PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Complex Large-Bore Radial Percutaneous Coronary Intervention: Rationale of the COLOR trial study protocol
AUTHORS	Meijers, Thomas; Aminian, Adel; Teeuwen, Koen; van Wely, Marleen; Schmitz, Thomas; Dirksen, Maurits; van der Schaaf, Rene; Iglesias, Juan; Agostoni, Pierfrancesco; Dens, Joseph; Knaapen, Paul; Rathore, Sudhir; Ottervanger, Jan Paul; Dambrink, Jan-Henk; Roolvink, Vincent; Gosselink, Marcel; Hermanides, Renicus; van Royen, Niels; van Leeuwen, Maarten

VERSION 1 – REVIEW

REVIEWER	Dr Tim Kinnaird University Hospital of Wales, Cardiff, UK
REVIEW RETURNED	23-Mar-2020

GENERAL COMMENTS	Although there exists quite a lot of observational data on TRA for complex CTO this may well be confounded by operator bias. As the authors describe, there are very little RCCT data and therefore the trial in itself is inherently interesting and relevant. There are some major limitation in the study design however. In my view the primary end-point is the wrong one. Multiple trials and registeries have demonstrated a reduction in vascular complications and bleeding with TRA vs. TFA. This is therefore not novel and study will undoubtedly show this. The more relevant end-points would be whether the procedure can be completed in a similar way using TRA i.e. the primary end-point should be composite of procedural success and cross-over with a focus on the secondary end-points of radiation, procedure time and contrast. As a result, the sample size may well need to be adjusted. The definition of procedural success should be made more explicit. The entry criteria are too vague especially around calcium. These need to be made more explicit otherwise there is a very real risk that low complexity will be included and this would confound the results. What are the volumes and the default access site characteristics of the centres and operators involved? This should be made explicit. Sub-group analyses should be pre-specified and definitely include gender, pre-existing operator volume, pre-existing operator default

	access site strategy, J-CTO score, shaft vs. distal LMS intervention. Is every complex case meeting the criteria at the centres to be included? Otherwise operator bias will hugely influence the outcomes. I don't understand how the study will adjust for dual access for CTO. In contemporary practice almost all CTO-PCI should have dual access. If CTO makes up a large percentage of the study, the results will be significantly blurred. One option would be to mandate dual access to be the same ie bilateral radials if randomised to radial. Otherwise it might be better to exclude CTO where dual access is deemed necessary. The discussion misses out several important complex PCI access site studies published over the last three years from the BCIS registry.

REVIEWER	Asim Cheema University of Toronto
REVIEW RETURNED	16-Apr-2020

GENERAL COMMENTS	Clinical Trial Protocol submission. No major concerns. The protocol is well written with apprpriate endpoints and planned statistical analysis.

REVIEWER	Adhir Shroff University of Illinois – Chicago
REVIEW RETURNED	17-Apr-2020

GENERAL COMMENTS	The authors should be credited with developing and executing an important trial that will answer a clinically relevant question. As the trial is almost completed enrollment, questions about design seem irrelevant. My only real concern is about the power calculation. I worry that the event rate for the TF group seems pretty high when one compares to the event rate in RIVAL and MATRIX, another contemporary, primarily European trial. The TF event rates were lower. If the TF event rate is lower than expected, it may make it difficult to detect a difference with the given sample size. Otherwise, I look forward to seeing the results.

VERSION 1 – AUTHOR RESPONSE

Reviewer I
'Although there exists quite a lot of observational data on TRA for complex CTO this may well be confounded by operator bias. As the authors describe, there are very little RCCT data and therefore the trial in itself is inherently interesting and relevant. There are some major limitation in the study design however.' 'In my view the primary end-point is the wrong one. Multiple trials and registeries have demonstrated a reduction in vascular complications and bleeding with TRA vs. TFA. This is therefore not novel and study will undoubtedly show this. The more relevant end-points would be whether the procedure can be completed in a similar way using TRA i.e. the primary end-point should be composite of procedural success and cross-over with a focus on the secondary end-points of radiation, procedure time and contrast. As a result, the sample size may well need to be adjusted.'
We thank the reviewer for his remark about the relevancy of this trial and for his suggestions

