Appendix 1: Review of studies reporting mortality from Cardiogenic Shock.

Paper	Nature of Cardiogenic Shock Patients included	Mortality Rates reported
Strom et al, Eurointervention 2018; 13:e2152-e2159.	US adults admitted with CGS from 2004 to 2014, comparing those receiving MCS and no MCS (n=183,516)	In-hospital mortality No MCS = 41.5% With MCS = 32.7%
Overtchouk et al. Eurointervention 2018; 13:e2160-e2168.	Observational single centre study from the ACTION study group recruiting 106 consecutive patients, with CS secondary to MI to ECLS pre or post PCI with or without IABP. Revascularisation successful in 76% of patients, half of the patients had severe triple vessel coronary artery disease.	30-day mortality rate = 63.2%.
Kolte et al, JAHA 2014; 3:e000590.	2003–2010 US Nationwide Inpatient Sample databases to identify all patients ≥40 years of age with STEMI and cardiogenic shock. Compared outcomes with and without early mechanical revascularisation and/or IABP.	In-hospital mortality No early mechanical revascularization/IABP = 44.6% Early mechanical revascularization/IABP = 33.8%
Goldberg et al, Circ Cardiovasc Qual Outcomes, 2016; 9:117-25.	5,686 patients analyzed between 2001 and 2011 who developed cardiogenic shock while in hospital following initial admission without features of cardiogenic shock but acute MI.	In-hospital case fatality rate = 41.4%.
Goldberg RJ et al. Circulation 2009; 119:1211-9.	13,663 patients hospitalized with AMI between 1975 and 2005, with 6.6% of patients developing cardiogenic shock.	In hospital mortality = 65.4%. Case fatality rate lower from 2001 onwards (42.1% in 2001, 48.9% in 2003, 42.0% in 2005).
Babaev et al, JAMA 2005; 294:448-54.	Prospective, observational study of 293,633 patients with ST-elevation myocardial infarction (25,311 [8.6%] had cardiogenic shock; 7356 [29%] had cardiogenic shock at hospital presentation) enrolled in the National Registry of Myocardial Infarction (NRMI) from January 1995 to May 2004 at 775 US hospitals with revascularization capability.	In-hospital cardiogenic shock mortality decreased from 60.3% in 1995 to 47.9% in 2004.
Holmes et al, Circulation 1999; 100:2067-73.	Patients enrolled from GUSTO-IIb trial admitted with STEMI/NSTEMI; n=12,804 with 4.2% of STEMI and 2.5% of NSTEMI patients developing cardiogenic shock.	In-hospital mortality in cardiogenic shock patients: STEMI patients = 63% NSTEMI patients = 73%
Jensen JK et al. Int J Cardiol Heart Vasc 2015; 6:19-24.	Study including all patients admitted with STEMI from 2002 to 2010 in a single centre, comparing mortality with and without cardiogenic shock and also with and without use of IABP	30-day cumulative mortality in cardiogenic shock = 57.3%
McNeice A et al. Cath Cardiovasc Interv2018; 92:E356-e367.	A retrospective study of 649 patients from the British Columbia Cardiac Registry with cardiogenic shock, AMI and MVD. Specifically looking at impact of culprit vs complete revascularization in cardiogenic shock patients.	30-day mortality = 34.5% in MVPCI, 23.7% in Culprit PCI only. 1 year mortality = 44.3% in MVPCI, 32.6% in Culprit PCI only.

