

Clinical endpoint adjudication in a contemporary all-comers coronary stent investigation: Methodology and external validation [☆]

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ABSTRACT

Background: Globalisation in coronary stent research calls for harmonization of clinical endpoint definitions and event adjudication. Little has been published about the various processes used for event adjudication or their impact on outcome reporting.

Methods and results: We performed a validation of the clinical event committee (CEC) adjudication process on 100 suspected events in the RESOLUTE All-comers trial (Resolute-AC). Two experienced Clinical Research Organisations (CRO) that had already extensive internal validation processes in place, participated in the study. After initial adjudication by the primary-CEC, events were cross-adjudicated by an external-CEC using the same definitions. Major discrepancies affecting the primary end point of target-lesion failure (TLF), a composite of cardiac death, target vessel myocardial infarction (TV-MI), or clinically-indicated target-lesion revascularization (CI-TLR), were analysed by an independent oversight committee who provided recommendations for harmonization. Discordant adjudications were reconsidered by the primary CEC. Subsequently, the RAC database was interrogated for cases that based on these recommendations merited re-adjudication and these cases were also re-adjudicated by the primary CEC.

Final discrepancies in adjudication of individual components of TLF occurred in 7 out of 100 events in 5 patients. Discrepancies for the (hierarchical) primary endpoint occurred in 5 events (2 cardiac deaths and 3 TV-MI). After application of harmonization recommendations to the overall RAC population (n = 2292), the primary CEC adjudicated 3 additional clinical-TLRs and considered 1 TV-MI as no event.

Conclusions: A harmonization process provided a high level of concordance for event adjudication and improved accuracy for final event reporting. These findings suggest it is feasible to pool clinical event outcome data across clinical trials even when different CECs are responsible for event adjudication.

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1. Introduction

The process by which clinical trials in cardiovascular medicine, and coronary stent devices in particular, are designed, conducted, analysed, presented, and published has

evolved dramatically over the last decade. Large, truly global studies with relatively long-term clinical endpoints are conducted to evaluate the effects of a particular treatment strategy on mortality and major morbidity within a disease entity. Unrestricted study populations, including more complex patients, have become the norm [1–4]. Uniform endpoint definitions, terminology and clinical trial design paradigms are an essential prerequisite [5,6]. Yet, an important challenge is to maintain accuracy and consistency in the interpretation of clinical endpoints across geographic areas and over the course of the study. Clinical Event Committees (CEC) are used routinely to adjudicate efficacy and/or safety endpoints in clinical investigations. These expert groups comprise physicians with particular expertise in the relevant therapeutic area but without any active involvement in the study. It is the responsibility of the CEC to review all relevant source data and provide an independent, blinded determination of trial endpoints or events. Little data have been published regarding the processes of CEC event adjudication or their validation; or the potential impact of variability of the overall process on reported event rates. Variability is a particular concern in global programs involving multiple clinical trials possibly with different CECs.

We studied the level of consistency in event adjudication for the resolute-all comers trial [1], between two independent CECs, hosted by two different academic research organisations (AROs). We determined the cause for discordant adjudications and analysed the potential impact of this external validation on the final reported patient outcomes.

2. Methods

2.1. the resolute all-comers trial study design

The Resolute-AC trial (ClinicalTrials.gov number: NCT00617084) is a prospective, multi-center, randomized, two-arm international, open-label, non-inferiority trial designed to compare on a 1:1 basis the efficacy and the safety of the Medtronic Resolute zotarolimus-eluting stent (R-ZES; Medtronic Inc, Santa Rosa, CA, USA) and the Abbott Xiience everolimus-eluting stent (EES; Abbott Vascular, CA, USA). The rationale, design and methodology of the RAC trial have been detailed elsewhere [1].