considering the primary end-point. We have been giving this important aspect of the trial lots of thought,
and we will try to explain our choice for this design.
We concur with the reviewer that TRA is superior to TFA in many previous trials and registries. The reason to study this subject in complex large bore PCI has several reasons. First, large bore access is known to increase bleeding and vascular complications for TFA, but will also increase complications in
TRA, because of sheath-artery mismatch in a significant proportion of patients (> 50% for men and women combined). Second, our study uses a clinically significant outcome parameter for bleeding (according to BARC criteria), while previous studies use a variety of bleeding definitions that are not necessarily associated with major clinical outcomes (e.g. MACE). Therefore we believe it is important to
demonstrate a reduction of the combined endpoint of clinically significant bleeding and vascular complications in this complex PCI group as well. If the study can demonstrate that radial access with large-bore guiding is as efficient as femoral access in complex PCI but safer (the primary end-point), it could have an important impact on clinical practice. Most of all, to our knowledge, such a beneficial impact of radial access for complex PCI has never been shown within a dedicated randomized trial (the
highest level of evidence).
The majority of complex PCI consists of CTO PCI. For the design of our trial, high-volume and highexperience centers were selected, performing CTO PCI according to the hybrid approach with all recognized modern techniques. At the time of trial design, most centers were used to perform CTO PCI
with a hybrid vascular approach (radial and femoral). Most operators reported they feel uncomfortable using complete radial or complete femoral access. This is confirmed by registry data, showing complete
femoral approach in 11-43%, complete radial approach in 7-24% and radial/femoral approach in 51-65%
of all dual access PCI CTO (1–4). Next to operators' preference, biradial or bifemoral approach may be
impossible in a subset of patients with for example severe peripheral vascular disease, previous radial artery harvesting for CABG or arteriovenous dialysis shunt. The suggestion of the reviewer to set-up a trial with a primary efficacy endpoint is very interesting indeed. We believe that such a trial could be performed once the COLOR trial outcome data have been published and operators are more used to biradial approach. Currently, many ' radial centers' have concerns performing CTO PCI with TFA, especially bifemoral, and the same applies for ' femoral centers' being uncomfortable with biradial access for PCI CTO, which may complicate the design for such a trial. Since the present trial has already started including patients we will not be able to change its design anymore, but the reviewers' suggestions concerning a primary efficacy endpoint will be very valuable for future studies. We thank in
advance the reviewer for his understanding on this matter.
The definition of procedural success should be made more explicit.
We have now specified the definition of procedural success to 'Procedural success (defined as successful PCI of the target lesion with a residual stenosis of less than 20% without in-hospital MACE)'
(page 6, line 262-263).
The entry criteria are too vague especially around calcium. These need to be made more explicit otherwise there is a very real risk that low complexity will be included and this would confound the results.
We thank the reviewer for his valuable remark about preventing the inclusion of low complex lesions in
our study. We will try to explain our choice to not explicitly define the heavily calcified lesions. Indeed,

any complex calcified lesion is expected to pose a major challenge for stent crossing and delivery. As such, the additional back up provided by large bore guiding catheters might be very helpful. It will also facilitate the use of calcium modifying equipment, such as intravascular lithotripsy or rotational atherectomy. Moreover, 7 Fr guiding catheters will often be essential for larger burr sizes. Finally, a calcified lesion is only one of the numerous factors accounting for the definition of complex PCI and many other factors will point towards PCI complexity (CTO lesions, left main lesions, complex bifurcation techniques, use of rotational atherectomy,…). The participating centers have been chosen based on the experience of their operators with complex PCI, which includes heavily calcified lesions. We trust therefore on their proficiency to adequately appraise every complex case and lesion for the need for large bore access and guiding catheters. We hope we have adequately addressed concerns raised by the reviewer.

What are the volumes and the default access site characteristics of the centres and operators involved? This should be made explicit.

We concur with the reviewer that volumes and default access site characteristics of the involved centers
and operators should be made more explicit. We added a section describing average volumes, access
site characteristics and use of large bore access in the study design section (page 4-5 lines 194-202).

Sub-group analyses should be pre-specified and definitely include gender, pre-existing operator volume, pre-existing operator default access site strategy, J-CTO score, shaft vs. distal LMS intervention.

We agree with the reviewer that sub-group analyses should be pre-specified. We have now added these
sub-groups in the methods section: Sample size calculation and statistics (page 7, line 312-323).
Subgroup analyses are also described in a prespecified Statistical Analysis Plan (SAP).

