Health Technology Assessment (HTA)

Stakeholder Feedback: Revascularization versus optimal medical therapy (OMT) for the treatment of chronic coronary syndrome (CCS)

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Preface

This document details the authors' responses to stakeholder feedback on the protocol for an HTA on *revascularization versus optimal medical therapy (OMT) for the treatment of chronic coronary syndrome (CCS)*

The stakeholder feedback and corresponding author responses are detailed in tables. The tables are listed by stakeholder, in alphabetical order.

Where multiple stakeholders provided similar feedback, the authors have only provided a response to the first comment; subsequent comments instruct the reader to cite the original response in the format i. ii. iii., representing the i. Stakeholder, ii. Domain, and iii. Comment number.

1. Curafutura

Domain	Comment	Author response
1. Comments on research questions	1. In der Fragestellung sollte auch miteinbezogen werden, welche interventionelle Revaskularisationsstrategie besser ist (CABG vs. PCI) 2. Es ist darauf zu achten, dass die aktuellen amerikanischen Guidelines (ACC/AHA/SCAI) nicht übereinstimmen in ihren COR für die interventionellen Strategien (CAGB / PCI) mit den europäischen Guidelines von ESC/EACTS. 3. Es ist fraglich, ob sich die Frage 2 in 6.1 beantworten lässt respektive ob sich bei allen primären OMT-Patienten die Anzahl der betroffenen Gefässe beziffern lässt. Das würde ja heissen, dass bei den Einschlusskriterien zwingend eine Koronarangiographie vorhanden sein müsste. 4. Frage 3 in 6.1 dürfte, wenn man sich auf die DES der dritten Generation beschränkt, nicht mehr relevant sein, respektive die Anzahl der Patienten zu tief für eine Aussage.	1. Feedback we have received from clinicians, and guidelines, suggests that CABG and PCI are invariably used for different clinical presentations, and are not necessarily comparators to one another. 2. Noted. International guidelines will be summarised in the HTA report. 3. This question will be removed from the HTA protocol. 4. This question will be removed from the HTA protocol.
2. Comments on PICO	1. PICO ist korrekt, allerdings müsste noch erwähnt werden, ob auch Patienten mit Vorinterventionen (PCI, CABG) ein- oder ausgeschlossen werden. 2. Der Surrogat-Marker «subsequent coronary artery revascularisation» für Hospitalisation ist nur bedingt brauchbar, da einfache Revaskularisationen (PCI) als outpatient procedure gemacht werden können.	1. It is stated in **Section 5.1** that patients who have previous undergone revascularisation will be included. A subgroup analysis described in **Section 7.1.5** intends to investigate whether previous revascularisation has an impact on outcomes vs. treatment naïve patients. 2. Acknowledged. Please note, hospitalisation is defined in the ICHOM Standard Set for coronary artery disease by i) indication (i.e. acute myocardial infarction, stroke, heart failure), and ii) procedural intervention. In this case, revascularisation is included as a separate outcome from hospitalisation.
3. Comments on databases and search strategy	1. Zeile 683: Das Kriterium hier genügt nicht, es sollte auch quantifiziert werden (< oder > 70%). 2. Zeile 690: "prior revascularisation" ist zu unspezifisch: Man sollte unterscheiden zwischen PCI und CABG. 3. 844: 5 Jahre sind nicht ausreichend, um die Überlegenheit von CABG im Vergleich zu PCI zu etablieren. Besser: 10 Jahre	1. Thank you for this feedback. We have updated this to LMCA >50% per the ESC guidelines on revascularisation of CCS patients (Neuman et al., 2018). 2. Thank you for this feedback. We have changed this into two subgroups, one reflecting prior PCI vs. treatment naïve patients, and one reflecting prior CABG vs. treatment naïve patients. 3. See author response **1.1.1**. Neumann F-J, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *European heart journal* 2019;40(2):87-165.
4. Comments on data	1. Diese HTA soll aus der Perspektive des KVG erfolgen. Trotzdem würden wir es begrüssen, wenn die gesundheitsökonomische Evaluation die durch	1. There are invariably indirect costs associated with every medical intervention. The main policy interest of the Swiss HTA program is efficiency in the health

Domain	Comment	Author response
extraction, analysis and synthesis	Krankheit oder frühzeitigen Tod verursachten Produktivitätsverluste zumindest schätzen bzw. diskutieren könnte. Die CCD betreffen auch Personen im arbeitsfähigen Alter, die Einschränkung auf die Perspektive der OKP ist deshalb zu eng gefasst.	system. In this regard, only direct medical costs are considered, by taking a healthcare payer perspective. Broader, societal costs are considered to be outside the scope of work.