Xie A et al. J Cardio Vasc Anaest 2015; 29:637-45.	Meta-analysis of patients with cardiogenic shock or Cardiac arrest undergoing ECMO. Data here are based on meta-analysis subgroup analysis of patients receiving ECMO treatment for cardiogenic shock alone.	30-day mortality = 47.5%.
Thiele et al. N Eng J Med 2012; 367:1287-96.	IABP-SHOCK II trial. 300 patients presenting with CS randomized to IABP or no-IABP	30-day mortality = 41.3% in non-IABP group.
Thiele et al. N Eng J Med 2017; 377:2419-2432.	CULPRIT-SHOCK.	30-day all-cause mortality: Multivessel PCI group = 51.6% Culprit-only PCI group = 43.3%
Shah M et al. Circ Heart Failure 2018; 11:e004310.	43212 Patients with AMI and cardiogenic shock from the 2013 to 2014 Healthcare Cost and Utilization Project National Readmission Database.	In-hospital mortality = 39.8%. (30-day readmission for CCF = 20.6%).
Anderson ML et al. Circ Cardiovasc Qual Outcomes 2013; 6(6):708-15.	Analysis of patients presenting with NSTEMI and STEMI to 392 US Hospitals between 2007 and 2011 (approx. 24,000 patients with Cardiogenic shock)	STEMI patients in-hospital mortality = 33.1% NSTEMI patients in-hospital mortality = 40.8%
Wayangankar S et al. JACC Interv 2016; 9:341-351.	Review of trends in management and outcomes of patients with cardiogenic shock from the NCDR CathPCI registry. The patients were analyzed according to 4 time blocks: 2005 to 2006, 2007 to 2008, 2009 to 2010, and post–2010 (2011 to 2013).	Unadjusted in-hospital mortality: 2005 – 2006: 27.6% 2007 – 2008: 27.4% 2009 – 2010: 28.2% 2011 – 2013: 30.6%
Patel SM et al. ASAIO Journal 2019; 65:21-28.	Retrospective analysis of patients with refractory cardiogenic shock treated with either VA ECMO +/- surgical venting (n=36) or VA ECMO + Impella (n=36).	30-day mortality rates: VA-ECMO = 78% VA-ECMO+Impella = 57%
Isorni MA, Danchin N et al. Arch Cardiovasc Disease 2018; 111:555-563.	Retrospective analysis of incidence, management and 1 year mortality in patients from the FAST-MI registry (1995 – 2010).	1-year mortality in 2010 Male: 48% Female: 54%
Aissaoui et al. Eur J Heart Failure 2016. 18:1144-52.	Retrospective analysis of elderly patients (defined as age ≥75yrs) presenting with MI and Cardiogenic shock from the FAST MI registry.	1 year mortality in 2010 = 59%.
Lee JM et al. JACC 2018; 71:844-856.	Retrospective analysis from the KAMIR-NIH registry	1-year mortality: Multivessel PCI = 21.3% IRA only PCI = 31.7%

Kunadian et al. JACC Interv 2014; 7:1374-85.	Retrospective analysis of Data from the BCIS NICOR registry of patients with cardiogenic shock.	30-day mortality = 37.3%.
Chung et al. Int J cardiol 2016; 223:412-417.	65 patients with profound cardiogenic shock post MI requiring ECMO support.	In-Hospital mortality = 53.8%
Sheu et al. Crit Care Med 2010; 38:1810-7.	335 patients, including those with profound and non-profound cardiogenic shock and those with and without ECMO.	Overall 30-day mortality without ECMO = 60.9% 30-day death without ECMO or profound CS = 33.3% 30-day death without ECMO but profound CS = 72%
Ouweneel et al. JACC 2017; 69:278-287.	IMPRESS study	30-day Mortality: IABP group = 50%, Impella group = 46%.

Appendix 2: Work Package Summary

The work is funded by the European Union Horizons 2020 research and innovation programme under grant agreement No. 754946. The applicants were a Consortium of 13 Partners with work separated into 9 work packages (WP):

WP 1: Data Management. Lead: Dr S Keane, Prof I Ford (Glasgow CTU)
WP 2: Trial Set-Up. Lead: Prof A Gershlick (University Leicester)
WP3 : Clinical Trial Programme. Lead: Prof A Gershlick (University Leicester)
WP4 : Clinical Follow-Up, Data Monitoring and Safety Evaluation. Lead: Prof S Haine, Prof C Vrints (University Antwerpen)
WP5 : Statistical Analysis. Lead: Dr K Bogaerts (Katholieke Universiteit Leuven)
WP6 : Health Economic Cost Efficacy Analysis. Lead: Prof M Flather and Proof R Fordham (University East Anglia)
WP7 : CMR Sub-Study. Lead: Prof C Berry (University of Glasgow)
WP8 : Public Engagement, Dissemination and Exploitation. Lead: Prof. T Adriaenssens (Katholieke Universiteit Leuven)
WP9: Coordination and Management. Lead: Prof A Gershlick (University Leicester)
Trial PI: Prof. A Gershlick
Co-chairs trial Steering Committee: Prof. A Gershlick, Prof. F Van de Werf
DSMB chair: Prof. F Verheugt
Clinical events committee Chair: Dr. F Alfonso