Is every complex case meeting the criteria at the centres to be included? Otherwise operator bias will hugely influence the outcomes.

Every complex case will be screened for inclusion. Patients that are not included in this study will be logged in a separate screening file in the eCRF including the reason for screening failure.

I don’t understand how the study will adjust for dual access for CTO. In contemporary practice almost all CTO-PCI should have dual access. If CTO makes up a large percentage of the study, the results will be significantly blurred. One option would be to mandate dual access to be the same ie bilateral radials if randomised to radial. Otherwise it might be better to exclude CTO where dual access is deemed necessary.

We agree with the reviewer that PCI of CTO nowadays is almost exclusively performed with dual arterial
access. This is confirmed with the volume and access preference data of the participating centers and operators, as mentioned earlier in this letter. The majority of complex lesions in our study will probably consist of CTO lesions. Therefore, excluding CTO lesions would be detrimental for the design and scope of this study. As emphasized before, biradial or bifemoral access will be undesirable for many operators and can be impossible in a subset of patients with contraindications for using the contralateral
access site. For this reason, we decided to not use efficacy of TRA versus TFA as primary endpoint, which would be severely blurred by dual arterial access indeed. However, the primary endpoint of clinically significant bleeding and vascular complications of this study is exclusively scored for the randomized access site, and is therefore not influenced by a secondary access site in case of dual arterial access for CTO PCI.

The discussion misses out several important complex PCI access site studies published over the last three years from the BCIS registry.

We agree with the reviewer that several studies published from the BCIS registry should not lack in the

discussion. Data extracted from the BCIS is invaluable for TRA and TFA safety and efficacy for complex
PCI, even though sheath size is not registered. We added several BCIS studies in the discussion (page
8; line 372 (reference number 45), line 381 (reference number 47) and line 385 (reference number 50)).

Reviewer II
The protocol is well written with appropriate endpoints and planned statistical analysis.
We thank the reviewer for his positive feedback.

Reviewer III
The authors should be credited with developing and executing an important trial that will answer a clinically relevant question. As the trial is almost completed enrollment, questions about design seem irrelevant. My only real concern is about the power calculation. I worry that the event rate for the TF group seems pretty high when one compares to the event rate in RIVAL and MATRIX, another contemporary, primarily European trial. The TF event rates were lower. If the TF event rate is lower than expected, it may make it difficult to detect a difference with the given sample size. Otherwise, I look forward to seeing the results.
We thank the reviewer for his remark about the importance and relevancy of this trial. Event rates for TRA and TFA in the larger trials (i.e. RIVAL and MATRIX) are indeed lower than the expected event rates used in our power calculation. However, in these trials primarily 5 and 6 Fr sheaths were used, while large bore access increases event rates (5–7). Another retrospective study shows a much larger incidence of bleeding events for TFA (12%) in a population with mainly 6 Fr access, although specifically shown for radial operators (8). Complex PCI, especially CTO PCI, is associated with increased procedural duration and higher activated clotting time (ACT) values, which may lead to increased access site related bleeding. A retrospective study by Rathore et al shows a high event rate for TFA in a CTO population as well, even though the majority of procedures is done with 6 Fr guiding catheters (9). Other large registry-based retrospective studies showed a much lower incidence of TFA related events. However access site related complications are often ill-defined and possibly underreported in these registries (3,10). Previous studies used variable bleeding end-point definitions, for example large hematoma. Our study combines clinically relevant bleeding with vascular complications requiring intervention, leading to the estimated event rate as used for the power calculation.

References
1. Jan Bakker E, Maeremans J, Zivelonghi C, Faurie B, Avran A, Walsh S, et al. Fully transradial versus transfemoral approach for percutaneous intervention of coronary chronic total occlusions applying the hybrid algorithm insights from recharge registry. Circ Cardiovasc Interv. 2017;
2. Maeremans J, Walsh S, Knaapen P, Spratt JC, Avran A, Hanratty CG, et al. The Hybrid Algorithm for Treating Chronic Total Occlusions in Europe: The RECHARGE Registry. J Am Coll Cardiol. 2016;
3. Kinnaird T, Anderson R, Ossei-Gerning N, Gallagher S, Large A, Strange J, et al. Vascular Access Site and Outcomes Among 26,807 Chronic Total Coronary Occlusion Angioplasty Cases From the British Cardiovascular Interventions Society National Database. JACC Cardiovasc Interv. 2017;
4. Alaswad K, Menon R V., Christopoulos G, Lombardi WL, Karmpaliotis D, Grantham JA, et al. Transradial approach for coronary chronic total occlusion interventions: Insights from a contemporary multicenter registry. Catheter Cardiovasc Interv. 2015;