2. Santésuisse

Domain	Comment	Author response
1. Comments on research questions	1. Wichtige Fragen zum Vergleich von invasiven mit konservativen Behandlungen des CCS werden adressiert. In Anbetracht der verschiedenen Formen, Ausprägungen und Pathologien etc. der CCS sowie der unterschiedlichen invasiven und/oder konservativen Behandlungen erscheinen die Forschungsfragen trotz Zusatzfragen sowie Subgruppenanalysen möglicherweise zu summarisch. Damit bleibt unklar, wieweit relevante und robuste Erkenntnisse zur Beantwortung der Entscheidungsfragen gewonnen werden können. Wichtig wäre die Klärung, welche Patienten zu welchem Zeitpunkt von welchen invasiven Behandlungen (z.B. PCI oder CABG) am Meisten profitieren? 2. Wir empfehlen die Überprüfung der Fragestellung mit den zuständigen Facharztgesellschaften (bzw. aufgrund deren Stellungnahmen) sowie anhand der vertiefen Analyse der vorhandenen Literatur bzw. Daten.	1. The pre-planned subgroup analyses aim to address this research question, noting that these analyses will always be limited by the availability of data. The HTA can only answer the questions within the limitations of secondary research. 2. Thank you for this suggestion. Independent Swiss clinicians were engaged during the production of the HTA Protocol, and will continue to be engaged during the HTA report. Stakeholders will have the opportunity to comment on the draft HTA report, in accordance with the FOPH's review process.
2. Comments on PICO	1. Population, Intervention: S. Anmerkung unter 1. 2. Die fehlende Berücksichtigung der Unterschiede in der OMT sowie der nicht-pharmakologischen Lifestyle-Modifikation könnte potentielle relevante Störgrössen darstellen. 3. Outcome: Die Validität von MACE kann anhand der Angaben nicht beurteilt werden. Die Eignung der Revaskularisation als Indikator für die Hospitalisation ist zu prüfen.	1. See author response **2.1.1**. 2. We acknowledge that differences between OMT regimens may introduce confounding across included studies. Practically, it is not possible to discern and define OMT in the inclusion criteria, as the majority of RCTs identified during scoping have not done this. In the HTA, we will identify and report what was included as "OMT" in each trial, and compare and contrast this with expected practice in Switzerland. Importantly, assuming trials are randomised correctly, the risk of confounding will be minimised in the reported relative effects reported in the RCTs, and will mainly be applicable to the absolute effects reported across studies. Non-pharmacological lifestyle modifications are outside the scope of the research question. 3. Thank you for this feedback. MACE will be kept as it is a composite outcome that is routinely used in clinical practice. The sentence defining revascularization as an indicator for hospitalization has been reviewed. However, revascularization will remain as a relevant outcome as it has been included as a separate outcome, per the ICHOM standard outcome sets. ICHOM distinguishes between admissions due to a condition (i.e. myocardial infarction, stroke, heart failure), and due to a procedural intervention (i.e. PCI or CABG)
3. Comments on databases	1. Auch wenn bei der Suche in mehreren Datenbanken Überschneidungen zu erwarten sind, sollten für eine Literaturrecherche im Rahmen eines HTA mehr als vier Datenbanken verwendet werden. In der Regel werden die	1. The method we use for clinical evaluations in HTAs is largely guided by the Cochrane handbook, which recommends MEDLINE, Embase, and the Cochrane Library (Higgins et al, 2022). Additional databases may be

