PROTOCOL: DISCHARGE Kick-off Meeting
11-13 February, 2014 at Charité Berlin

Diagnostic Imaging Strategies for Patients with Stable Chest Pain and Intermediate Risk of Coronary Artery Disease: Comparative Effectiveness Research of Existing Technologies

Attendance List

Marc Dewey, Adriane Napp, Georg Schuetz, Christine Germershausen, Michael Laule, Robert Röhle, Robert Haase, Viktoria Wieske, Paolo Ibes, Felicitas Richter, Daniel Preuß, Markus Ehrlich, Florian, Michallek, Malwina Kaniewska, Petra Kozma, Dawid Okoye, Benjamin Kendziora, Simon Drees, Carsten Kendziorra, Fabian Knebel, Jacqueline Müller-Nordhorn, Nina Rieckmann, Wiebke Stritter, Olaf Bender, Rita Pilger, Corinna Meier-Windhorst, Guy Friedrich, Bharati Shivalkar, Rodrigo Salgado, David Zemanek, Natalie Strouhalova, Klaus Kofoed, Tobias Kühl, Tanja Drosch, Thomas Zelesny, Matthias Gutberlet, Lukas Lehmkuhl, Fabian Juhrich, Alexisz Panajotu, Andrea Bartykowszki, Patrick Donnelly, Paul Carlin, Jonathan Dodd, Luca Saba, Bruno Loi, Iacopo Carbone, Simone Calgagno, Agnese Knipse, Ligita Zvaigzne, Zanda Krastina, Madara Grinsteine, Antanas Jankauskas, Gintare Sakalyte, Piotr Klimeczek, Malgorzata Ilnicka Suckiel, Ewa Zdunczyk, Nuno Bettencourt, Nuno Dias Ferreira, Theodora Benedek, Imre Benedek, Oto Ađić, Nada Cemerlić Ađić, Ljiljana Pupić, José Rodriguez Palomares, Bruno Garcia, Anais Gonzales, Eva Swahn, Anders Persson, Niklas Ehl, Cornelia de Martin, Christian Delles, Gershan Davis, Arun Ranjit, Anke Strenge-Hesse, Christine Kubiak, Koos Geleijns, Iñaki Gutiérrez-Ibarluzea, Gaizka Benguria-Arrate, Vladimir Rogalewicz, Ivana Jurickova, Peter Schlattmann, Harold Sox, Martina Seifert, Anita Kucharska

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February 12, DAY 2 (8:30-18:00h)

2. Welcome and Round of Introduction

2.1 Welcome by Marc Dewey and Introduction to the DISCHARGE Project

2.2 Round of Introduction Marc Dewey

3. Lectures and Discussions

3.1 The DISCHARGE Trial Marc Dewey

Translations

Issue:

Dr. Bettencourt: Will translations of patient information be paid by the DISCHARGE budget?

Outcome:

A. Napp: Translations are an own contribution and do not need to be officially translated. Your staff could, for example, do this. In general no subcontracts to companies are foreseen in DISCHARGE for any task.

Prof. Sakalyte: Regarding language concerns no problems are to be expected. Disease specific questionnaires exist in each language and they are validated.

Dr. Rieckmann: Some Questionnaires are not available in Serbian and Latvian. The solution would be to translate them as an own contribution, possibly with the publisher‘s assistance.

Size of informed consent

Issue:

Prof. Swahn: Can the patient information be cut down, i.e. to a maximum of two pages?

Outcome:

Prof. Dewey: You are free to adapt the text and it does not have to be identical. In this case, however, we need an explanation why certain paragraphs are deleted or why you do not need them.

Certifications

Issue:

Dr. Adjić: Is the official documentation needed from the established organisation for level 2 and 3 certifications?

Outcome:

Prof. Dewey: Yes, but equivalency is okay.

Pre-test-probability

Issue:

Prof. Sox: What instruments are used to assess the pre-test probability? Is it the same across all sites?

Outcome:

Prof. Dewey: Pre-test probability was established from the CoMe-CCT consortium where we had 7500 patients based on the clinical characteristics age, gender and symptoms plus CT results plus the catheter results as main features. The mentioned three clinical characteristics need to be known for randomisation.