5. Smilowitz NR, Kirtane AJ, Guiry M, Gray WA, Dolcimascolo P, Querijero M, et al. Practices and complications of vascular closure devices and manual compression in patients undergoing elective transfemoral coronary procedures. In: American Journal of Cardiology. 2012.
6. Marques Gomes MP, de Andrade Falcão FJ, Alves CMR, de Sousa JMA, Herrmann JL, Moreno ACC, et al. Vascular Complications in Patients Undergoing Early Percutaneous Coronary Intervention via the Femoral Artery after Fibrinolysis with Tenecteplase: Registry of 199 Patients. Rev Bras Cardiol Invasiva (English Ed. 2012;
7. Doyle BJ, Ting HH, Bell MR, Lennon RJ, Mathew V, Singh M, et al. Major Femoral Bleeding Complications After Percutaneous Coronary Intervention. Incidence, Predictors, and Impact on Long-Term Survival Among 17,901 Patients Treated at the Mayo Clinic From 1994 to 2005. JACC Cardiovasc Interv. 2008;
8. Rafie IM, Uddin MM, Ossei-Gerning N, Anderson RA, Kinnaird TD. Patients undergoing PCI from the femoral route by default radial operators are at high risk of vascular access-site complications. EuroIntervention. 2014;
9. Rathore S, Hakeem A, Pauriah M, Roberts E, Beaumont A, Morris JL. A comparison of the transradial and the transfemoral approach in chronic total occlusion percutaneous coronary intervention. Catheter Cardiovasc Interv. 2009;
10. Maeremans J, Palmers PJ, Dens J. Initial experience and feasibility of the new low-profile stingray catheter as part of the antegrade dissection and re-entry revascularization strategy for coronary chronic total occlusions. Am J Case Rep. 2017;

VERSION 2 – REVIEW

REVIEWER	Tim Kinnaird University Hospital of Wales, Cardiff, UK
REVIEW RETURNED	21-May-2020

GENERAL COMMENTS	Although the investigators have addressed some of the limitations, several of my comments have largely been ignored. As before I believe the potential novelty is that complex PCI can be undertaken form the wrist with procedural success. There is no doubt that the trial will show a big decrease in vascular complications, hence the modest sample size required. However, to persuade the femoralists to switch (given than many argue they don't have vascular complications anyway....!), procedural success would be a far more compelling argument. The sample size will likely need to be bigger but otherwise the risk of this study is that femoral operators will say "so what". Personally I would still switch the primary and secondary endpoints around and do a sample size calculation based on procedural success. I also find the inclusion criteria too woolly: "for complex PCI of CTO (defined as lesion exhibiting TIMI 0-1 flow in a native coronary artery with an occlusion duration of ≥3 months), left main, complex bifurcation or heavy calcification, in whom the operator anticipates that a 7 Fr guiding catheter is indicated,". These are all extremely subjective and heavily influenced by opinion rather than science. I still don't understand how the investigators will correct for dual access. They state that "sub-group analyses will be performed for use of secondary access site". But surely its an access site whether or not its secondary. So is a femoral puncture and a radial

	puncture allowed for dual access regardless of the randomisation access site? This needs to be clarified.

VERSION 2 – AUTHOR RESPONSE

Reviewer I:

Although the investigators have addressed some of the limitations, several of my comments have largely been ignored.

We regret the fact that the reviewer feels that not all comments were sufficiently addressed in the first rebuttal letter and the revised manuscript. We will try to give a more comprehensive response in this document to these specific comments.

As before I believe the potential novelty is that complex PCI can be undertaken form the wrist with procedural success. There is no doubt that the trial will show a big decrease in vascular complications, hence the modest sample size required. However, to persuade the femoralists to switch (given than many argue they don't have vascular complications anyway....!), procedural success would be a far more compelling argument. The sample size will likely need to be bigger but otherwise the risk of this study is that femoral operators will say "so what". Personally I would still switch the primary and secondary endpoints around and do a sample size calculation based on procedural success.