	and search strategy	Datenbanken Cochrane Library, Embase, GoogleScholar, PubMed sowie ClinibalTrials.gov berücksichtigt. 2. Insbesondere letztere ist wichtig, um laufende Studien und Informationen berücksichtigen zu können.	searched, depending on the research question and topic area. For this project, we have included MEDLINE, Embase, The Cochrane Library, the INAHTA database, EconLit, and the International Clinical Trials Registry Platform. In addition, a long list of grey literature sources, including Google, are included in the targeted search strategy for literature relating to the auxiliary domains. Google Scholar is not recommended as a reproducible data source for systematic reviews (Gusenbauer and Haddaway, 2019). 2. The search strategy (**Section 7.1.1**) specifies that we will search the International Clinical Trials Registry Platform, which indexes 18 different clinical trials registries, including clinicaltrials.gov. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook. Gusenbauer M, Haddaway NR. Which academic search systems are suitable for systematic reviews or meta-analyses? Evaluating retrieval qualities of Google Scholar, PubMed, and 26 other resources. *Res Synth Methods* 2020;11:181-217.
4.	Comments on data extraction, analysis and synthesis	1. Eine unabhängige Kosten-Nutzen-Analyse unter Berücksichtigung der Schweizer Verhältnisse wird unterstützt.	1. Thank you for the feedback. No change required.

3. Schweizerische Gesellschaft für Kardiologie (SGK)

Domain	Comment	Author response
1. Comments on research questions	1. Generally, SGK voices concerns regarding the expertise of the authors of this HTA it is obvious that non-experts were involved in view of numerous substantial errors and misinterpretations (space limitation does not allow further specification). The "Executive Summary" is not specific, the aim is unclear. General statements are used and not a specified plan. The statement that the efficacy and safety of PCI or CABG vs OMT is unclear is outdated. 2. Different meta-analyses exist on this specific topic. It should be evaluated whether an update of previous meta-analyses should be considered a. (doi: https://doi.org/10.1136/bmj.i3507) to answer some of these questions. 3. Not only quality of life and mortality are important endpoints but in addition the reduction of angina and spontaneous myocardial infarctions. 4. The external validity of RCT data has to be explored. E.g. in the ISCHEMIA trial, 3 patients per site&year were enrolled and <30% of CCS patients are reflected by the eligibility criteria.	1. The policy question has been directed by the FOPH, on the basis of ongoing debate around the optimal choice of treatments in this population. The aim of the HTA will be to provide a contemporary analysis of the evidence addressing the policy question. 2. As stated in **Section 7.1.2** and **Section 7.1.5**, we will endeavour to include existing reviews where available. 3. As stated in **Section 5**, cardiac-specific quality of life tools that measure the impact of angina have been included in the PICO criteria (e.g. SAQ-7), as has hospitalisation due to myocardial infarction, in accordance with the ICHOM Standard Set for patients with coronary artery disease. 4. The external validity of all included studies will be considered as part of the GRADE appraisal, which considers the applicability of the evidence base to the policy context. This will be conducted during the HTA phase.
2. Comments on PICO	1. Under "Study design" (page 26) it is not clearly defined the design of studies will be considered eligible in this review. It should be clearly defined the design of studies will be considered for this (prospective/retrospective non-randomized, randomized, meta-analysis). 2. The individual interventions are not comparable. Patients undergoing PCI with either 3rd generation DES or DCB cannot be compared with patients undergoing CABG. (PICO criteria – TABLE 1). In the same way, patients/lesions undergoing treated with PCI with 3rd generation DES are not comparable with those treated with PCI with BMS or DCB. 3. How different definitions of the same outcome, or different components of the same composite endpoint in different studies will be jointly considered? 4. The outcome of symptom relief in terms of angina, should be clearly and separately considered, and not only as part of QoL tools. The primary aim of PCI in CCS is relief of angina and the efficacy in this regard is overly proven.	1. The study selection criteria in **Section 7.1.2** clearly state that both randomised and non-randomised studies are eligible for inclusion. This implies all study designs within each level of evidence, except those specifically excluded from the report, will be eligible for inclusion, and subjected to risk of bias assessment using appropriate tools. 2. These comparisons are not relevant to the current HTA. PCI and CABG are not being compared in the proposed HTA, neither are types of PCI. These are being compared individually to the listed comparator, which is OMT. 3. All outcomes have been defined in accordance with the ICHOM Standard Set for patients with coronary artery disease. Each outcome is either a composite (e.g. MACE) or specific, patient-relevant primary outcome. These will be reported separately in the report. Variations in the way that individual studies have defined these outcomes will be considered during the HTA phase, and the comparability of the outcomes will be considered carefully before any decisions are made about which studies to include in meta-analyses. 4. See author response **3.1.3**.

