Protocol for an economic evaluation of the randomised controlled trial of culprit lesion only PCI versus immediate multivessel PCI in acute myocardial infarction complicated by cardiogenic shock: CULPRIT-SHOCK trial

Zahidul Quayyum,1,2 Andrew Briggs,1 Jose Robles-Zurita,1 Keith Oldroyd,3 Uwe Zeymer,4 Steffen Desch,5 Suzanne de Waha,5 Holger Thiele6

ABSTRACT

Introduction Emergency percutaneous coronary intervention (PCI) of the culprit lesion for patients with acute myocardial infarctions is an accepted practice. A majority of patients present with multivessel disease with additional relevant stenoses apart from the culprit lesion. In haemodynamically stable patients, there is increasing evidence from randomised trials to support the practice of immediate complete revascularisation. However, in the presence of cardiogenic shock, the optimal management strategy for additional non-culprit lesions is unknown. A multicentre randomised controlled trial, CULPRIT-SHOCK, is examining whether culprit vessel only PCI with potentially subsequent staged revascularisation is more effective than immediate multivessel PCI. This paper describes the intended economic evaluation of the trial.

Methods and analysis The economic evaluation will be conducted using a pre-trial decision model and within-trial analysis. The modelling-based analysis will provide expected costs and health outcomes and incremental cost-effectiveness ratio over the lifetime for the cohort of patients included in the trial. The within-trial analysis will provide estimates of cost per life saved at 30 days and in 1 year, and estimates of health-related quality of life. Bootstrapping and cost-effectiveness acceptability curves will be used to address any uncertainty around these estimates. Different types of regression models within a generalised estimating equation framework will be used to examine how the total cost and quality-adjusted life years are explained by patients’ characteristics, revascularisation strategy, country and centre. The cost-effectiveness analysis will be from the perspective of each country’s national health services, where costs will be expressed in euros adjusted for purchasing power parity.

Ethics and dissemination Ethical approval for the study was granted by the local Ethics Committee at each recruiting centre. The economic evaluation analyses will be published in peer-reviewed journals of the concerned literature and communicated through the profiles of the authors at www.twitter.com and www.researchgate.net.

First economic evaluation of culprit only percutaneous coronary intervention (PCI) compared with immediate multivessel PCI within a trial with patients in cardiogenic shock.

The economic evaluation within the pragmatic multicountry trial design will enrich the external validity of results.

The methodological approach of a ‘fully pooled with multicountry costing’ will address heterogeneity in costs of resource use and drug prices across trial participating countries.

A pre-trial model is considered to extrapolate within-trial results in the long term for a lifetime economic evaluation.

Data completeness and plausibility checks are instituted in the electronic case report form to ensure robust and complete data collection.

BACKGROUND

Among all the patients admitted to hospitals in Europe with acute myocardial infarction (AMI),1 about 7%–8% develop cardiogenic shock and most of these patients (about 70%–80%) have multivessel coronary artery disease.2-4 In these patients, early mechanical reperfusion of the culprit lesion by percutaneous coronary intervention (PCI) is considered to be the most effective and important therapeutic measure.
However, even with advanced haemodynamic support, the mortality rate remains as high as 40%–70%.2–7 Immediate multivessel PCI may prevent potentially recurrent ischaemic cardiac events and improve outcomes but may also be associated with a higher risk of serious adverse events including iatrogenic myocardial infarction, contrast-induced nephropathy and an increased need for subsequent revascularisation procedures due to restenosis.8

There are uncertainties and differences regarding patient management. Current guideline recommendations in Europe suggest that primary PCI should be restricted to the culprit vessel with exception of cardiogenic shock and continuing ischaemia after PCI of the culprit lesion,8–10 while there are no specific recommendations by the American Heart Association/American College of Cardiology.1,8

Given the lack of randomised clinical trial data, a collaborative consortium of European partners (in Austria, France, Germany, Italy, Lithuania, The Netherlands, Poland, Slovenia, Belgium, Switzerland and UK) has been formed to conduct a large-scale prospective randomised, controlled, international multicentre trial.8 The trial is an attempt to determine the optimal percutaneous revascularisation strategy in patients with AMI and multivessel disease complicated by cardiogenic shock (see ref. 8 for further detail on trial design). The decision problems that the trial attempts to address are:

- Whether performing immediate culprit vessel only PCI with potential subsequent staged revascularisation reduces the incidence of the combined endpoint of 30-day mortality and severe renal failure (requiring renal replacement therapy) compared with immediate multivessel percutaneous revascularisation.
- Whether immediate culprit vessel only PCI improves quality of life compared with immediate multivessel percutaneous revascularisation.
- Whether culprit vessel only PCI with potential subsequent staged revascularisation is cost-effective compared with immediate multivessel revascularisation.