Stress tests

Issue:

Prof. Swahn: Are stress tests allowed to do before enrolment?

Outcome:

Prof. Dewey: Perform them as in clinical routine at your site but record them in the eCRF, especially the type of stress test and the results. The results from the stress test will influence the pre-test probability. There is unfortunately no pre-test calculator available to include this information. The DISCHARGE study will establish a database with recent patient data.

Prof. Dewey: The different ischemia tests with their magnitudes of being positive, negative or non-diagnostic are not integrated in the current pre-test calculator. At our institution, for the CAD-Man study, we include patients with a maximum of one positive stress test. There is no formal way to handle this issue. Potentially eligible patients should be captured in the screening log. A compromise might be to exclude patients with two positive stress tests.

Prof. Donnelly: Therefore, we tend to move to a primary imaging test. The recommendations are favouring cardiac CT making use of the negative predictive value to discharge the patients appropriately. That would hopefully represent the best utilisation of resources that we have from the National Health Service.

Prof. Dewey: Robert Röhle has conducted an analysis with the pre-test calculator and has made a comparison to the NICE guidance: The CT did work of course for patients with 10-20% pre-test probability, but it also worked for patients with 30-70% and yielded wonderful results. The question is, if ischemia test in between adds information which the CT does not have. I would recommend doing it as pragmatic as possible.

Calcium score

Issue:

Dr. Bettencourt: How to integrate calcium score (CACS) into the study?

Outcome:

Prof. Dewey: According to the proposal, CACS is done first without influencing whether to undergo CTA or not. Based on the large MESA cohort, a CACS of at least 400 should trigger OMT as a fair recommendation. CACS is used to trim the Z-axis coverage of CTA to reduce dose in each patient to a minimum.

Measuring FFR and EF

Issue:

Dr. Ranjit: What are the recommendations about measuring fractional flow reserve (FFR) in the catheter laboratory?

Prof. Carbone: What are the recommendations about measuring ejection fraction (EF) in the catheter laboratory?

Outcome:

Prof. Dewey: The sites need to use their clinical routine and do not make changes from what they clinically do. It has to be specifically mentioned that NO CT perfusion or CT FFR will be allowed to be performed within the trial.

3.2 Coronary CT Angiography – Minimal Standards and Requirements for the DISCHARGE Trial Georg Schütz

Medication

Issue:

Dr. Davis: How to use ivabradine?

Outcome:

Prof. Dewey: Use it as in clinical practice in patients with contraindications to beta blockers. DISCHARGE is a pragmatic trial and therefore standardisation should be sparse.

Issue

Dr. Klimeczek: What about patients with contraindications for beta blockers in countries where ivabradine is not approved, may one use verapamil instead?

Outcome:

Prof. Dewey: Please put the information of intended verapamil use instead of ivabradine into the protocol and do not change it.

Issue:

Prof. Carbone: Will a patient non-responding to beta-blockers be scanned?

Outcome:

Prof. Dewey: Yes, this is an intention of the study. Please give as much beta blocker and ivabradine as needed for achieving the target heart rate.

Prof. Swahn: Do not use beta blockers mostly for women because it would introduce bias.

Prof. Dewey: Yes, put the same thresholds for both genders.

Violation of CT-Protocol

Issue:

Prof. Kofoed: Is there a definition for protocol violation in terms of CT protocol?

Outcome: Prof. Dewey: Yes, there is and it is very strict especially regarding image quality, nitro and beta blocker usage.

Report of non-diagnostic coronary segments

Issue:

Prof. Zemánek: In case of non-diagnostic coronary segments, is it required to report the cause, i.e. low image quality versus plaques?

Outcome:

Prof. Dewey: Yes, it must be in the eCRF. Patients with non-diagnostic segments and without further stenosed segments in CT should undergo ICA to rule out CAD.

Prospective and retrospective gating

Issue:

Prof. Sakalyte: Is it possible to switch from prospective to retrospective gating in case of elevated heart rate?

Outcome:

Prof. Dewey: It is allowed to switch depending on the site‘s technology but it needs to be defined before in your site-specific CT protocol. Also, new CT scanners are allowed as long as the coordinating lab is informed about these changes and the new protocol which needs to be in agreement with the planned 10 steps guide to cardiac CT success.

