoperative and postoperative values will be modelled jointly in preference to the preoperative value being modelled as a covariate. Joint modelling will avoid the necessity to either exclude cases with missing preoperative measures or to impute missing preoperative values.

5.2.2 Analysis models

All outcomes listed in the study protocol will be presented in tables using for patients in the analysis population group. General methods of presentation and assessing treatment effects are outlined below. For all treatment comparisons the ONCABG group will be the reference group. Details specific to each outcome are described as appropriate.

- **Binary outcomes** (primary outcome) will be presented as numbers and percentages of patients in each treatment group. Outcomes will be compared between treatment groups using logistic regression with treatment estimates presented as adjusted odds ratios (OR) and 95% confidence intervals (95% CI). Formal statistical comparisons of treatment effects will only be performed if more than ten patients in total experience the outcome (with at least one event in each treatment group). A secondary analysis will be performed whereby any events occurring post randomisation but prior to surgery are included as primary outcome events.
- **Time to event outcomes** (duration of CICU stay and duration of hospital stay) will be presented as median and IQR and compared using adjusted Cox proportional hazards models. Therefore treatment comparisons will be presented as hazard ratios (HR) and 95% CI. The validity of the assumption of proportional hazards will be tested and, if this assumption is violated, a Cox model with a time-dependent covariate (the interaction term between the treatment and the survival time) will be used. This type of model will allow the difference between OPCABG and ONCABG to be estimated within discrete time periods, to describe further the difference in outcome due to the treatment group. Patients who die prior to hospital/CICU discharge will be censored at their time of death.

- **Categorical data measured at multiple time points** (Rose angina, CCS class, categorical EQ-5D variables) will be presented as numbers and percentages of patient in each treatment group at both preoperative and 4-8 week visit time points.
  - For rose angina and CCS class outcomes, for analysis purposes the 4-8 week data will be dichotomised into binary outcomes of no angina symptoms vs any angina symptoms. Treatment comparisons will then be made using logistic regression with 4-8 week dichotomised outcomes, adjusting for preoperative class as a categorical variable. Again, formal statistical comparisons of treatment effects will only be performed if more than ten patients in total experience the angina outcome (with at least one event in each treatment group).
  - For categorical EQ-5D variables (i.e. responses to mobility, self-care, usual activities, pain/discomfort and anxiety/depression questions) initially no formal comparisons will be made between treatment groups. Treatment differences for different EQ-5D versions will be commented upon but not formally estimated.
- **Continuous data measured at multiple times points** (EQ-5D single summary index and visual analogue scale and CROQ) will be summarised as means and SDs (or medians and IQRs if any distributions are skewed) and analysed using linear mixed effects methodology. Multivariate normal models will be fitted incorporating separate parameter estimates for the mean baseline response and for each treatment at the 4-8 week time point (i.e. saturated model with time fitted as a categorical variable). In addition study design variables will be fitted as per the guidelines outlined in Section 5.2.1. As there is only one postoperative time point, time x treatment interaction terms are not relevant and a compound symmetry variance/covariance matrix will be used.

Outcomes may also be presented graphically, if appropriate. For time to event outcomes this will usually consist of Kaplan-Meier survival curves. For continuous outcomes this may consist of graphs depicting estimated means (plus 95% CI or standard error) for each treatment group.

5.2.3 Statistical significance

For hypothesis tests p-values<0.05 are considered statistically significant. Likelihood ratio tests will be used in preference to Wald tests for hypothesis testing. As the trial was stopped early it is very underpowered to detect clinically important differences but p-values are reported for completeness.

5.2.4 Model assumptions

For all methods outlined underlying assumptions will be checked using standard methods, e.g. residual plots, tests for proportional hazards, etc. If assumptions are not valid then alternative methods of analysis will be sought. If outlying observations are found which mean models do not fit the data adequately, such observations will be excluded from the main analyses and comments made in footnotes.

5.2.5 Subgroup analyses

No subgroup analyses will be undertaken.

5.2.6 Sensitivity analyses

No sensitivity analyses will be undertaken.

5.2.7 Ancillary analyses

It is intended to perform meta-analyses combining the primary outcome from this study with the most recent systematic review. Two meta-analyses are planned: a) updating the recent Cochrane review [3] of off-pump and on-pump surgery in all patients (i.e. not just restricted to high-risk patients) with the results of CRISP and the recently published CORONARY trial [4], which was published after the Cochrane review; b) performing a meta-analysis of four studies (three studies identified in the Cochrane review and CRISP) that focussed on high-risk patients exclusively. The second analysis will be performed in two different ways: a) using outcome data at the last follow-up for each study; b) restricting to outcomes at 30 days postoperatively, which is more consistent with CRISP.

The outcomes which will be analysed for the meta-analyses are those analysed in the Cochrane review which formed part of the CRISP primary outcome: death, MI, stroke and new onset renal failure. Standard meta-analysis methods for binary outcomes, using random effects models, will be used,

5.2.8 Missing data

It is anticipated that missing data will be very low due to the reduced sample size, and the discontinuation of the one-year follow-up. In all tables missing data will be indicated by footnotes. The amount of missing data by group will be examined and if it differs substantially between groups potential reasons will be explored.

Missing data in any analysis models is now discussed:

- For the primary outcome and time to event secondary outcomes it is anticipated that missing data will be less than 5%. Therefore although the amount of missing data will be described, no formal allowance will be made (i.e. complete case analyses will be performed).
- For categorical data measured at multiple time points, patients with missing 4-8 week data will be excluded from the analysis. Patients with missing preoperative data (but complete 4-8 week data) will have the most common category across both treatment groups imputed.
- For continuous data measured at multiple time points preoperative values will be modelled jointly with those measured postoperatively, as described previously, thereby allowing all cases with at least one observation to be included. If appropriate (the level of missingness is >20%) then any variables that are predictive of missingness will be identified, and if there is reason to suggest that an assumption of missing at random (MAR) given these variables is reasonable (especially likely if the variable was measured pre-operatively) then such variables will be adjusted for in the models of interest. These models can be shown to provide unbiased estimates of the treatment effect and moreover multiple imputation approaches would not be expected to recover any additional information.
- By design, there will be no missing predictor data, other than already discussed in the points above.

5.2.9 Multiple testing

No formal adjustment will be made for multiple testing. However as previously described formal statistical comparisons will be limited. Consideration must be taken in interpretation of results to reflect the number of statistical tests performed.

5.3 Adverse events

Adverse events occurring between the point of consent and the 4-8 week follow-up visit (or time of withdrawal, or patient is "lost to follow-up") will be tabulated for all patients in the safety population. Events will be presented grouped by the treatment received, rather than the treatment allocated. Firstly expected adverse events will be presented (with events that meet the criteria[4] of a SAE indicated) following cardiac surgery but prior to hospital discharge, as listed in the study protocol. Such events are captured through the study CRFs, but the number of occurrences per patient of each expected adverse event has not been recorded.

[4] Either: prolonged an ongoing hospitalisation/resulted in hospitalisation; resulted in death; was life threatening; or resulted in persistent or significant disability/incapacity

Appendix 6 Trial Steering Committee and Data Monitoring and Safety Committee members

Trial Steering Committee

Professor William Wijns (chairperson)

Dr Jonathan Cook

Professor John Dark

Mr Neville Jones (patient representative)

Dr Belinda Lees

Mr Patrick Magee

Professor John Pepper

Data Monitoring and Safety Committee

Professor Tom Treasure (chairperson)

Dr Tim Clayton

Professor Desmond Julian

Professor Paul Sergeant

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