Appendix 3: Inclusion and Exclusion Criteria

Inclusion Criteria

All of the following are required for inclusion

1. Willing to provide informed consent/consultee declaration.
2. Presentation with a diagnosis of CGS within 24 h of onset of ACS symptoms
3. CGS secondary to ACS (Type 1 MI STEMI or N-STEMI) or secondary to ACS following previous recent PCI (acute/sub-acute stent thrombosis ARC definition).
4. PCI has been attempted
5. Persistence of CGS 30 minutes after successful or unsuccessful revascularisation of culprit coronary artery

CGS will be defined by:

- Systolic blood pressure <90 mmHg for at least 30 minutes, or a requirement for a continuous infusion of vasopressor or inotropic therapy to maintain systolic blood pressure > 90 mmHg.
- Clinical signs of pulmonary congestion, plus signs of impaired organ perfusion with at least one of the following manifestations:
  - altered mental status
  - cold and clammy skin and limbs
  - oliguria with a urine output of less than 30 ml per hour
  - elevated arterial lactate level of >2.0 mmol per litre on admission.

6. Provision of verbal consent followed by patient consent [or consultee declaration if the patient is unable to provide consent]
7. Age >=18yrs and <90yrs.

Exclusion Criteria

1. Unwilling to provide informed /consent/consultee declaration.
2. Echocardiographic evidence (recorded within 30 minutes of end of PCI procedure) of mechanical cause for CGS: e.g. ventricular septal defect, LV-free wall rupture, ischaemic mitral regurgitation.
3. Age <18yrs and >=90 years
4. Deemed too frail [Canadian frailty score>5].
5. Shock from another cause (sepsis, haemorrhagic/hypovolaemic shock, anaphylaxis, myocarditis etc.)
6. Significant systemic illness
7. Known dementia of any severity
8. Comorbidity with life expectancy <12 months
9. Severe peripheral vascular disease (precluding access making ECMO contra-indicated)
10. Severe allergy or intolerance to pharmacological or antithrombotic anti-platelet agents.
11. Out-of-hospital cardiac arrest (OHCA) under **any** of the following circumstances:
    - without return of spontaneous circulation (ongoing resuscitation effort)
    - with pH <7
    - without bystander CPR within 10 minutes of collapse
12. Involved in another randomised research trial within the last 12 months.
13. Pregnant or nursing mother.

Appendix 4: Primary and Secondary Endpoints for EUROSHOCK

Primary Endpoint

- All-Cause mortality at 30 days

Key Secondary Endpoints

- All-cause mortality or admission for heart failure at 12 months
- All-cause mortality at 12 months
- Admission for heart failure at 12 months

Other Secondary Endpoints – During Hospital Admission

- All-cause mortality
- Cardiovascular (CV) mortality
- Any stroke (categorized as haemorrhagic, ischaemic or unknown)
- Recurrent myocardial infarction (MI)
- Bleeding (BARC type 3-5)
- Escalation to other (non-ECMO) support device for refractory shock
- Any Vascular complications (VARC-2 classification)
- Acute kidney injury according to the modified RIFLE classification

Other Secondary Enpdoints – at day 30

- Failure of discharge from primary admission

Other Secondary Endpoints – at 12 months post discharge

- MACCE (Combined endpoint of all-cause mortality, repeat MI, stroke and repeat hospitalisation for heart failure).
- CV mortality
- Recurrent MI
- Any stroke (categorized as ischaemic, haemorrhagic or unknown)
- Need for unplanned (ischaemia-driven) repeat revascularisation (either PCI and/or CABG) after index procedure (planned staged procedures excluded)
- Bleeding (BARC Type 3-5)