We thank the reviewer once more for his remark about the relevancy and potential novelty of the trial design, and for his remark about the primary endpoint. In our opinion, the demonstration of a similar procedural success between radial and femoral access for complex PCI will not necessarily persuade femoral operators to switch, unless we can show that radial access is not only as effective but also safer (less clinically relevant bleeding and vascular complications). That's why we chose this as the primary endpoint. At the same time, procedural success will be accurately analyzed as an important secondary end-point.

Also, if we would change the primary endpoint to procedural success, we would have to switch to a non-inferiority design, with potentially large implications for sample size. Since the study is already ongoing this is not possible. Naturally, if the study is positive for the primary endpoint but at the same time shows a significant decrease in procedural success, this will be reported and discussed in the main paper in a balanced fashion. This will give operators, physicians (and even patients) the chance to interpret both safety and efficacy of the two access routes. We have now described this more clearly (*page 10 line 458-461*)

I also find the inclusion criteria too woolly: "for complex PCI of CTO (defined as lesion exhibiting TIMI 0-1 flow in a native coronary artery with an occlusion duration of ≥3 months), left main, complex bifurcation or heavy calcification, in whom the operator anticipates that a 7 Fr guiding catheter is indicated,". These are all extremely subjective and heavily influenced by opinion rather than science.

We thank the reviewer for this comment about the inclusion criteria definitions. It must be acknowledged that the definition of complex PCI is not universally standardized and there is usually no clear definition. For instance, the "CHIP" (complex high risk PCI) acronym in the United States of

America takes into account several aspects of complexity of coronary anatomy, but also patient specific and hemodynamic characteristics. Anatomical aspects of complexity in CHIP include unprotected left main, bifurcation with severe side branch lesion, severe calcification, saphenous vein graft, CTO, three vessel PCI and severe tortuosity (1,2). When it comes to defining PCI complexity as a means of adapting DAPT duration, the “Giustino criteria” are increasingly used to define “complex PCI”. Those criteria include: three vessel PCI, at least 3 stents implanted, at least 3 lesions treated, bifurcation with 2 stents implanted, total stent length > 60 mm and CTO (3,4). Although we use in our study some of these criteria (CTO, complex bifurcation) to define complex PCI requiring large bore guiding catheters to improve back-up support and materials’ compatibility, some other criteria (e.g. 3 stents implanted, 3 lesions treated) do not accurately reflect complex coronary lesions (implantations of > 60 mm stent for example can be performed even with a 5 Fr guiding catheter). Of note, the vast majority of complex lesions in our trial will probably consist of CTO, which undoubtedly fulfill the definition of complex PCI. The same applies for left main stem PCI. However, we agree that our definition of complex PCI can be refined with standard scores, definitions and classification used in daily clinical practice. Bifurcation lesions are usually classified according to the Medina classification, as recommended by the European Bifurcation Club (EBC) (5,6). The term ‘complex bifurcation’ refers to Medina 1.1.1, 1.0.1 or 0.1.1 bifurcation lesions (7). For heavy calcified lesions, the Syntax definition of ‘multiple persisting opacifications of the coronary wall visible in more than one projection surrounding the complete lumen of the coronary artery at the site of the lesion’ is usually used (5). However this definition is rather broad, not accurately predicting the use of calcium modifying techniques as rotational atherectomy or intravascular lithotripsy. Other factors such as diameter of the target vessel, location of the lesion, tortuosity and side branch involvement all have to be taken into account by the operator to guide up-front use of these tools, which in turn may guide the selection of large bore guiding catheters. Therefore, further specification of the inclusion criteria for complex bifurcation lesions and heavily calcified lesions is cumbersome for this trial. However, we have better specified the inclusion criteria:

*“*All patients of 18 years or older, presenting with stable coronary artery disease, unstable angina or non-ST elevation myocardial infarction and planned for PCI of the following complex coronary lesions: CTO, left main stem, heavily calcified lesions which may require calcium modification techniques (rotational atherectomy or intravascular lithotripsy) and complex bifurcations in whom the operator anticipates that a 7 Fr guiding catheter is indicated, are screened for inclusion. CTO is defined as a lesion exhibiting TIMI 0-1 flow in a native coronary artery with an occlusion duration of ≥3 months (8). Heavily calcified lesions are characterized by multiple persisting opacifications of the coronary wall visible in more than one projection surrounding the complete lumen of the coronary artery at the site of the lesion (9). Complex bifurcation includes lesions with Medina classification 0.1.1, 1.1.1 or 1.0.1 (7)*” (page 5 line 230-240)”*

Furthermore, all characteristics of the complex lesions will be carefully registered, such as J-CTO score, Medina score, size of side branch diameter, location of left main lesion and the use of calcium modification techniques. These lesions characteristics will be reported together with the results of this trial.