Domain	Comment	Author response
3. Comments on databases and search strategy	1. The medical literature searches are not adequate. It is very specific but not sensitive. Also dedicated broadly used websites for clinical trials registration are not included (i.e.clinicaltrials.gov). 2. Why did you include "grey literature" 3. How will be addressed the issue of different reports on overlapping study populations of follow-ups at different time-points? 4. Dedicated searches should be built focusing on the interventions of interest and avoiding the names of the trials among the keywords. 5. A dedicated search should be focused on identifying meta-analyses in the specific field, to better understand the "lack of evidence" or the need to update previously published meta-analyses. 6. Dedicated searches should be built to identify relevant "economic evaluation" studies of the interventions of interest 7. Why only studies performed in WHO Mortality Stratum A will be included?	1. This is incorrect. The searches have been designed to capture all evidence that relates to the Population, Intervention, and Comparators (PIC). As we are only including comparative evidence, all of these fields need to be identified in an article for it to be considered for inclusion. We have not included Outcome terms as this limits the sensitivity of the searches. The keywords used within each of the PIC domains are combined with the Boolean operator "OR", and each PIC domain is combined in the string with the Boolean operator "AND". This means that every additional keyword added (including clinical trials names) within each of the PIC domains increases the sensitivity of the search. Further, the search strategy (**Section 7.1.1**) specifies that we will search the International Clinical Trials Registry Platform, which indexes 18 different clinical trials registries, including clinicaltrials.gov. 2. Grey literature is sourced for three main reasons: First, to identify ongoing clinical trials that may impact the results of the HTA in the near future; second, to identify government reports that may inform the auxiliary (i.e. social, legal, ethical, organisational) and economic domains of the report; third, to identify existing HTA reports on the same topic. This is a standard method in HTA reports. 3. Each RCT only contributes a single data point into each analysis. During data extraction, all relevant outcomes from included studies are extracted, and the most appropriate data point from each RCT is included (e.g. largest sample size, most appropriate time-point). 4. This is incorrect. See comment **3.1.1**. Removing these keywords would reduce the sensitivity of the searches and potentially miss key trials. 5. This is incorrect. Adding a methods filter will reduce the sensitivity of the searches. The searches, as constructed, will identify all relevant publication types that meet the PICO criteria, including meta-analyses. 6. This is incorrect. Adding a methods filter will reduce the sensitivity of the searches. The searches, as constructed, will identify all relevant publication types that meet the PICO criteria, including economic studies. 7. Mortality Stratum A countries are selected as they represent countries with a similar level of disease burden, mortality burden, and socio-economic development as Switzerland. This is done to minimise applicability issues with studies from settings that do not reflect Swiss practice.

Domain	Comment	Author response
4. Comments on data extraction, analysis and synthesis	1. The data extraction items should be adapted according to the design of the included studies. The current version doesn't precisely define this. 2. It is unclear which kind of data will be derived from provided graphs/figures with the WebPlotDigitizer? 3. It is not clear what is considered "enough evidence", which will not require further quantitative synthesis in terms of meta-analysis. 4. The current analysis plan is broad and non-specific. It should be better clarified, once the study inclusion criteria are defined. If different study designs will be considered, 5. In this setting, what is the purpose of imputing missing data? Missing data is already an important information on quality assessment of the available evidence. 6. Regarding the economic evaluation: the CHEERS 2022 statement (doi: 10.1136/bmj-2021-067975) is recommended which ensures that health economic evaluations are identifiable, interpretable, and useful for decision making.	1. We have added a note that the templates will be refined during the HTA phase, depending on the study design. Please note, data extraction templates are not designed until after study selection has been completed during the HTA phase, i.e. once we know what types of study designs need to be extracted, and why type of data are reported. 2. WebPlotDigitizer measures the scale of a graph, and uses this scale to provide quantitative values for data that is otherwise only presented graphically (e.g. it converts dot points on a graph into a numerical value). 3. For meta-regressions, at least 10 studies must be included. This is stated in **Section 7.1.5**. For pairwise meta-analysis, at least 2 studies must be included, this has been added to the protocol. 4. We disagree. The study selection criteria are defined (See **Table 2**), and the analysis section describes how different types of outcomes and subgroups will be evaluated. 5. In this context, imputation is planned to be used to transform data from one measure into another (e.g. transforming a 95% confidence interval or standard error into a standard deviation). It is not necessarily an indicator of poor study design or reporting. Risk of bias issues are considered through the application of study design-appropriate tools, e.g. Cochrane ROB 2.0 for RCTs. 6. Thank you for this suggestion. We will consider the CHEERS 2022 statement when reporting the economic evaluation in the HTA phase.