Decisions:

- Usage of nitroglycerin is mandatory, except for patients with an extreme low blood pressure.

- A heart rate of 50 beats per minute is aimed at.

3.3 Conventional Angiography – Conduct and Minimal Standards Michael Laule

Segment Models

Issue:

Prof. Laule: Which segment model will be used?

Outcome:

Prof. Dewey: AHA 17 is suggested. We may have to consider SCCT and the respective working group will make a proposal.

QCA

Issue:

Prof. Zemánek / Dr. Laule: Should QCA be avoided in the catheter laboratory?

Outcome:

Prof. Dewey: No QCA will be necessarily applied in the catheter laboratory due to artificially increasing radiation dose and being pragmatic. In CT, stenoses need to be measured. Please report about the invasive coronary angiography systems that will be used.

Dose and contrast

Issue:

Prof. Zemánek: In most of our centres we have fellows doing diagnostic procedures, so we must have more dose or more contrast. Is that eligible?

Outcome:

Prof. Dewey: Perform it as you do in clinical routine with the same personnel, if that includes fellows please do not exclude them from performing ICA.

Reporting of Radiation

Issue:

Prof. Carbone: Is it required to report the total radiation dose in CTA?

Outcome:

Prof. Dewey: Yes, for both CTA and ICA.

Certification of CT and ICA

Issue:

Dr. Strenge-Hesse: Who will be certified?

Outcome:

Prof. Dewey: CT is certified only. There is no international certificate for ICA that we could use.

Equipment changes

Issue:

Prof. Dodd: How to handle equipment changes?

Outcome:

Prof. Dewey: The protocol for every specific scanner has to be sent to the coordinator team for approval. The primary CT scanner is already included as default in your site-specific eCRF. Any additional scanner requires individual approval from the core lab at Charité.

Decisions:

- AHA 17 segment model will still be decided on.

- QCA will not be required in ICA.

- Radiation dose needs to be reported in CTA and ICA.

3.4 WP Cost-Effectiveness Analysis Vladimir Rogalewicz

3.5 WP Health Related Quality of Life Nina Rieckmann

3.4 and 3.5 are discussed together.

Prof. Dewey: Micro-costing presentation (3.4) is not provided in print in the folder and will be provided later.

Questionnaires in pilot study

Issue:

Questionnaires from the package included in the pilot study

Outcome:

Prof. Dewey: In order to minimise the burden for the patients in the PRCT please test the questionnaires in advance and make suggestions to dismiss them accordingly after the pilot phase. The QoL team will suggest how to include them into the eCRF before the final randomised trial.

Prof. Rogalewicz: It remains open how to deal with QALYs as well as how address it in the cost-effectiveness paper.

Number of Patients in Pilot Study

Issue:

Number of pilot patients.

Outcome:

Prof. Dewey: The big number of pilot patients of 60 (30 each, CT and ICA) is related to micro-costing. For quality of life it would be acceptable to use less, e.g. 10 each.

Prof. Rogalewicz: The extent of the micro-costing assessment for each patient will be maximally 2 pages.

Prof. Dewey: Therefore, 30 patients for each branch on each site is feasible.

Currency for cost measuring

Issue:

Currency for cost measuring

Outcome:

Prof. Rogalewicz: Measure costs exclusively in the site‘s respective currency..

Anonymised transport of data

Issue:

Prof. Kofoed: Does transport of the data to the Charité require anonymisation?

Outcome:

Dr. Rieckmann: No identifiable information will be collected for the questionnaires in the Quality of Life pilot study.

Prof. Dewey: Image quality assessment of both CT and ICA requires that all data need to be anonymised before sending to core lab.

Ethical implications

Issue:

Dr. Panajotu: What are the ethical implications of the pilot study and do they need to be achieved before the 1st of March?

Outcome:

Prof. Dewey: Please refer to the proposals where we have clearly dealt with this topic. In more detail, this is also part of our IRB approval and it is our own contribution that we realised as a result

of a two year‘s work by three team members. Now it is time for own contributions at the individual sites to get started as fast as possible. Furthermore, during the pilot testing at our place patients do not give written informed consent for micro-costing analysis. It is the site‘s responsibility to conform with local regulations.

