Perera, D; Clayton, T; Petrie, MC; Greenwood, JP; O’Kane, PD; Evans, R; Sculpher, M; McDonagh, T; Gershlick, A; de Belder, M; +3 more... Redwood, S; Carr-White, G; Marber, M; (2018) Percutaneous Revascularization for Ischemic Ventricular Dysfunction: Rationale and Design of the REVIVED-BCIS2 Trial. Percutaneous Coronary Intervention for Ischemic Cardiomyopathy, 6 (6). pp. 517-526. DOI: https://doi.org/10.1016/j.jchf.2018.01.024

Downloaded from: http://researchonline.lshtm.ac.uk/id/eprint/4647878/

DOI: https://doi.org/10.1016/j.jchf.2018.01.024

Usage Guidelines:

Please refer to usage guidelines at https://researchonline.lshtm.ac.uk/policies.html or alternatively contact researchonline@lshtm.ac.uk.

Available under license: http://creativecommons.org/licenses/by-nc-nd/2.5/
### A. British Cardiovascular Intervention Society Jeopardy Score Calculator

*Start at row 1 and proceed as instructed*

<table>
<thead>
<tr>
<th>Row</th>
<th>Coronary Artery/Graft</th>
<th>Instructions</th>
<th>Score</th>
</tr>
</thead>
</table>
| 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     | 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