4. Schweizerische Gesellschaft der Vertrauens- und Versicherungsärzte (SGV)

Domain	Comment	Author response
1. Comments on research questions	Mit dem Zweck, eine Kosten - Nutzen - Analyse der Behandlungsmöglichkeiten des chronischen Koronarsyndroms durchzuführen, ist eine grosse HTA-Arbeit vorgesehen. Aus medizinischer Sicht ist die Literatur bei den zuständigen Ärzten bestens bekannt, wird im Einzelfall gemäss aktuellem Stand des Wissens entschieden, wer welche Behandlung bekommt. Die geplante Analyse dient der Kostenaufschlüsselung bezüglich Lebensqualitätsgewinn. Aus Sicht der Vertrauensärzte ist dies zwar eine wichtige Fragestellung, es ist aber zweifelhaft, ob sich aus den vorgesehenen Informationsgewinnen effektiv eine praktische Auswirkung auf irgend einen Anteil der Kosten ergibt. Zu viele Faktoren spielen eine Rolle, zu heterogen ist die Population der Patienten in der kleinen Schweiz. Jedoch kann eine Beleuchtung der Schweizer Situation wichtige Inhalte zu den aktuellen Realitäten bei uns, verglichen mit anderen Gesundheitswesen, aufzeigen. Dass aufgrund dessen Tarife/Abgeltungen abgeändert werden, scheint unsicher.	Thank you for taking the time to provide feedback on the HTA protocol. The HTA will indeed evaluate the cost-effectiveness of different options for treating patients with Stable CAD, considering Swiss-specific costs and Tariff structures.
2. Comments on PICO	N/A	N/A
3. Comments on databases and search strategy	N/A	N/A
4. Comments on data extraction, analysis and synthesis	N/A	N/A