I still don't understand how the investigators will correct for dual access. They state that "sub-group analyses will be performed for use of secondary access site". But surely its an access site whether or not its secondary. So is a femoral puncture and a radial puncture allowed for dual access regardless of the randomisation access site? This needs to be clarified.

We thank the reviewer for asking for clarification of this important subject. If the patient is randomized to radial access but needs a secondary access in case of CTO PCI (hybrid approach)(10), a 7 Fr Glidesheath Slender must be placed in the radial artery (randomized access site). The primary end-point will be based on this randomized access site. Then, the operator can decide which secondary access site he/she will use and which sheath size is needed for this secondary access. This can be the contralateral radial artery (bi-radial approach) or the femoral artery. Any clinically significant bleeding or vascular complication related to the secondary access will be analyzed as a secondary endpoint. If the patient is randomized to femoral access and needs dual access, a 7 Fr femoral sheath must be placed in the femoral artery (randomized access site) and the operator can decide which second access he/she will use (radial or femoral). Therefore, randomization of the primary access site will provide comparable groups for the assessment of the primary end-point, which encompasses only clinically significant bleeding or vascular complications related to this randomized access site. We acknowledge that an imbalance between the radial and femoral group can occur regarding secondary access used for CTO patients. This is why we will analyze the secondary access site bleeding and vascular complications as a secondary end-point. Then a per-protocol analysis will be performed to account for imbalance between groups, as reported in the statistical plan. We have now described this in more detail in the methods section *(page 6, line 278-289).* We hope we have sufficiently addressed the reviewer comment regarding the access sites.

Reference list

1. Iftikhar SF, Hu P. Complex Coronary Artery Lesions. StatPearls. 2019.

2. Bass TA. High-Risk Percutaneous Coronary Interventions in Modern Day Clinical Practice: Current Concepts and Challenges. Circulation: Cardiovascular Interventions. 2015.

3. Giustino G, Chieffo A, Palmerini T, Valgimigli M, Feres F, Abizaid A, et al. Efficacy and Safety of Dual Antiplatelet Therapy After Complex PCI. J Am Coll Cardiol. 2016;

4. Azzalini L, Carlino M, Bellini B, Marini C, Pazzanese V, Toscano E, et al. Long-Term Outcomes of Chronic Total Occlusion Recanalization Versus Percutaneous Coronary Intervention for Complex Non-Occlusive Coronary Artery Disease. Am J Cardiol. 2020;

5. Medina A, Suárez de Lezo J, Pan M. A New Classification of Coronary Bifurcation Lesions. Rev Española Cardiol (English Ed. 2006;

6. Louvard Y, Thomas M, Dzavik V, Hildick-Smith D, Galassi AR, Pan M, et al. Classification of coronary artery bifurcation lesions and treatments: Time for a consensus! Catheterization and Cardiovascular Interventions. 2008.

7. Zlotnick DM, Ramanath VS, Brown JR, Kaplan A V. Classification and treatment of coronary artery bifurcation lesions: Putting the Medina classification to the test. Cardiovasc Revascularization Med. 2012;

8. Stone GW, Reifart NJ, Moussa I, Hoye A, Cox DA, Colombo A, et al. Percutaneous recanalization of chronically occluded coronary arteries: A consensus document - Part II. Circulation. 2005.

9. Sianos G, Morel M-A, Kappetein AP, Morice M-C, Colombo A, Dawkins K, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention. 2005;

10. Brilakis ES, Grantham JA, Rinfret S, Wyman RM, Burke MN, Karmpaliotis D, et al. A percutaneous treatment algorithm for crossing coronary chronic total occlusions. JACC Cardiovasc Interv. 2012;

VERSION 3 – REVIEW

REVIEWER	Tim Kinnaird University Hospital of Wales, Cardiff, UK
REVIEW RETURNED	11-Jun-2020

GENERAL COMMENTS	Thank you to the authors for addressing my concerns.