A. British Cardiovascular Intervention Society Jeopardy Score Calculator

Start at row 1 and proceed as instructed

Row	Coronary Artery/Graft	Instructions	Score
1	LMS	if ≥50% lesion, score 8 and go to row 11 if <50% lesion, score 0 and go to row 2	
2	Proximal LAD (Before DG)	if ≥70% lesion, score 6 and go to row 5 if <70% lesion, score 0 and go to row 3	
3	Mid LAD (After DG)	if ≥70% lesion, score 2 and go to row 4 if <70% lesion, score 0 and go to row 4	
4	Major DG	if ≥70% lesion, score 2 and go to row 5 if <70% lesion, score 0 and go to row 5	
5		If Cx dominant, go to row 8 If RCA dominant, go to row 6	
6	Proximal RCA (Before PDA)	if ≥70% lesion, score 4 and go to row 10 if <70% lesion, score 0, go to row 7	
7	PDA	if ≥70% lesion, score 2 and go to row 10 if <70% lesion, score 0, go to row 10	
8	Proximal Cx (Before OM)	if ≥70% lesion, score 6 and go to row 14 if <70% lesion, score 0, go to row 9	
9	Mid Cx (After OM)	if ≥70% lesion, score 2 and go to row 10 if <70% lesion, score 0, go to row 10	
10	Major OM	if ≥70% lesion, score 2 and go to row 14 if <70% lesion, score 0 and go to row 14	
11		If Cx dominant, score 4 and go to row 14 If RCA dominant, score 0 and go to row 12	
12	Proximal RCA (Before PDA)	if ≥70% lesion, score 4 and go to row 14 if <70% lesion, score 0 and go to row 13	
13	PDA	if ≥70% lesion, score 2 and go to row 14 if <70% lesion, score 0, go to row 14	
14		Previous CABG? If yes, go to row 15 If no, go to row 21	
15	LAD graft beyond DG	if <70% graft lesion, score -4, go to row 16 if >70%, poor run-off or n/a, score 0, go to row 16	
16	Major DG graft	if <70% graft lesion, score -2, go to row 17 if ≥70%, poor run-off or n/a, score 0, go to row 17	
17	Major OM graft	if <70% graft lesion, score -2, go to row 18 if ≥70%, poor run-off or n/a, score 0, go to row 18	
18	Cx graft beyond OM (Cx dominant system)	if <70% graft lesion, score -4, go to row 19 if ≥70%, poor run-off or n/a, score 0, go to row 19	
19	RCA graft (before PDA)	if <70% graft lesion, score -4, go to row 21 if ≥70% poor run-off or n/a, score 0, go to row 20	
20	PDA graft	if <70% graft lesion, score -2, go to row 21 if ≥70% poor run-off or n/a, score 0, go to row 21	
21	**TOTAL SCORE**	**Add filled in scores and enter (range: 0 to 12)**	

B. Trial Organization

Trial Steering Committee

Prof Andrew Clark, Chair of Clinical Cardiology, Castle Hill Hospital, Hull (chair)

Mrs Helen Williams, Pharmacist, NHS Southwark Clinical Commissioning Group

Dr Pablo Perel, Epidemiologist, London School of Hygiene and Tropical Medicine

Dr David Walker, Cardiologist, Conquest Hospital, St. Leonards-on-Sea

Prof Rod Stables, Cardiologist, Liverpool heart and Chest Hospital

Prof Divaka Perera, King's College London

Ms Liz Bestic, patient representative

Mrs Paula Young, patient representative

Data and Safety Monitoring Committee

Dr Peter Ludman, Consultant Cardiologist, Birmingham (chair)

Dr Suzanna Hardman, Consultant Cardiologist, The Whittington Hospital, London

Dr Louise Brown, Senior Statistician, MRC Clinical Trials Unit at UCL

Clinical Events Committee

Prof Roxy Senior, Professor of Clinical Cardiology, Royal Brompton Hospital, London (chair)