5. Swiss Medtech

Domain	Comment	Author response
1. Comments on research questions	1. Wir schätzen die breite Anlegung des systematischen evidence review. Die im Protokoll-Entwurf genannten ergänzenden Untersuchungsfragen (HTA Protokoll S. 16) und das dargestellte Subgruppen-Design (HTA Protokoll S. 22 ff.) sind zur Ausdifferenzierung hilfreich. Um dem heterogenen Charakter der CCS Patienten noch besser gerecht zu werden, schlagen wir außerdem vor: a) den Schweregrad der CCS zu berücksichtigen (z.B. Syntax score), b) Hochrisikogruppen, z.B. last remaining patent vessel situation, "surgical turndown patients" (mit zu hohem Risiko für CABG) getrennt zu betrachten, und c) verschiedene PCI- (unterstützende) Techniken (u.a. Rotablation, Atherektomie, Scoring-, Cutting-, Kissing Balloon, mechanische Kreislaufunterstützung bei PCI) bei der Analyse zu berücksichtigen. 2. Wir weisen außerdem darauf hin, dass der Patientenwunsch in den aktuellen Leitlinien bei Therapieentscheidungen als wichtig erachtet wird und deshalb in den HTA conclusions zu berücksichtigen ist.	1. Thank you for this suggestion. Currently, ***Section 6.1 questions 1 and 2*** already assess high risk groups (e.g. co-morbidities, LMCA, LVEF, etc.) and the impact of disease severity (e.g. LMCA). Last remaining patent vessel (LRPV) situation will not be added as a subgroup as it is extremely rare to preform PCI in LRPV patients, for example during a 7 year period in England and Wales, only less than 0.5% of 500,691 PCIs were performed on LRPV patients (Shoaib et al. 2020). Similarly, the use of mechanical circulatory support (MCS) in PCI will not be included as a subgroup as it is an extremely rare occurrence. In the USA, between 2007 and 2017 the use of MCS during PCI ranged between 0.2% and 0.6% (Zeitouni et al. 2022). The use of rotablation and atherectomy as concurrent procedures to PCI will not be considered as it is beyond the scope of this HTA. Finally, clinical experts did not highlight the importance and frequent use of kissing and cutting balloons during PCI in CCS patients, therefore, these techniques will not be assessed using subgroups. 2. Thank you for this suggestion. Patient and social factors will be considered in the auxiliary domains of the HTA report (see **Section 7.3** of the protocol). Shoaib A, Rashid M, Kontopantelis E, Sharp A, Fahy ,EF, Nolan J, Townend J, Ludman P, Ratib K, Azam ZA, Ahmad A. Clinical characteristics and outcomes from percutaneous coronary intervention of last remaining coronary artery: an analysis from the British Cardiovascular Intervention Society Database. Circulation: Cardiovascular Interventions. 2020 Sep;13(9):e009049 Zeitouni M, Marquis-Gravel G, Smilowitz NR, Zakroysky P, Wojdyla DM, Amit AP, Rao SV, Wang TY. Prophylactic Mechanical Circulatory Support Use in Elective Percutaneous Coronary Intervention for Patients With Stable Coronary Artery Disease. Circulation: Cardiovascular Interventions. 2022 May;15(5):e011534.

2. Comments on PICO	1. Patients: Ausschlusskriterium sollten CCS Patienten ohne Angina oder Ischämienachweis sein. 2. Intervention: Ausschlusskriterium sollten Studien der ersten DES Generation sein, nicht jedoch der zweiten DES Generation, d.h alle "new generation" DES (gem. ESC Leitlinien, vgl. HTA Protokoll Ref. 34) sollten miteingeschlossen werden. 3. Outcomes: Gemäß Leitlinien (vgl. HTA Protokoll Ref. 34, Kap. 5.3.1.3) ist eine möglichst vollständige Revaskularisierung Therapieziel für CCS Patienten. Deshalb schlagen wir vor "Completeness of revascularisation" als endpoint aufzunehmen. 4. S.12 und 14 erwähnen MACE als relevanten Endpunkt wie folgt: "MACE will only include all-cause mortality, MI, revascularisation, hospitalisation and stroke". Andere relevante MACE Definitionen existieren und sollten in Erwägung gezogen werden. Wichtige Endpunkte wie Death from Cardiovascular Causes, sollten ebenfalls berücksichtigt werden. 5. S.14., Linie 522 - "Inadequate Data" – Dieser Punkt könnte genauer erklärt werden.	1. Thank you for this suggestion. The PICO criteria currently states that asymptomatic patients will be excluded from the analysis. 2. Thank you for this suggestion, clinical reviewers overwhelmingly indicated that third generation DES are predominantly used in Switzerland. We could reconsider adjusting the study selection criteria if we had evidence for how much of each generation of device is used in Switzerland; in the absence of such data, we defer to expert advice. 3. Thank you for this suggestion. Unfortunately, this outcome is not included in the ICHOM Standard Set for patients with coronary artery disease. We note that the consequences of “revascularisation completeness” will effectively be captured under other outcomes included in the PICO criteria (e.g. patient-reported, disease-specific quality of life scores [SAQ-7]). 4. We acknowledge that there are other definitions of MACE in the literature. The definitions included in this HTA are defined per the ICHOM Standard Set for coronary artery disease. Cardiovascular mortality was excluded as it is less meaningful outcome than all-cause mortality in CCS patients (McNamara et al. 2015). Cardiovascular-related mortality only captures deaths attributable to cardiac events. All-cause mortality captures deaths attributable to revascularisation procedures (e.g. infection, bleeding, etc.) or OMT. Furthermore, the validity of cardiovascular-related mortality data is limited as it can be difficult to clinically adjudicate the cause of death. 5. “Inadequate data” can refer to many reasons that would prevent the data from being reliably included in an analysis, e.g., missing measures of variance, data that contains errors (e.g. identified through comparing figures to values reported in-text), mis-matched sample sizes, etc. We have added some examples to the protocol. McNamara RL, Spatz ES, Kelley TA, et al. Standardized Outcome Measurement for Patients With Coronary Artery Disease: Consensus From the International Consortium for Health Outcomes Measurement (ICHOM). *J Am Heart Assoc* 2015;4(5)
3. Comments on databases and search strategy	N/A	N/A