This study protocol addresses the third decision problem. The need for a cost-effectiveness analysis (CEA) relies on the fact that we could expect culprit vessel revascularisation to be a safer strategy for patients with cardiogenic shock and, at the same time, there are reasons to anticipate higher costs due to the need for subsequent staged revascularisation and different resources like mechanical support devices.

METHODS
Population, setting and location, and comparators
The details of the methods and design of the trial have been published previously in a separate manuscript.8 The CULPRIT-SHOCK study is a prospective, randomised, open-label trial in patients with multivessel coronary artery disease and AMI including both ST-elevation and non-ST-elevation myocardial infarction complicated by cardiogenic shock. The trial will recruit 706 patients with AMI with cardiogenic shock and multivessel disease, half of this population will be receiving culprit vessel only PCI with potentially subsequent staged revascularisation and the rest will receive immediate multivessel revascularisation by PCI. This international trial is conducted in approximately 100 centres of the 11 participating countries.8

Type of economic evaluation
The economic evaluation will be composed of both CEA and cost-utility analysis (CUA). The CEA will use the outcome measures of 30-day mortality and renal failure. Quality-adjusted life years (QALYs) will be used for the CUA.

Time horizon
The CEA will rely on the information collected during the first 30-day period after revascularisation. On the contrary, two different CUA will be considered: a within-trial economic evaluation using information collected during a 1-year follow-up period and economic evaluation based on a long-term model.

Study perspective
The economic evaluation will have health systems and societal perspectives. Initially, the costs for each type of revascularisation strategies will be derived from Germany’s national health service perspective. In addition, the perspective of each country’s national health service will also be considered.

Discount rate
The base case analysis rate that will be used for discounting future costs and effects will be 3% in accordance with the Institute for Quality and Efficiency in Health Care guideline.13 The discounting rate will be adapted to suit different payers’ perspectives in the 11 trial participating countries.

Identification, measurements and valuation of outcomes
The health outcome measures that will be used for the economic evaluation and endpoints of the data collection are presented in table 1.

The EuroQol five-dimensions (EQ-5D) three-level12 will be used to assess the quality of life for each patient. EQ-5D data will be collected at 1 month post procedure (follow-up on 30 days), 6 and 12 months after randomisation. The utility weights for each health states at different periods will be obtained by using the EQ-5D index tariff developed for the German population. Mean differences in EQ-5D between the groups will be estimated and will be presented with statistical tests of significance for the different follow-up periods. Country-specific tariffs will also be analysed. The probable imbalances in baseline utility will be adjusted to estimate differential mean QALYs as suggested by Manca et al.13
Identification, measurement and valuation of resource use

The primary objective of the cost analysis will be identifying, quantifying and valuing resources use accompanying the revascularisation strategies. The registry data on patients not randomised for the trial but collected within the project will also be used for supplementary information on resources use. The costs will be classified into the following major groups:

Intervention costs

The main items of the intervention costs (CInt) will include the resource use for index revascularisation procedure (PCI) and repeat/staged revascularisation procedure (PCI or coronary artery bypass surgery (CABG)). The resource use for investigations (eg, non-invasive evaluation for residual myocardial ischaemia at 1–4 weeks post index PCI of the culprit lesion such as nuclear perfusion scintigraphy, stress echocardiography or stress MRI) and other procedures (angiography, stenting, internal cardioverter defibrillator implants, extracorporeal membrane oxygenation, intra-aortic balloon pump, left ventricular assist devices, heart transplantation), treatments of renal failure, heart failure and major advanced cardiac events (MACE) will constitute the cost of health services use (CHServ). The electronic case report forms (eCRFs) are used for collecting all the above mentioned resources.