Dr Zaheer Yousef, Consultant Cardiologist, University Hospital of Wales

Dr Rajan Sharma, Consultant Cardiologist, St George's Hospital, London

Project Management Group

Prof Divaka Perera, King's College London

Mr Tim Clayton, London School of Hygiene and Tropical Medicine

Mrs Rosemary Knight, London School of Hygiene and Tropical Medicine

Mr Steven Robertson, London School of Hygiene and Tropical Medicine

Mr Richard Evans, London School of Hygiene and Tropical Medicine

Mrs Karen Wilson, Guy's and St Thomas' Hospital, London

Mrs Sophie Arnold, Guy's and St Thomas' Hospital, London

Dr Bhavik Modi, Guy's and St Thomas' Hospital, London

Dr Natalia Briceno, Guy's and St Thomas' Hospital, London

Medical Therapy Committee

Prof Michael Marber, Professor of Cardiology, King's College London

Prof Aldo Rinaldi, Consultant Cardiologist, St Thomas' Hospital, London

Dr Stam Kapetaenakis, Consultant Cardiologist, St Thomas' Hospital, London

Prof Mark Petrie, University of Glasgow

List of sites and investigators

The following participating sites have all randomized at least one patient to REVIVED as of 24th August 2017

Center	PI	Co-investigators	Coordinator
Guy's and St Thomas' Hospital	Prof Divaka Perera	Dr Gerry Carr-White, Dr Amedeo Chiribiri	Sophie Arnold, Dr Haseeb Rahman,
Golden Jubilee National Hospital, Glasgow	Prof Mark Petrie	Dr Stuart Watkins	Marion McAdam
Royal Bournemouth Hospital	Dr Peter O'Kane	Dr Christopher Boos	Sarah Kennard, Cathie Purnell
Leeds General Infirmary	Prof John Greenwood	Dr Jonathan Blaxill	Michelle Anderson
King's College Hospital, London	Dr George Amin-Youssef	Dr Narbeh Melikian, Prof Philip Macarthy,	Jonathan Breeze
Barts Heart Centre, London	Dr Roshan Weerackody	Dr Ceri Davies, Dr Elliot Smith	Bindu Matthews, Mervyn Andiapen
Royal Victoria Hospital, Belfast	Dr Lana Dixon	Dr Mark Spence	Patricia Glover
Freeman Hospital, Newcastle	Dr Richard Edwards	Dr Mohaned Egred	Alla Narytnyk, Vera Wealleans
New Cross Hospital, Wolverhampton	Dr James Cotton	Dr Richard Horton	Stella Metherell
Royal Free Hospital, London	Dr Tim Lockie	Dr Niket Patel	Angelique Smit
Kettering General Hospital	Dr Kai Hogrefe	Dr Adrian Cheng	Charmaine Beirnes
Manchester Royal Infirmary	Dr Cara Hendry	Dr Fozia Ahmed, Dr Mamas Mamas	Anu Oommen
Glenfield Hospital, Leicester	Prof Iain Squire	Prof Anthony Gershlick	Joanna Davison
Royal Infirmary of Edinburgh	Dr Miles Behan	Dr Alan Japp	Belinda Rif
Liverpool Chest and Heart Hospital	Dr Pradeep Magapu	Prof Rod Stables, Dr David Wright	Janet Barton
Southampton General Hospital	Dr Michael Mahmoudi	Dr Andrew Flett, Prof Nick Curzen	Judith Radmore
Sunderland Royal Hospital	Dr Nicholas Jenkins	Dr Sam McClure	Pauline Oates
Lister Hospital, Stevenage	Dr Neville Kukreja	Dr Mary Lynch	Claire Barratt
University Hospital, Coventry	Dr Prithwish Banerjee	Dr Luke Tapp	Valerie Ansell
Royal Devon & Exeter Hospital	Dr Andrew Sharp	Dr Andrew Ludman	Samantha Keenan
Worthing Hospital	Dr Nick Pegge	Dr Sukhbir Dhamrait	Sally Moore
Pinderfields Hospital, Wakefield	Dr Dwayne Conway	Dr Paul Brooksby	Judith Wright
Northern General Hospital, Sheffield	Dr Julian Gunn	Dr Abdallah Al-Mohammad	Michael Agyemang