A. Napp: We are sending the English version to all the sites. Some parts will need to be translated (e.g., single QoL questions that patients fill out). It should not take more than 8 weeks to collect these few questionnaires from 60 patients. There will still be enough time from May to July.
To this regard, micro-costing is quite simple, too, because it comes from standard salaries, e.g., the site‘s own salaries and how much time is spent with the patient for typical CT and ICA in suspected CAD. Some sites can already start earlier but 8 weeks should be enough.

Issue:
Procedure for ethical approval at the clinical sites.

Outcome:
A. Napp: We will provide you all documentation in English for non-German speaking countries and in German for the German-speaking countries. You will then send the project management office your patient information (English/German) with tracked changes and explanations for the changes for approval. Once you have the approval from the project management office, you will translate the patient informed consent into local language and send it once more to Charité for final approval.

Decision:
- 30 patients for each modality will be recruited due to micro-costing.
- All questionnaires will be included during pilot phase and decisions about which to maintain will be made for the main study.

3.6 How to Get Patients Referred to DISCHARGE?
Viktoria Wieske, Christine Germershausen

Patient information

Issue:
How is patient information organised?

Outcome:
Prof. Dewey: In order to increase recruitment base in terms of announcement to physicians and patients, information may be helpful. English translations of patient information leaflets will be provided. You may put your own logo onto it. Remember to change the hotline. Keep in my mind that you need approval by Charité project management office for advertisement/distribution of information in advance. Please make sure to be in concordance with local requirements, e.g., ethical approvals.

Organisation of first patient contact

Issue:
Prof. Sox: How is the first contact be organised?

Outcome:

Prof. Dewey: It will be differing across sites. Primary doctors as well as cardiologists are involved. The eCRF includes the option to specify who referred that patient. For follow-up, three addresses need to be captured: the address of the patient, the spouse (or next relative) and the referring physician including his or her specialisation.

3.7 Patient Inclusion Paolo Ibes, Robert Roehle

Stress testing

Issue:

P. Ibes: Somebody asked the role of stress testing before randomisation.

Outcome:

P. Ibes: Stress testing results have no influence on the inclusion process in the DISCHARGE study but patients with unevaluable (nondiagnostic) results are very good candidates.

Requirements for pre-test-calculator

Issue:

Requirements for pre-test-calculator

Outcome:

Prof. Dewey: Age, gender and characterisation of chest discomfort. Stress tests results are not included.

Prof. Swahn: Mostly the symptoms are the same between genders and so treat it like that. Do not separate.

Inclusion criteria

Issue:

Dr. Bettencourt: Is indication for ICA required before inclusion?

Outcome:

Prof. Dewey: Clinical indication for ICA is strictly required. Otherwise patients may not accept to be randomised into the catheter group which would lead to increasing numbers of withdrawal. Please ensure that the patients would equally accept both examinations after randomisation.

Issue:

Prof. Kofoed: A lot of patients with intermediate probability for CAD will be in the study. However, the indication for ICA differs between regions. This might potentially be a challenge.

May it be a solution to change inclusion criteria to patients referred for coronary evaluation? Physicians would have the opportunity to decide whether the patient needs coronary evaluation and thus might be a candidate for the study.

Outcome:

Prof. Dewey: ICA indication is required because 50% get ICA after randomisation according to the project proposal selected by the EU for funding. So indication for coronary evaluation is not enough. Germany is the world leader in numbers of performing ICA. Too many patients receive

ICA. Local situations should be discussed here as we require consensus for all the sites. The pre-test probability cannot be adjusted for the different sites. Changing the inclusion criteria would not be acceptable for the funding institutions and would increase the withdrawal rate. There have been 2% withdrawals in the CAD-Man study. A MACE reduction from 1.4 % to 0.8 % is sought. Therefore, the indication for ICA is crucial. Otherwise, there is an ethical and a primary end point issue.