Cost of medication

Information on use of medications during the trial period is collected in eCRF to estimate the cost of medication (CMed).

Loss of productivity

Data on loss of days of work are collected using the eCRF. The cost of productivity loss (CostLp) for trial patients will be calculated using a human capital approach. Table 2 presents the resources items, data collection and source of unit cost. The costs will be converted into base year 2014 and will then be converted into euros using consumer price index and purchasing power parity conversion rates, respectively, provided by the Organisation for Economic Co-operation and Development.

The total cost (CTot) for each strategy will be given by the next equation:

\[ CTot = CInt + CHServ + CMed + CostLp. \]

The within-trial analyses of this multinational economic evaluation will employ a ‘multicountry costing’; that is, the source of clinical effectiveness and resource use data will be pooled, combined with country-specific unit costs. This will be contrasted with a ‘single-country’ approach of applying a single country’s unit costs to the whole trial dataset.

Modelling

A pre-trial decision model will be used for the long-term analysis.

Initially, the modelling exercise for the economic evaluation will be from Germany perspective and will be later adapted for the rest of the trial participating countries keeping the basic structure unchanged.

The population that will be considered in the model is similar to the patients included in the trial. The model is presented in schematic diagrams in figures 1 and 2. The figures show the stages or pathways of the patients. First stage (figure 1—initial procedure decision) is where the patients are provided with the revascularisation treatments. At this stage, the model will be based on a decision tree for the first year after randomisation. Assuming that the diagnostic angiography can correctly identify culprit lesions, the two options of treatment that are available for the patients are (1) immediate multivessel revascularisation of all vessels by PCI or (2) revascularisation by PCI of culprit lesion only and potentially staged revascularisation (either by PCI or CABG).

The patients after the index revascularisation and the planned staged revascularisation can die or can be alive with initial success of the treatment. Within 30 days, patients can survive with index revascularisation or can die. It is assumed that those who survive can either remain stable and alive or (1) can have renal failure or (2) can suffer from MACE (viz. ie, myocardial infarction/repeat infarction, stroke and revascularisation) or (3) have heart failure or (4) die due to cardiac events or other causes. Patients who survive initially from all these health states will move to the next stage shown in figure 2.

The next stage of the model (figure 2), a Markov model, shows the different health states for the patients for their lifetime period. It is assumed that the patients can move to one of the five different health states (similar to what is noted in figure 1). A patient who is alive and stable after

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>Means of data collection</th>
<th>Time of collection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>eCRF</td>
<td>30 days after randomisation, 6 and 12 months follow-up</td>
</tr>
<tr>
<td>Severe renal failure*</td>
<td>eCRF</td>
<td>30 days after randomisation, 6 and 12 months follow-up</td>
</tr>
<tr>
<td>Heart failure*</td>
<td>eCRF</td>
<td>30 days after randomisation, 6 and 12 months follow-up</td>
</tr>
<tr>
<td>MACE†</td>
<td>eCRF</td>
<td>30 days after randomisation, 6 and 12 months follow-up</td>
</tr>
<tr>
<td>Quality of life</td>
<td>eCRF</td>
<td>30 days after randomisation, 6 and 12 months follow-up</td>
</tr>
</tbody>
</table>

*Heart and renal failure are health conditions for which specific long-term treatment is needed.
†Major advanced cardiac events (myocardial infarction, non-fatal stroke and need for repeat revascularisation).

Table 2  The resource use, cost measures and means of data collections in Germany