4. Comments on data extraction, analysis and synthesis	1. Auf Seite 23 des Protokolls (pdf-Seite 30), bei der Auflistung der Subgruppen, schlagen wir eine Ergänzung folgender Punkte vor: - Complexity of coronary anatomy with SYNTAX Score 1 - Last remaining patent vessel (LRPV) situation - Multivessel treatment during one procedure 2. Behandlungsziele sollten bei der Analyse berücksichtigt werden, vor allem bei der Gewichtung/Priorisierung der Endpunkte bei der Bewertung des "overall body of evidence". Symptom- und Lebensqualitätsverbesserung sind vor allem bei Patienten mit häufigen Episoden als Behandlungsziel mindestens genauso wichtig wie Morbiditäts- und Mortalitätsverbesserung.	1. See author response **5.1.1**. 2. Thank you for this suggestion. Please note that we have not weighted outcomes in terms of relative importance. Rather, we select only outcomes that are directly clinically relevant to the patient group. In accordance with the GRADE approach, we try to minimise the list of relevant outcomes to 7. Indeed, we have included quality of life measures in the list of relevant outcomes.
Appendix document	1. a.Ergänzende Ausführungen zur Forschungsfrage: Die Unterscheidung von Patienten mit koronarer Herzkrankheit (Coronary Artery Disease, CAD) in Patienten mit CCS oder ACS [HTA Protokoll Referenzen 1 & 5] stellt ein wichtiges, aber nicht das einzige Kriterium dar, welches beim Therapieentscheid herangezogen wird, und ist somit für die Beantwortung der Forschungsfrage nicht ausreichend differenziert. b. Die im Protokoll-Entwurf genannten ergänzenden Untersuchungsfragen (HTA Protokoll S. 16) und das dargestellte Subgruppen-Design (HTA Protokoll S. 22 ff.) sind zur Ausdifferenzierung hilfreich. Dennoch fehlen weitere wichtige Charakteristika und Fragestellungen. c. Neben dem Allgemeinzustand des Patienten, den Begleiterkrankungen und der Medikation, werden nach Bildgebung auch anatomische Unterschiede in Bezug auf die CAD beim Therapieentscheid berücksichtigt [vgl. HTA Protokoll Referenz 34]. Die ESC Guidelines zum CCS & ACS [HTA Protokoll Referenzen 1 & 5] und zur Myokardrevaskularisierung [HTA Protokoll Referenz 34] sind nur drei von vielen ESC Guidelines, welche je nach Begleit-erkrankung beim Therapieentscheid eine Rolle spielen; neben vielen anderen sollen hier als Beispiele nur die ESC Guidelines zum Vorhofflimmern [A1], zu Diabetes [A2], zu Klappen-erkrankungen [A3], zu Schrittmachern [A4] und zur Herzinsuffizienz [A5] genannt werden. Da viele CCS Patienten multimorbide sind, wäre es falsch, anzunehmen, dass die CCS Patienten eine homogene Gruppe sind. Vielmehr hat der Schweregrad der Erkrankung und der Begleit-erkrankungen einen starken Einfluss auf die Therapiewahl zwischen CABG, OMT oder PCI. Deshalb müssen die Ausprägung bzw. der Schweregrad der CCS sowie das Risiko der jeweiligen Behandlungsoption bei der Beantwortung der Forschungsfrage beachtet	1. a. Thank you for the feedback. **Section 5.1** in the HTA protocol details the inclusion criteria for CCS and ACS populations. The proposed subgroup analyses (**Section 7.1.5**) will not differentiate between included CCS and ACS patients. b. See author response **5.1.1**. c. See author response **5.1.1**. d. Thank you for the feedback. No change required. e. See author response **5.1.1**. In addition, the idiosyncrasy of CCS treatment is acknowledged in **Sections 3.4** and **5.1** of the HTA protocol. 2. See author response **5.2.2**.