Issue:
Inclusion of patients
Outcome:
Prof. Dewey: Only patients with an intermediate pre-test probability of 10%-70% can be included into the study for randomisation. If a patient has <10% or >70% he or she cannot be randomized and the eCRF will ask for the results of subsequent ICA, because this is the clinically indicated examination. If CT was done instead in those nonrandomized patients, sites will be able to provide the respective results via the eCRF.

Issue:
Dr. Panajotu: According to the ESC guidelines, we may include the provocative symptoms due to emotion in the inclusion criteria.

Outcome:
Prof. Dewey: Diamond and Forester, the CAD Consortium as well as the pre-test calculator do not include that based on the available scientific evidence so it should refer to physical stress only.

Eligibility for study

Issue:
Prof. I. Benedek: Is a patient with confirmed CAD now developing chest pain eligible for the study?

Outcome: *P. Ibes*: This would not be suspected but diagnosed CAD defined as >50% coronary artery diameter stenosis. That patient would not be eligible. Only suspected but not known CAD patients can be included.

Exclusion Criteria

Issue:
Prof. Dodd: Does contrast agent anaphylaxis or severe contrast allergy belong to the exclusion criteria?

Outcome:
Prof. Dewey: No, this is not a contra-indication.

Issue:
Dr. Panajotu: What about patients with renal disease?

Outcome:
Prof. Dewey: Only dialysis is an exclusion criterion.

3.8 Follow-Up - How to Achieve Best Possible Return

Viktoria Wieske, Christine Germershausen

Contact Person

Issue:

Dr. Klimeczek: Is it allowed to contact the contact person for reasons of data privacy?

Outcome:

Prof. Dewey: There is no recommendation. Collect phone, address, and email contact data from relatives, primary care physicians, and cardiologists and make sure you have data on all two follow-up time points.

Pregnancy tests

Issue:

Dr. Knipse: Do we need to test for pregnancy before ICA?

Outcome:

Prof. Dewey: Perform the standard at your site.

Storage of ICA-indication

Issue:

Prof. Kofoed: In order to reduce the amount of paper for the core lab, can the sites manage and store ICA indication locally?

Outcome:

Prof. Dewey: Two documents need to be transmitted to the core lab at Charité: First, ICA indication is critical and it is required to transmit it via PDF or image files that are anonymized within the eCRF. Second, the CEC and Prof. Schlattmann need the MACE documentation. Each site will have to deal with about 4 to 5 MACE during follow-up for which anonymized digital copies have to be transferred using the eCRF.

Randomisation

Issue:

Prof. Shivalkar: Is your approval required before randomisation?

Outcome:

Prof. Dewey: No. However, the eCRF requires the indication form to be uploaded and it will be randomly checked by the clinical trial unit.

Issue:

Prof. Sox: Who is performing the randomisation?

Outcome:

Prof. Schlattmann: Randomisation is achieved centrally by a computer program.

Recruitment

Issue:

Prof. Sox: Patient recruitment is a crucial concern. Referring to the 80-20 rule we should get 80% of the patients from 20% of the doctors on behalf of the study. It is important to think about how all sites will identify and reach the relevant doctors in the individual regions.
Prof. Friedrich: The referring physicians need to be informed in order to avoid communication issues between the referring physicians and the hospital about patient management. It is crucial to collaborate with the physicians in order to get them onboard and support DISCHARGE.
Prof. Dewey: The aim of the study needs to be explained to the referring physician: The patient needs a catheter but has a 50% chance to receive a CT instead. However, the patient must be aware that ICA is standard care. The study focusses on patients with an intermediate pre-test probability for CAD. Therefore, non-diagnostic ischemia tests, which occur quite often, may also be a promising recruitment base.

3.9 DISCHARGE Quiz Robert Röhle

Berlin Air is great!

3.10 Management of Patients based on CT/ICA Results and European Guidelines Georg Schütz

Incorporation of CT information

Issue:

Prof. Dewey: How to incorporate CT information like plaque size, dimension or length for intervention into the study? How are plaque features defined and how will they be managed?

Outcome:

Prof. Kofoed: I would suggest to evaluate proximally and define the diameter individually. The vessels are larger and easier to evaluate and the prognostic implications are higher whereas small branches are not that critical.