<table>
<thead>
<tr>
<th>Center</th>
<th>PI</th>
<th>Co-investigators</th>
<th>Coordinator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guy's and St Thomas’ Hospital</td>
<td>Prof Divaka Perera</td>
<td>Dr Gerry Carr-White, Dr Amedeo Chiribiri</td>
<td>Sophie Arnold, Dr Haseeb Rahman,</td>
</tr>
<tr>
<td>Golden Jubilee National Hospital, Glasgow</td>
<td>Prof Mark Petrie</td>
<td>Dr Stuart Watkins</td>
<td>Marion McAdam</td>
</tr>
<tr>
<td>Royal Bournemouth Hospital</td>
<td>Dr Peter O’Kane</td>
<td>Dr Christopher Boos</td>
<td>Sarah Kennard, Cathie Purnell</td>
</tr>
<tr>
<td>Leeds General Infirmary</td>
<td>Prof John Greenwood</td>
<td>Dr Jonathan Blaxill</td>
<td>Michelle Anderson</td>
</tr>
<tr>
<td>King's College Hospital, London</td>
<td>Dr George Amin-Youssef</td>
<td>Dr Narbeh Melikian, Prof Philip Macarthy</td>
<td>Jonathan Breeze</td>
</tr>
<tr>
<td>Barts Heart Centre, London</td>
<td>Dr Roshan Weerackody</td>
<td>Dr Ceri Davies, Dr Elliot Smith</td>
<td>Bindu Matthews, Mervyn Andiapen</td>
</tr>
<tr>
<td>Royal Victoria Hospital, Belfast</td>
<td>Dr Lana Dixon</td>
<td>Dr Mark Spence</td>
<td>Patricia Glover</td>
</tr>
<tr>
<td>Freeman Hospital, Newcastle</td>
<td>Dr Richard Edwards</td>
<td>Dr Mohamed Egred</td>
<td>Alla Narytnyk, Vera Wealleans</td>
</tr>
<tr>
<td>New Cross Hospital, Wolverhampton</td>
<td>Dr James Cotton</td>
<td>Dr Richard Horton</td>
<td>Stella Metherell</td>
</tr>
<tr>
<td>Royal Free Hospital, London</td>
<td>Dr Tim Lockie</td>
<td>Dr Niket Patel</td>
<td>Angelique Smit</td>
</tr>
<tr>
<td>Kettering General Hospital</td>
<td>Dr Kai Hogrefe</td>
<td>Dr Adrian Cheng</td>
<td>Charmaine Beirnes</td>
</tr>
<tr>
<td>Manchester Royal Infirmary</td>
<td>Dr Cara Hendry</td>
<td>Dr Fozia Ahmed, Dr Mamas Mamas</td>
<td>Anu Oommen</td>
</tr>
<tr>
<td>Glenfield Hospital, Leicester</td>
<td>Prof Iain Squire</td>
<td>Prof Anthony Gershlick</td>
<td>Joanna Davison</td>
</tr>
<tr>
<td>Royal Infirmary of Edinburgh</td>
<td>Dr Miles Behan</td>
<td>Dr Alan Japp</td>
<td>Belinda Rif</td>
</tr>
<tr>
<td>Liverpool Chest and Heart Hospital</td>
<td>Dr Pradeep Magapu</td>
<td>Prof Rod Stables, Dr David Wright</td>
<td>Janet Barton</td>
</tr>
<tr>
<td>Southampton General Hospital</td>
<td>Dr Michael Mahmoudi</td>
<td>Dr Andrew Flett, Prof Nick Curzen</td>
<td>Judith Radmore</td>
</tr>
<tr>
<td>Sunderland Royal Hospital</td>
<td>Dr Nicholas Jenkins</td>
<td>Dr Sam McClure</td>
<td>Pauline Oates</td>
</tr>
<tr>
<td>Lister Hospital, Stevenage</td>
<td>Dr Neville Kukreja</td>
<td>Dr Mary Lynch</td>
<td>Claire Barratt</td>
</tr>
<tr>
<td>University Hospital, Coventry</td>
<td>Dr Prithwish Banerjee</td>
<td>Dr Luke Tapp</td>
<td>Valerie Ansell</td>
</tr>
<tr>
<td>Royal Devon &amp; Exeter Hospital</td>
<td>Dr Andrew Sharp</td>
<td>Dr Andrew Ludman</td>
<td>Samantha Keenan</td>
</tr>
<tr>
<td>Worthing Hospital</td>
<td>Dr Nick Pegge</td>
<td>Dr Sukhbir Dhamrait</td>
<td>Sally Moore</td>
</tr>
<tr>
<td>Pinderfields Hospital, Wakefield</td>
<td>Dr Dwayne Conway</td>
<td>Dr Paul Brooksby</td>
<td>Judith Wright</td>
</tr>
<tr>
<td>Northern General Hospital, Sheffield</td>
<td>Dr Julian Gunn</td>
<td>Dr Abdallah Al-Mohammad</td>
<td>Michael Agyemang</td>
</tr>
<tr>
<td>Hospital</td>
<td>Principal Investigator</td>
<td>Co-investigator</td>
<td>Co-investigator</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>---------------------------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>James Cook Hospital, Middlesbrough</td>
<td>Dr Mark de Belder</td>
<td>Dr Jeet Thambyrajah</td>
<td>Cath Richardson</td>
</tr>
<tr>
<td>Royal Oldham Hospital</td>
<td>Dr Tim Gray</td>
<td>Dr Jolanta Sobolewska</td>
<td>Louise Morby</td>
</tr>
<tr>
<td>Salisbury District Hospital</td>
<td>Dr Tim Wells</td>
<td>Dr Anthony Jones</td>
<td>Linda Frost</td>
</tr>
<tr>
<td>The York Hospital</td>
<td>Mr Maurice Pye</td>
<td>Dr Simon Megarry</td>
<td>Yvonne McGill</td>
</tr>
<tr>
<td>Basingstoke and North Hampshire Hospital</td>
<td>Dr Jason Glover</td>
<td>Dr Dominic Kelly</td>
<td>Janet Knight</td>
</tr>
<tr>
<td>North Wales Cardiac Centre</td>
<td>Dr Paul Das</td>
<td>Dr Nick Waterfield</td>
<td>Emily Harman</td>
</tr>
<tr>
<td>Birmingham Heartlands Hospital</td>
<td>Dr Kaeng Lee</td>
<td>Dr James Beattie</td>
<td>Alan Chung</td>
</tr>
</tbody>
</table>
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 REVISED-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: DSMC discussion 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**

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

**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.