<table>
<thead>
<tr>
<th>Resources use and costs measures</th>
<th>Means for data collection</th>
<th>Time of collection</th>
<th>Source of data for unit cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td></td>
<td></td>
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<tr>
<td>Multivessel revascularisation</td>
<td>eCRF</td>
<td>Baseline, 30 days, 6 and 12 months</td>
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<tr>
<td>Culprit vessel revascularisation</td>
<td>eCRF</td>
<td>Baseline, 30 days, 6 and 12 months</td>
<td>InEK</td>
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<tr>
<td>Repeat revascularisation</td>
<td>eCRF</td>
<td>Baseline, 30 days, 6 and 12 months</td>
<td>InEK</td>
</tr>
<tr>
<td>Health services use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>eCRF</td>
<td>Baseline, 30 days, 6 and 12 months</td>
<td>InEK</td>
</tr>
<tr>
<td>Other procedures</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Angiography</td>
<td>eCRF</td>
<td>Baseline, 30 days, 6 and 12 months</td>
<td>InEK</td>
</tr>
<tr>
<td>Stenting</td>
<td>eCRF</td>
<td>Baseline, 30 days, 6 and 12 months</td>
<td>InEK</td>
</tr>
<tr>
<td>ICD implant</td>
<td>eCRF</td>
<td>Baseline, 30 days, 6 and 12 months</td>
<td>InEK</td>
</tr>
<tr>
<td>ECMO</td>
<td>eCRF</td>
<td>Baseline, 30 days, 6 and 12 months</td>
<td>InEK</td>
</tr>
<tr>
<td>IABP</td>
<td>eCRF</td>
<td>Baseline, 30 days, 6 and 12 months</td>
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<td>eCRF</td>
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</tr>
<tr>
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<td>eCRF</td>
<td>Baseline, 30 days, 6 and 12 months</td>
<td>InEK</td>
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<tr>
<td>Treatment for MACE</td>
<td>eCRF</td>
<td>Baseline, 30 days, 6 and 12 months</td>
<td>InEK</td>
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<tr>
<td>Renal failure</td>
<td>eCRF</td>
<td>Baseline, 30 days, 6 and 12 months</td>
<td>InEK</td>
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<tr>
<td>Heart failure</td>
<td>eCRF</td>
<td>Baseline, 30 days, 6 and 12 months</td>
<td>InEK</td>
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<tr>
<td>Stroke</td>
<td>eCRF</td>
<td>Baseline, 30 days, 6 and 12 months</td>
<td>InEK</td>
</tr>
<tr>
<td>Medication</td>
<td>eCRF</td>
<td>Baseline, 30 days, 6 and 12 months</td>
<td>InEK</td>
</tr>
<tr>
<td>Loss of Productivity</td>
<td>eCRF</td>
<td>6 and 12 months follow-up</td>
<td>Destatis</td>
</tr>
</tbody>
</table>

Destatis, Federal Statistical Office; ECMO, extracorporeal membrane oxygenation; eCRF, electronic case report form; InEK, Institute for the Hospital Remuneration System; IABP, intra-aortic balloon pump; ICD, internal cardioverter defibrillator; LVAD, left ventricular assist device; MACE, major advanced cardiac events.

One year may suffer MACE and go back to alive and stable health state. It is also assumed that patients after having heart or renal failure can suffer from MACE and can go back and remain stable with the condition. Only the patients who remain alive and stable are assumed to transit to health states of renal or heart failure but the opposite pathway is not permitted. Finally, patients can also end up at absorbing health state death from all those health states.

Model parameters
The Markov model will be populated with transition probabilities and with cost and utility data conditional on health status. For the Markov stage, the transitions to different health states will be conditional on previous health state and on the type of revascularisation. The cycle length will be assumed to be 1 month. It is expected that there will be utility decrements accompanying renal failure, the possible adverse cardiac events and hence loss of QALYs. Values of the effectiveness parameters, transition probability of moving from health states and utilities will be based on the review of selected studies on clinical effectiveness and economic evaluations studies, previous reviews and expert advice from clinicians from trial participating countries. The model’s parameters are listed in online supplementary annex 1.

Statistical analyses of the trial data and registry data will provide more information that will enable us to have robust values for the pre-trial model parameters. With the survival analysis using trial data, the survival probability will be calculated to populate the model with revised transition probability to deaths that can be attributed to clinical conditions and MACE. The validation of model will be conducted by looking at the internal and external validity.

Analysis
Within-trial analysis
Statistical analyses and CEAs will be carried out using trial data where information on a range of resource use and outcome measures are collected at the patient level across the trial participating countries. The basis of analysis will be intention to treat.