		werden. Hochgradige Hauptstammstenosen und Mehrgefäßerkrankungen sind als prognostisch bedeutender einzustufen als eine einzelne kurze Stenose distaler kleiner Gefäße [vgl. HTA Protokoll Referenz 34]. Leichte und schwere Formen der CCS sollten bei der Forschungsfrage getrennt betrachtet werden [siehe auch HTA Protokoll Referenz 12 - Fig. 3 und Appendix S. 76-77 bzw. pdf.-Seiten 77-78 und S. 81-82 bzw. pdf.-Seiten 82-83]. Die unterschiedlichen Schweregrade der Erkrankung von CCS Patienten hatten zum Beispiel Einfluss auf die Ausschlusskriterien in der ISCHEMIA Studie [siehe zu HTA Protokoll Referenz 12 - Anhang Protokoll S. 6-7 bzw. pdf.-Seiten 7-8/223]. Im Protokoll werden 23 Ausschluss-kriterien genannt, dazu gehören: bedeutende Hauptstammstenosen >50%, PCI oder CABG im Jahr vor Einschluss, NYHA III-IV, schwere Klappenerkrankungen, stark eingeschränkte Nierenfunktion und eine Lebenserwartung unter 5 Jahren [siehe zu HTA Protokoll Referenz 12 - Anhang Protokoll S.6-7]. Von den 26.000 für ISCHEMIA gescreenten Patienten wiesen 47% klinische Ausschlusskriterien auf. Nur 32% der Patienten wiesen gar keine Ausschlusskriterien auf [siehe zu HTA Protokoll Referenz 12 - Appendix S. 75 bzw. pdf.-Seite 76]. d. Beim Vergleich von ISCHEMIA mit dem START Real World Register (5070 CCS Patienten) wurden nur 3,8% der START Patienten als ISCHEMIA-like beurteilt; 84,7% der START Patienten erfüllten die ISCHEMIA Einschlusskriterien nicht und 11,5% der START Patienten wiesen ISCHEMIA Ausschlusskriterien auf [A6]. Der Vergleich zeigte zudem, dass die ISCHEMIA-like Patienten eine leichtere CCS Form aufwiesen und deshalb eine bessere Prognose hatten als die meisten anderen START Patienten [A6]. Von 388.212 US CCS PCI Patienten erfüllten nur 125.302 Patienten (32,3%) die ISCHEMIA Kriterien [A7]. In der Untersuchung wurde zudem festgestellt, dass zwischen den einzelnen Studienzentren erhebliche Unterschiede im Hinblick auf den Untersuchungsendpunkt bestanden [A7]. e. Die ebenfalls von uns empfohlene Berücksichtigung weiterer PCI-Techniken bzw. PCI-unterstützender Techniken könnte ebenfalls dazu beitragen, die Heterogenität innerhalb der CCS Patienten zu verringern.	

	Neben Empfehlungen der Fachgesellschaften und verfügbaren Studienergebnissen werden Therapieentscheidungen zur CAD heute oft interdisziplinär getroffen, wobei der Patienten-wunsch eine immer größere Rolle spielt [siehe auch A8 – Central Illustration]. 2. Ergänzende Ausführungen zum PICO: Zu Intervention: Zur Unterteilung der DES nach drei Generationen gemäß vorliegendem Protokollentwurf sei erwähnt, dass diese Unterteilung in der Literatur nur von wenigen Autoren so vertreten wird. Hingegen unterteilt die European Society of Cardiology (ESC) in ältere (1. Generation) und neuere DES [HTA Protokoll Referenz 34 - Kapitel 16.1.2.]. Zudem spezifiziert die ESC die neueren DES Marken [HTA Protokoll Referenz 34 - Supplementum Tabelle 6].	