James Cook Hospital, Middlesbrough	Dr Mark de Belder	Dr Jeet Thambyrajah	Cath Richardson
Royal Oldham Hospital	Dr Tim Gray	Dr Jolanta Sobolewska	Louise Morby
Salisbury District Hospital	Dr Tim Wells	Dr Anthony Jones	Linda Frost
The York Hospital	Mr Maurice Pye	Dr Simon Megarry	Yvonne McGill
Basingstoke and North Hampshire Hospital	Dr Jason Glover	Dr Dominic Kelly	Janet Knight
North Wales Cardiac Centre	Dr Paul Das	Dr Nick Waterfield	Emily Harman
Birmingham Heartlands Hospital	Dr Kaeng Lee	Dr James Beattie	Alan Chung

Extract from Data and Safety Monitoring Committee Charter (Nov 2013)

Roles and responsibilities of DSMC
The DSMC role is to examine the data accumulated during progress of the trial and ensure that the benefit/risk ratio remains acceptable for participating patients.
It is the only committee which will have access to data broken down by treatment from the trial and on this basis, the primary responsibility of the DSMC is to review interim analyses of outcome data and to recommend to the Trial Steering Committee (TSC) whether the study needs to be changed or terminated based on these analyses.

The DSMC will review the progress of the trial, including updated figures on recruitment, data quality, and main outcomes and safety data. More specifically, this will include:

- monitoring evidence for treatment differences in the main efficacy outcome measures
- monitor evidence for treatment harm (e.g. SAEs, deaths)
- assess the impact and relevance of external evidence
- decide whether to recommend that the trial continues to recruit participants or whether recruitment should be terminated either for everyone or for some treatment groups and/or some participant subgroups
- assess data quality, including completeness
- review recruitment figures and monitor losses to follow-up
- monitor compliance with the protocol by participants and investigators
- monitor continuing appropriateness of patient information
- monitor compliance with previous DSMC recommendations
- considering the ethical implications of any recommendations made by the DSMC

DSMC input into the protocol
All potential DSMC members should have sight of the protocol before finalising their agreeing to join the committee. Before recruitment begins the trial will have undergone review by the sponsor, scrutiny by other trial committees and a research ethics committee. Therefore, if a potential DSMC member has major reservations about the trial (e.g. the protocol or the logistics) they should report these to the REVIVED‐BCIS2 Clinical Trials Unit and may decide not to accept the invitation to join. DSMC members should be independent and constructively critical of the ongoing trial, but also supportive of aims and methods of the trial.

DSMC first meeting
The DSMC should meet within 6 months of recruitment commencing.
A DSMC statistical analysis plan, including a list of tables, will be provided to familiarise the DSMC members with the intended content of the DSMC reports. The DSMC will review the statistical analysis plan at the first meeting and confirm the final content of the report to be provided at subsequent meetings. Alterations to the report can be made at subsequent meetings to reflect the requirements of the DSMC.

Issues specific to the disease under study
In accordance with the Protocol, the DSMC has the responsibility for deciding whether, while randomisation is in progress, the results broken down by treatment (or the results by treatment for a particular subgroup), should be revealed to the TSC.

Stopping guidelines
The DSMC will review accumulating data at regular intervals, however, formal interim analyses for safety (all‐cause death outcome) and efficacy (primary outcome: all‐

cause death or hospitalisation for heart failure) will also be performed. Formal analyses will be carried out when 25% (safety only), 50% and 75% of the expected number of primary outcomes have occurred. The DSMC can modify the number and timing of interim analyses on the basis of data patterns observed and on the basis of the timing of the DSMC meeting. For the formal interim analyses, a hazard ratio comparing the two treatments and its 95% confidence interval will be presented with a likelihood ratio test p‐value, calculated using an unadjusted Cox proportional hazards model. As a guideline, the DSMC may consider stopping for safety if there is evidence that PCI plus OMT treatment is worse than OMT alone with a p‐value of <0.01 for the all‐cause death outcome. The DSMC may consider stopping for efficacy if there is evidence that PCI plus OMT treatment is better than OMT alone with a p‐value of <0.001 for the primary outcome. In addition, the DSMC may recommend stopping or amending the trial if recruitment and trial progress are poor. There will be no formal interim futility analysis. These guidelines should not be seen as absolute stopping rules. In particular, there are likely to be large margins of imprecision at the early stages of the trial. The recommendations will be the decision of the DSMC, whether the statistical monitoring guidelines are met or not. The DSMC will also consider the overall event rates, the strength of any formal statistical comparison and the circumstances of the events. In addition, the DSMC will be provided with any emerging information from other clinical trials of the same or similar compound by the REVIVED‐BCIS2 Chief Investigator (CI) (Dr Divaka Perera).