Prof. Dewey: A plaque working group will be formed to define the plaque features to apply for patient management based on the publications that define the features in the proposals, e.g., CACS is simple and could be set to a threshold of 400. This team should elaborate a one page description to define those features and how to incorporate them. CT technology will change in the next five years and information hereof will be incorporated in the catheter laboratory automatically.
Prognostic information of these plaques would change management. 80% of patients will be discharged, the other 20% with disease will greatly affect the MACE. MACE reduction is based on discharging patients thus avoiding complications of an invasive test. It is additionally based on improving the treatment of the patient. This can come only from information of the CT. If we provide too much freedom here, we will not make use of the information to the full extent.
The proposal also includes how to deal with patients where the CT reader is in doubt whether the patient may need re-vascularisation or any kind of treatment. This also includes non-significant lesions, whether occurring singularly or subsequently: Use the best locally available ischemia test, if it has not been applied prior to CT. If applied before CT, please use the information thereof to make a decision, i.e. a negative result of ischemia testing would be sufficient. In case of a non-

diagnostic test, add another ischemia test for instance. Send the patient home if there are clean coronary arteries in CT. Also reassure the referring physician in this case.
More than 10% of ischemic myocardium is a prognostic marker and suggests that patients will benefit from re-vascularisation. In order to be pragmatic and give freedom, we stayed vague in the proposal and did not implement a clear cut. The management working group will propose a threshold.

Syntax and DUKE score

Issue:

Prof. Dewey: Should the SYNTAX and/or the DUKE score be derived automatically from the input in the eCRF?

Outcome:

Dr. Gutiérrez-Ibarluzea: We should incorporate both.

Prof. Dewey: We will calculate them both in the background in order to prove that our study is well balanced and randomised.

OMT and RFM

Issue:

Prof. Zemánek: Are optimal medical treatment (OMT) and risk factor modification (RFM) obligatory in the study?

Outcome discussion:

Prof. Shivalkar: OMT and RFM should be obligatory.

Prof. Dewey: It is a recommendation because it is a PRCT. Without any recommendations we would however miss a chance as MACE could be equal in both groups because effects get diluted.

Prof. Kofoed: An important cost-effectiveness parameter refers to the number of expected normal tests which are about 80%. We need to ensure that these 80% do not get unneeded medication on the basis of the CT result.

Dr. Davis: Clinical practice varies widely. At our site the patient receives ICA with a CACS of over 400 and we would put on a statin therapy for secondary prevention. If the CACS was lower then 400 and it is non-obstructive coronary disease we look at risk factors. That information would be used to determine if statin therapy.is recommended

Prof. Kofoed: Concerning the CACS, there are no trials of outcome benefit regarding statin treatment. I am not sure if we can deem the patient lifetime treatment of statins based on the CACS.

Prof. Donnelly: We should not complicate the trial here. It would be extremely challenging to force a guidance which could be a hornet‘s nest, e.g., to force OMT and recommend high dose statin therapy. Therefore, we should leave the decisions at the individual sites.

Prof. Dewey: This is a non-mandatory compromise included in the proposal. If we do not give any recommendations, this concept will not lead to a reduction in MACE. A CACS of 400 is a compromise cut-off. If we do not use that information from CT, the pure discharge effect would require our study to be much bigger than it is now in order to be powerful. Using the information from CT for patients having disease, which is a small cohort of 15-20% would help in management decisions. This small cohort of 15-20% of patients will drive the MACE and therefore make the

effect. That is the advantage of a recommendation approach. Patients may or may not follow that recommendation.

Today‘s best prognostic evidence is applied in order to establish a perspective for CT and cardiovascular imaging and a proposal of how to use this in 5 years. All the things that are included will influence management. Therefore, this trial is unique.

Prof. Schlattmann: Then it should be part of protocol instead of a recommendation to avoid the hornet‘s net.

Prof. Kofoed: The full package of CT includes valuable advantageous information. We want to randomise patients to conventional care which is invasive and to the new test to try any potential benefit that may be in there and prosper from it.

Regarding CACS we can use it for statin treatment but for high risk plaques we need quality assurance in my opinion.