Cost efficacy outcomes

- incremental cost-effectiveness ratio (ICER)
- EQ-5D-3L (measured at discharge, 6 and 12 months)
- Minnesota living with heart failure questionnaire (measured at discharge)

CMR sub-trial endpoints

- infarct size
- micro-vascular obstruction
- myocardial hemorrhage
- Left ventricular systolic function
- Left ventricular volume

Appendix 5: Substudies

CMR Sub-study

The purpose of CMR imaging is to assess the nature of myocardial infarct pathology, LV function and remodelling, and correlate these findings with other parameters of outcome, including NT-pro BNP, renal function, and NYHA heart failure grade. Information from control Group 1 will be particularly relevant. We will also investigate mechanistic differences between the treatment groups (infarct size, micro-vascular obstruction, myocardial hemorrhage, LV systolic function, LV volume, renal size, perfusion etc.). Multiparametric cardiovascular MRI, including renal imaging where feasible, will be performed following randomization in up to 30 days as soon as clinically feasible when feasible) and repeated at 6 months. Participation in the CMR sub-study will be confirmed through a feasibility questionnaire. We anticipate that the sub-study may be feasible in about ~40% of early survivors in the trial population (allowing for centre feasibility, patient compliance, etc.), thus the sample size in this sub-study is 180. For a minimum between-group difference in peak circumferential strain of 0.05 and a standard deviation of 0.10, a 2-sided t-test at a significance level (alpha of 0.05 then 63 and 84 subjects with data in each group would be needed to reject the null hypothesis of no difference with 80% and 90% power (1-beta), respectively.

Platelet Sub-study

Our Industry partner Chalice Medical Ltd (UK) have incorporated a CE mark propriety coating for its oxygenator. We will test further its impact on platelet activation in a simple small sub-study run by Prof. Stan Heptinstall from ”Plateletsolutions Ltd” . Since not all clinical sites use Chalice ECMO and as we wish centres to use what they are currently using, we will compare platelet function in 100 patients (50 who have been supported with an ECMO circuit incorporating the Chalice oxygenator and 50 with an oxygenator from any other manufacturer). The patients will not be randomised. The samples will be analysed at “Plateletsolutions Ltd UK”. Small (5ml) blood samples will be taken from the patients at up to 5 time points before, during and after the clinical procedure for analysis of platelet function. They will be collected using a one tenth volume (0.5ml) of 3.8% (w/v) trisodium citrate dihydrate as anticoagulant. Each sample will be analysed using a kit supplied by Platelet Solution Ltd (Nottingham, UK) to investigate the level of platelet activation before (baseline) and after activation with three platelet stimulants, followed by fixation. The fixed and stabilised samples are then posted to a central flow cytometry facility for analysis of platelet surface located P-selectin thus enabling quantitation of the level of platelet activation achieved. The overall analytical procedure will provide valuable information on changes in platelet function consequent to the clinical procedure

Appendix 6: Lead Principal Investigators and Recruiting Centres for the EURO SHOCK Study
(lead/country PIs in bold)

Centres Involved in EURO SHOCK	Lead Investigator
England	
0101 UHL	Banning/Yusuff
0103 Papworth Hospital	Hoole
0104 Barts Heart Centre London	Jain
0105 Kings College Hospital	Patel
0106 Harefield Brompton London	Rosenberg
0107 Guys	Barrett
0109 Derby	Chitkara
0110 Kettering	Raju
0111 Lincoln	Lee
Germany	
0201 Deutsches Herzzentrum München	**Kastrati**
0202 Klinikum rechts der Isar	Ibrahim / Laugwitz
0203 Universitäts-Herzzentrum Freiburg-Bad Krozingen	Valina
0801 Medizinische Universität Wien	Hengstenberg / Distelmaier
0207 Ludwig-Maximilians-Universität München	**Massberg / Orban**
0208 Klinikum Campus Innenstadt	Brunner
0210 Uniklinikum Tübingen	Schlensak
Scotland	
University of Glasgow	**Berry**
0108 Golden Jubilee National Hospital	Berry