The responsibilities of the DSMC statistician

- An Independent Statistician (IS), is responsible for producing the report to the DSMC. This is to ensure all trial related staff (including the trial Statistician) remain blind to the interim analysis.
- Pooled data will be sent to the IS, by the REVIVED‐BCIS2 Clinical Trials Unit.
- He/she will prepare the reports in accordance with the DSMC reporting requirements and disseminate the required reports in a timely fashion to the DSMC members.
- The IS may participate in DSMC meetings if required for the purpose of guiding the DSMC through the reports.
- DSMC discussions will remain confidential and will not be communicated to the REVIVED‐BCIS2 Clinical Trials Unit

DSMC Meetings

After their first meeting, it is intended that the DSMC will next meet to review interim results in 6‐9 months time and then at least annually depending on the rate of accrual of data. Only DSMC members and others whom they specifically invite (e.g. Independent Statistician) are present in closed sessions.

In open sessions, all those attending the closed session are joined by the CI and/or relevant members of the REVIVED‐BCIS2 Clinical Trials Unit. The format of the meetings will be as follows:

1. Open session: Introduction and any “open” parts of the report
2. Closed session: DSMCdiscussion of “closed” parts of the report and, if necessary,
3. Further Open session(if required by DSMC):to address further questions to the CI/ Trial Manager

DSMC Documentation and Procedures

Open sessions: Accumulating information relating to recruitment and data quality (e.g. data return rates, treatment compliance) will be presented.

Closed sessions: In addition to all the material available in the open session, the closed session material will include safety and efficacy data by treatment group.

- The DSMC will not be blinded to treatment group in the reports.
- DSMC members do not have the right to share confidential information with anyone outside the DSMC, including the CI or Sponsor.
- Identification and circulation of external evidence (e.g. from other trials/ systematic reviews) will be the responsibility of the CI.
- The DSMC will report its recommendations in writing to the TSC. This should be copied to the CI and Clinical Trials Unit and, if possible, sent in time for consideration at a TSC meeting. If the trial is to continue largely unchanged then it is often useful for the report from the DSMC to include a summary paragraph suitable for trial promotion purposes
- The DSMC will receive all documents and reports for consideration at least 1 week before any meetings unless urgency prevails. These reports will be circulated by the Independent Statistician.
- The DSMC members must ensure the safety and confidentiality of data reports after each meeting. If in doubt, these may be destroyed and copies subsequently requested from the Independent Statistician with the newest report.

DSMC recommendations

Possible recommendations could include:

1. No action needed, trial continues as planned
2. Stopping recruitment within a subgroup or for the whole trial
3. Extending recruitment (based on actual control arm response rates being different to predicted rather than on emerging differences) or extending follow-up
4. Sanctioning and/or proposing protocol changes

It is recommended that every effort should be made for the DSMC to reach a unanimous decision. If the DSMC cannot achieve this, a vote may be taken, although details of the vote should not be routinely included in the report to the TSC as these may inappropriately convey information about the state of the trial data. It is important that the implications (e.g. ethical, statistical, practical, regulatory) for the trial be considered before any recommendation is made. The role of the Chair is to summarise discussions and encourage consensus; it may be best for the Chair to give their own opinion last.

A letter sent to the Chair of the TSC within 3 weeks of the meeting will communicate the DSMC recommendations/decisions. A copy of the letter should be sent to the CI and Clinical Trials Unit for the Trial master File. If the DSMC has serious problems or concerns with the TSC or Sponsor's decision a meeting of these groups should be held. The information to be shown would depend upon the action proposed and the DSMC's concerns. Depending on the reason for the disagreement confidential data may have to be revealed to all those attending such a meeting.