Handling missing data
Cost data are characterised by severe skewness in their probability distribution and it may be the case
that a few patients may have very high resource use and hence high cost, and a large number of patients may have low cost. There may be incomplete data and cost data can be missing at individual item level. Appropriate methods will be used to treat missing information. Multiple imputation method has been widely recommended by experts and by ISPOR as this method helps to reveal the uncertainty that occurs where the missing data are replaced in the imputation process. A descriptive analysis will be undertaken to check the nature of missing data before such method is used. As suggested by Faria et al, a sensitivity analysis will be conducted to examine the impact of alternative assumptions about the mechanism of missing data.

Base case analysis and regression

Baseline characteristics of the patients in the two different intervention groups will be summarised. Differences in resource use and costs between the two groups will be tested using two-sample t-tests (or non-parametric equivalents) and $\chi^2$ tests for continuous and categorical variables, respectively. The mean costs of resource use in each arm of the care intervention and the differences in costs between the two arms will be calculated with 95% CIs. Similarly, the mean QALY score for each group will be estimated.

Regression analyses will be conducted to examine how the total cost and health outcomes may be explained by the patient characteristics, intervention type, country and centres. Different types of models will be explored within generalised estimating equation framework that can take into account the clustering of the data within the countries.

**CEA with trial data**

CEA will be presented as incremental cost per 30-day mortality averted and incremental cost per QALY gained. The incremental cost-effectiveness ratio (ICER) will be calculated as:

$$\text{ICER} = \frac{\text{Cost}_{\text{mv}} - \text{Cost}_{\text{co}}}{\text{QALY}_{\text{co}} - \text{QALY}_{\text{mv}}}$$

where $\text{Cost}_{\text{co}}$ is the total cost of treating the patients by revascularisation of the culprit vessel only and $\text{Cost}_{\text{mv}}$ is the total cost of treating the patients by immediate multivessel revascularisation. $\text{QALY}_{\text{co}}$ is total QALYs for the patients having culprit vessel revascularisation only and $\text{QALY}_{\text{mv}}$ is total QALYs for the patients having immediate multivessel revascularisation.

Subgroup analyses for gender, age groups (<50 years, 50–75 years, >75 years) and patients with diabetes will be considered to address the issue of underlying heterogeneity. The results of the cost-effectiveness including the subgroup and sensitivity analyses will be presented both in terms of point estimates and cost-effectiveness planes, and cost-effectiveness acceptability curves (CEACs).

The two revascularisation strategies will be also compared on the basis of incremental net monetary benefits. The net monetary benefit of revascularisation multivessel (strategy 1) or revascularisation of culprit vessel only (strategy 2) will be calculated as: the mean QALYs ($q_i$) multiplied by the acceptable threshold values for a QALY.

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**Figure 1** Post index revascularisation, from 30 days to 1 year. AMI, acute myocardial infarction; MACE, major advanced cardiac events.
(\(\lambda\)), minus the mean cost of implementing the strategy.\(^1\)
This can be given as:

\[ NMBi = \lambda qi - ci, \]
where \(i = \text{strategy 1 or strategy 2}. \)

The threshold value (\(\lambda\)) should be interpreted as the monetary value of a QALY. Different values will be used for different countries assuming that this parameter will be different or may be unknown.

**The effectiveness measure and CEA in the model-based analysis**

The effectiveness measure for economic outcomes in our model-based analysis will be QALYs. Model results will provide estimates for the ICER considering long-term health outcomes and costs.

The results of the economic evaluation including the subgroup and sensitivity analyses will be presented in terms of point estimates, cost-effectiveness planes and CEACs.\(^25\)

**Handling uncertainty**

To present the robustness of our estimation of cost-effectiveness non-parametric bootstrapping techniques will be used.\(^26\) CEACs will illustrate the uncertainty surrounding the estimate of cost-effectiveness.\(^25\) This curve will show us the probability of culprit only revascularisation strategy to be cost-effective compared with the immediate multivessel revascularisation strategy for a range of monetary values of a QALY. Both probabilistic and deterministic sensitivity analyses will be used to explore statistical and other forms of uncertainty arising from the imprecision with which model parameters are estimated.