Belgium	
0301 Katholieke Universiteit Leuven	**Adriaenssens**
0302 Algemeen Stedelijk Ziekenhuis Aalst	Buysschaert
0303 Onze Lieve Vrouw Hospital Aalst	De Raedt
0304 Jessa Ziekenhuis Hasselt	Timmermans
0305 Imelda Bonheiden	Dewilde
0306 University Hospital Antwerpen	**Haine / Vrints**
0307 ZNA Middelheim	Vermeersch
0308 AZ Gent	De Pauw
0309 AZ Monica	Everaert
0310 AZ Sint-Jan (Brugge)	Dewulf
0311 UCL (Bruxelles)	Van Caenegem
0401 Consorci Institut D'Investicacions Biomediques August Pi i Sunyer /Hospital Clinic de Barcelona	**Sabate**
0402 Hospital de Bellvitge	Ariza - Sole
0403 Hospital Germans Trias I Pujol	Mauri
0404 Hospital Vall d'Hebron	Garcia del Bianco
0405 Hospital de Sant Pau	Serra / Sionis
Norway	
0501 Universitetetsykehuset Nord Norge	**Myrmel**
Latvia	
0601 Paula Stradina Liniska Universitates Slimnica AS	**Erglis**
Italy	
0701 Azienda Ospedalierea Papa Giovanni XXIII	**Guagliumi**
0702 Azienda Universitaria Ospedaliera Careggi, Firenze	Di Mario

0703 Ospedale San Giovanni Bosco di Torino	Bocuzzi
0704 University Hospital of Bologna Policlinico S. Orsola – Malpighi	Saia

Appendix 7: Trial Committees

Trial Chief Investigator: Professor A H Gershlick
Sponsor : University of Leicester

Trial Committees

- **Steering Committee**

Chairs: Prof Anthony Gershlick; Independent Chair Prof Frans Van de Werf

- **Independent DSMB:**

Chair : Prof Freek Verheugt
Members Dr. Kadir Caliskan, Prof. Jan Tijssen

- **Clinical Events Committee:**

Chair: Dr Fernando Alfonso
Members Dr Rob Byrne , Dr. Marco Valgimigli, Dr. Elizabeth J Haxby

Trial Co-ordination

The trial central co-ordinating centre is the University of Leicester. The EURO SHOCK trial is a pan-European consortium of research centres, with the study being divided into nine interlinked work packages (see Appendix 2).
The trial organisation consists of a trial steering committee (Chairs: Prof A H Gershlick, Prof F Van de Werf), a clinical events committee (Chair: Dr F Alfonso) and an Independent Data Safety & Monitoring board DSMB (Chair: Prof F Verheugt).

The Trial Steering committee (TSC) will be responsible for scientific conduct of the study, ensure clinical governance, and provide guidance for issues arising during the study to recruiting centres. They will also co-ordinate a publication policy.
The Data Safety and Monitoring Board (DSMB) will monitor safety and ethical conduct of the study and outcomes, and with the support of an independent statistician, feed back to the TSC on a regular basis.

The clinical events committee (CEC) will independently adjudicate all clinical events.
In addition to the standard committees, EURO SHOCK also has the following advisory boards:

- External Advisory Board & Ethics Committee (Chair: Dr Art Slutsky)
- ECMO Advisory Panel (Chair: Dr A Vuylsteke)

The external advisory board will provide advice on scientific and technological matters as well as patient-related issues and will work with the DSMB regarding review of ethical conduct of the study. The ECMO advisory panel is composed of experts in the field of ECMO and will develop a standard guidance for the deployment of ECMO technology as well as providing technical expertise to the TSC pertaining to any issues around use of ECMO in the trial.

Clinical Trials Unit

University of Glasgow
Lead Dr Sharon Keane
Assistant Claire Kerr