DSMC roles around publication of results

The TSC will provide draft reports of the primary results of the trial to the DSMC for their consideration prior to submission for publication. The DSMC may provide comments to the TSC on the draft reports, and give advice about data interpretation. DSMC members will be named and their affiliations listed in the main report, unless they explicitly request otherwise. A brief summary of the timings and conclusions of DSMC meetings may be included if appropriate in the body of this paper.The DSMC may discuss issues from their involvement in the trial 12 months after the primary trial results have been published. If a DSMC needs to discuss their involvement any earlier, permission is required from the TSC.

Extract from Clinical Events Committee Charter (July 2016)

The CEC has been formed to review death, hospitalisation for heart failure, MI and unplanned revascularisation reported to the Clinical Trials Unit (CTU) at the London School of Hygiene and Tropical Medicine (LSHTM).

Terminology

Event	Reported death, MI, hospitalisation for heart failure or unplanned revascularisation
Classification	The name given to each event to describe it, i.e. cardiovascular death or non-cardiovascular death.
Adjudication	The process of classifying an event by teleconference when after the independent review by the CEC there is a difference of classification.
Validation	The status of an event once it has been independently reviewed and given a final classification.

Procedure for assessing events

a. Gathering event data

1. Events are reported by site staff using the REVIVED electronic Case Report Form (eCRF). Upon entering the event data the site is requested to send supporting documentation to the CTU.
2. The supporting documentation will be reviewed by the CTU to ensure that there is sufficient information for assessing the events. Every effort will be made to gather as much information as possible. Events with insufficient information are chased up with the sites.
3. Supporting documentation must not contain any identifiable information. This includes name, date of birth and addresses. The Study ID will be present on the supporting documents and will identify which patient the documents refer to. If identifiable data is present it must be permanently obscured.
4. If no further information is available, the committee will be informed and a decision must be made with the evidence provided.
5. Events with sufficient information are collected into batches for review. Each batch should contain around 10-15 events.
6. The batches are recorded in Study ID order on a spreadsheet, including the following information: Study ID, Event Type, Date randomized, Date of event, Event types, Sufficient data? (Yes/No), Notes – record any additional comments for the CEC such as "No further information available"

b. Event assessment

1. The batch spreadsheet will be emailed to the CEC committee members.
2. Each member of the CEC will be given sufficient time to make an independent assessment of each event, deciding on the appropriate classification for each.
3. Once all the events have been assessed and classified the completed spreadsheet is emailed back to the CTU. The completed spreadsheets are filed electronically at the CTU.

Events may comprise more than one of the categories, for example a death caused by an MI. In these cases the event will be considered as two separate events, with an individual classification for each. If both applicable categories are not present on the spreadsheet the CEC will report this to the CTU.

c. Validation and adjudication

1. The classifications from the previous batch or batches will be collated by the CTU into an adjudication spreadsheet. Any events with three matching classifications will be

considered validated. Any with differences in classification will be highlighted for adjudication.
2. The CEC will meet (in person or by teleconference) to review the events requiring adjudication
3. The agreed classification will be recorded on the adjudication spreadsheet at the time of the meeting. In cases where a unanimous decision cannot be made the majority classification will be used.
4. The adjudication spreadsheets from before and after the adjudication meeting are filed electronically at the CTU.

Quality Assurance (QA)
At least 5% of all events assessed will be QA sets. This procedure is put in place to ensure that potential differences in validation over time are captured and rectified.
If differences in validation over time are found the following steps should be taken;

- Ensure that the endpoint definitions are clear to the CEC. If understanding of the definitions has drifted over time it is important to verify with the CEC that the current understanding is correct. The trial CI should be involved in this discussion.
- Highlight the specific event-type and timescale that is affected and if necessary re-review a selection of relevant cases from various meetings.
- If there is a significant and systematic difference over time all of the affected cases should be re-reviewed. This decision will be made by the REVIVED project management group (PMG).
- Once remedial actions have been taken an additional QA pass may be necessary to verify that the issue has been resolved. This decision will be made by the PMG.