Prof. Sox: I want to repeat my point about making a recommendation without the evidence behind it. The hypothesis is that prognosis is worse in patients with certain findings in CT and should be followed by a recommendation of the investigators to consider risk reduction. You must be aware that there are no studies of risk reduction in this population. That kind of transparency would keep you out of potential trouble. Realistically, most physicians will probably recommend their patients to undergo risk reduction. Transparency can be the compromise.

Prof. Dewey: Speaking in terms of pharmaceutical studies, this is a phase 3 study in which we have got information from phase 2. We can only estimate if our approach helps the patient but we need to make a decision. Unlike a pharmaceutical agent, our “agent” is more complex and we can still modify it. We have some prognostic information that is not available for pharmaceutical trials at that stage but we need to prove this information by making the best use of it. We do not have RCTs for all the characteristics but several prognostic studies. Therefore, it is important to be very transparent about this lack. If we would be waiting for randomised evidence then we might be waiting forever. We should use the features that we are convinced of and that everybody can agree upon in order to prove our hypothesis.

Prof. Dewey: CACS has the largest evidence base we have for prognostics. Prognostics, however, does not mean management. I remember the DIAD study where SPECT was applied in a randomised diabetic cohort. SPECT information was used for changing management and it did not work although previous studies identified SPECT as being very prognostic in diabetics. It was discussed if the wrong route or parameters were taken or if patient treatment was so well without SPECT. Also remember a 1000-patients US study in which half of the patients that got recommendation to statin treatment after CTA CACS opted out from statin therapy, i.e. they did not continue to take the medication. I still believe it is worth trying. Otherwise we would not make use of the full package of CT.

Decisions:

- SYNTAX and Duke score will both be incorporated.

- A dedicated expert working group will define the relevant plaque features.

3.11 Primary Endpoint Definition and How to not Miss MACE Robert Haase

Definition of MACE and cardiovascular death

Issue

Prof. Shivalkar: A patient was enrolled in the study and was discharged. 3 years later he presents with unstable angina without biomarkers and gets a stress test and this shows abnormal ischemia and goes down to PCI or CABG. That is not considered to be a MACE, isn't it?

Outcome:

***R. Haase*:** This is not a MACE. As you saw there is a clear difference in outcomes considering hard and/or soft events as outcomes. We only consider hard events.

R. Pilger (explained this after the discussion for the protocol): Worsening of the medical conditions belong to the adverse events but not MACE.

Issue:

Definition of MACE and cardiovascular death

Outcome:

Prof. Dewey: Only hard events are considered as MACE which was explicitly mentioned in the EU evaluation. There is a lack of definition of MACE and the DISCHARGE study may be the first to establish a definition. Make sure to have a written consent from the patients in order to be able to contact their relatives, the physician or the national registry of deaths in your countries to get the information on MACE from the patients.

We defined cardiovascular death instead of cardiac death to include peripheral complications.

Reporting and use of incidental findings

Issue:

Reporting and use of incidental findings

Outcome:

The change has to be documented. Concerning silent infarcts we should not include them for primary outcome but report them in order to be able to include them in a secondary analysis. However, if done systematically in both arms, there might be many irrelevant findings. It is most important to capture serious clinically relevant adverse events that are directly related to the intervention.

3.12 WP Certification of Clinical Sites and CRF Working Groups Marc Dewey

Reporting of intramyocardial bridges

Issue:

Dr. Klimeczek: Reporting the presence of intramyocardial bridges in CRF?

Outcome:

Prof. Dewey: Report that there are no relevant intramyocardial bridges which is the case in the vast majority of patients with intramyocardial bridges. In case that there is, report them and in this unlikely event add ischemia imaging.

3.13 WP Good Clinical Practice and Safety Surveillance Olaf Bender, Rita Pilger

Events recording

Issue:

Dr. Strenge-Hesse: Will events be recorded during the pilot study and will patients receive treatment.

Outcome:

Prof. Dewey: There will be no event collection and no treatment during the pilot study.

Monitoring

Issue:

Monitoring at clinical sites

Outcome:

Prof. Dewey: A traffic-light approach (green, yellow, red) is planned by the KKS to evaluate the performance of the clinical sites in the eCRF during the PRCT.