**Value of information**

Value of information analysis will also be conducted. Such analysis will help to determine whether additional research will be required to inform the future decision.\(^27\)

**ETHICS AND DISSEMINATION**

Ethical approval for the study was granted by the local Ethics Committee at each recruiting centre. Ethical approvals by the lead ethical committees for each country are: (a) Germany, Ethical Committee at the University of Luebeck: reference number 13-142; (b) Netherlands, Medisch Ethische Toetsingkommissie (Academisch Medisch Centrum, University of Amsterdam): reference number E2-170; (c) Austria, Magistratsabteilung 15-Gesundheitsdienst der Stadt Wien: reference number EK-13-241-0214; (d) Lithuania, Lietuvos Bioetikos Komitetas: reference numbers L-14-01/1 and L-14-01/2; (e) France, Comité de Protection des Personnes, Ile de France 1: reference number 2014-janvier.-13464; (f) Poland, Klinika Intensywnej Terapii Kardiologicznej: reference number IK-NP-0021-97/1408/13; (g) Slovenia, Komisija Republike Slovenije za medicinsko etiko: reference numbers 63/12/13 and 60/09/14; (h) Switzerland, Kantonale Ethikkommission Bern (KEK): reference number 041/14; (i) Italy, Comitato Etico Provinciale di Reggio Emilia: reference number 2013/0029992; (j) Belgium, Universiteit Antwerpen (Ethics Committee): reference number 15/11/116; (k) UK, National Health Service (NHS) (Scotland Research Ethics Committee): reference number 14/YH/0116; and (l) Scotland, NHS (Scotland Research Ethics Committee): reference number 14/SS/0072.

The economic evaluation analyses will be published in peer-reviewed journals of the concerned literature and communicated through the profiles of the authors at www.twitter.com and www.researchgate.net.

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**Figure 2** Post 1 year and end of life—Markov model. MACE, major advanced cardiac events.
DISCUSSION
This will be the first economic evaluation where effectiveness of culprit only PCI with potential staged revascularisation will be tested against immediate multivessel PCI within a trial. A pre-trial decision model will provide estimates of incremental cost per QALY generated by culprit vessel revascularisation over the practice of all vessel revascularisation. According to a previous analysis performed by us, based on a simulation of this model populated with parameters from the literature, an ICER of about £2000/QALY is expected. However, there is a large uncertainty around these estimates since existing evidence on the two strategies compared is based on observational data rather than on randomised control trials. We acknowledge that parameters could be biased and changing just one parameter (eg, probability of MACE, or renal failure or cost of MACE) could increase the ICER to about £12 000.

On the contrary, the within-trial analysis would help to obtain robust values for the pre-trial model parameters and the survival analysis will provide revised transition probability to deaths that can be attributed to clinical conditions and MACE. Transferability of the decision-analytical model can be improved by using the jurisdiction-specific price weights and baseline risk of health states.

The results on predicted costs and outcomes from trial-based economic analysis will help to conduct extrapolated analysis beyond the trial period using the decision model incorporating the sensitivity analyses and subgroup analysis.

Strengths
This economic analysis of the largest randomised trial in cardiogenic shock will provide detailed health economic analyses further supporting potential treatment strategies in cardiogenic shock. The economic evaluation within the pragmatic multicountry trial design will enrich the external validity. This will enable us to assess the value of the revascularisation strategies for patients with cardiogenic shock in a real-world scenario.

Limitations
Given that there are differences in the health systems and reimbursement policy in the trial participating countries, potential differences in the unit prices of similar healthcare resources and medications are expected to be found. Trial-wide estimates of CEAs will suffer from problems associated with heterogeneity in costs of resource use and drug prices across trial participating countries. The methodological approach of a ‘fully pooled with multicountry costing’ framework will address this potential problem.

There is a particular challenge with respect to data collection given that the existence of missing information could affect the validity of the results. In that case, statistical techniques will be used to handle missing data. Nonetheless, an automated data check for completeness and data plausibility has been instituted in the eCRF to ensure robust and complete data collection. Furthermore, monitoring ensures data completeness and data plausibility—a final close-out monitoring visit is mandatory for all centres. In addition, case payment is only performed if all data are complete in the eCRF and data are checked for plausibility.

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Contributors
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