3.14 WP Clinical Data Management System The-Hoang Do

Audit-Trail in eCRF

Issue:

Prof. Schlattmann: Is there an audit-trail?

Outcome:

Dr. Pilger: Yes, the database SecuTrial is a well established and validated system.

Prof. Dewey: Every action in the database will be documented. Concerning the software, it is crucial to know about its convenience in usage. Therefore, indicate the person who will be using it and mail the name to Adriane Napp who will provide user name and passwords for these people to keep feedback to improve development before eCRF gets into action. We explicitly ask you to give feedback about the software.

4. After the Official Programme

4.1 Consulting of Individual Beneficiaries in Case of Scientific/Administrative Questions

4.2 Self-organised Evening Programme will be Suggested

February 13, DAY 3 (9-13:00h)

5. Welcome Back Marc Dewey

6. Lectures and Discussions

6.1 Summary of Essential Errors That We Want to Avoid Petra Kozma

Definition of indication for ICA

Issue:

Prof. Sox: Definition of indication for ICA due to a large range of intermediate probability for CAD.

Outcome:

Prof. Dewey: Exercise testing can be done prior but is not a prerequisite for inclusion of patients into the study. Documentation is necessary whether the patient is ready to undergo standard care, i.e. ICA. This documentation needs to be send as PFD via eCRF.

6.2 Finances in a Nutshell Adriane Napp

Registration of employees

Issue:

Prof. Schlattmann: Does every employee need to be registered in ECAS?

Outcome:

A. Napp: You need to add the financial signatory in ECAS. This is a staff member from, for example, the finance department of your University. Please have this person contact me. I will then send templates for the required financial documents. Be aware that your University needs to create a sub-account for DISCHARGE in order to prepare for financial audits. You can also add other scientific staff.

, 6.3 General Administrative and Financial and Aspects of the European Commission Anita Kucharska

No questions asked.

Payments

Issue:

Payments

Outcome:

Anita Kucharska points out, that if single partners do not submit their deliverables on time for the periodic report, the European Commission has the right to withhold further payments. The earliest next possible payment would be after the next periodic report upon submission of the deliverable. This implies, for example, that partners may not receive any payments for at least 18 months.

7. Naming of Project Manager, Steering Committee, and Dissemination Committee Marc Dewey

All partners agreed to the following nominations:

a) Project Manager

- Adriane Napp

b) Dissemination Committee

- **Chair, Cardiologist**
  - Guy Friedrich
- **Co-Chair, Radiologist**
  - Jonathan Dodd

- **Clinical Site Cardiologists:**
  - Nada Čemerlić Adjić
  - Gershan Davis
  - Nuno Bettencourt
  - José Rodriguez Palomares
  - Stephen Schröder
- **Clinical Site Radiologists:**
  - Gudrun Feuchtner
  - Anders Persson
  - Luca Saba
- **WP Leaders:**
  - Jacqueline Müller-Nordhorn (WP 10)
  - Iñaki Gutiérrez-Ibarluzea (WP8)
  - Marc Dewey (Coordinator)
- **Affiliated:**
  - Peter Schlattmann (Statistician)

c) Steering Committee:

- **Coordinator**
  - Marc Dewey
- **WP Leaders**
  - Jacob Geleijns (WP3 EU CT Quality Criteria and Radiation Exposure)
  - Christine Kubiak (WP4 Good Clinical Practice and Safety Surveillance)
  - Eva Swahn (WP7 Gender)
  - Iñaki Gutiérrez-Ibarluzea (WP8 Systematic Review of Evidence)
  - Vladimir Rogalewicz (WP9 Cost-Effectiveness Analysis)
  - Jacqueline Müller-Nordhorn (WP10 Health-related Quality of Life)
  - Peter Schlattmann (WP11 Statistical Analysis)
- **Regional Sites Representatives**
  - Klaus Kofoed: Northern Europe
  - Theodora Benedek: Eastern Europe
  - Rodrigo Salgado: Central Europe
  - Marco Francone: Southern Europe
  - Christian Delles: Western Europe
- **Affiliated**
  - Adriane Napp (Project Management)