In brief, 17 institutions enrolled a total of 2292 patients, undergoing percutaneous coronary intervention (PCI), on an all-comers basis, including patients with chronic stable angina, silent ischemia, and acute coronary syndromes between 30th April 2008 and 28th October 2008. DES effectiveness is measured by enduring relief of symptoms or objective evidence of ischemia related to treated flow-limiting coronary obstructions. The primary endpoint in the Resolute-AC trial was defined as target lesion failure (TLF), a composite of cardiac death, target-vessel myocardial infarction (TV-MI), or clinical indicated target-lesion revascularisation (CI-TLR) with the use of either PCI or coronary bypass graft surgery (CABG) within 12 months. Target lesion failure is a commonly used endpoint in coronary stent trials as it captures all potential adverse outcomes related to the stent itself or to the procedures needed to deliver the stent into the diseased vessel. Moreover, this device oriented composite allows to adjust for the potential bias introduced when patients who die or sustain

MI before the end of the target lesion revascularization (TLR) end point time are considered to be free from TLR. Comprehensive definitions of all the trial end-points used in this analysis have been previously published, a short description is provided in the supplementary appendix [1,6–8].

2.2. process for event adjudication in Resolute-AC. role of 'the global oversight committee,' external validation

The workflow and working procedures, including all administrative as well as methodological aspects of the CEC work were pre-specified in detail.

2.2.1. suspected event ('triggers')

Suspected events in the Resolute-AC trial could either be reported by the investigators at the clinical sites, identified through programmed queries from the clinical data base (e.g., laboratory values, ECG or coronary angiogram review) or detected by the CEC during their review process. Independent study monitors (Premier Research Group, Montagny-près-Yverdon, Switzerland) verified all suspected events from data on-site. Complete (100%) source data verification was performed for all items collected in the clinical report forms. Data were stored in a central database (MedNet Solutions Inc, Minnetonka, MN, USA), which was maintained by Cardialysis (Rotterdam, The Netherlands). Clinical follow-up visits for Resolute-AC were done at 1 month (± 5 days), 12 months (± 30 days), with a telephone follow-up at 6 months (± 14 days). Detailed clinical narrative summaries, created using automated information tracking from the eCRF, were provided to the CEC.

2.2.2. the CEC review process

The primary Resolute-AC CEC was a multidisciplinary expert group dedicated to review of adverse events and event adjudication hosted by an independent academic contract research organisation, Cardialysis (Rotterdam, The Netherlands); Harvard Clinical Research Institute (HCRI, Boston, MA, USA) served as the external counterpart CEC. The CEC adjudicated all events using the independent, web-based (FDA 21 CFR part 11 compliant), review method and/or the consensus meeting method. The CEC panels were asked to deliberate until every effort was made to reach a unanimous decision, whenever possible. In case of disagreement the decision was by majority vote ($>50\%$ of voting members present) of the members present. A summary of the rationale for the decision was recorded. Specific complex scenarios that warranted extended discussion and decisions that were not unanimous were recorded in the CEC meeting minutes. These minutes were provided to the GOC.

2.2.3. the external CEC validation process

An (external) check for variability in event adjudication was pre-specified on a random sample of events. A minimum of 10% of the events per study, with a maximum of 100 events for the study in total was re-adjudicated by the external CEC. The external CEC adjudicated the events without knowledge of the adjudication outcome by the primary CEC.

In an effort to ensure consistency in clinical data review and to harmonize the event adjudication process within the RESOLUTE coronary stent clinical trial program, a CEC-Global

Oversight Committee (GOC) was introduced (Fig. 1). The GOC consisted of the CEC Chairperson of each CRO, one clinical reviewer from each CRO (observer), one active CEC members from each CRO (ad hoc members) and a representative of the study sponsor. Only the Chairpersons and active CEC members had voting rights.

This GOC provided a forum for discussion of complex clinical cases and scenarios and served as an instrument for CEC adjudication quality control. The GOC reviewed the decisions of both CECs and determined the cause for discordance, if present. Based on its deliberations, the GOC issued explicit recommendations for adjudication of specific scenarios. Any event that was adjudicated differently by the external CEC was returned to the primary CEC for reconsideration. On their advice, we also interrogated the database to identify any “event triggers” (e.g. cases where the primary CEC had adjudicated a periprocedural MI where the troponin level was exactly 3 ULN), where the adjudication might potentially have been modified by the GOC recommendations. All such “triggers”, identified from the database, were returned for re-consideration to the primary CEC. Criteria were determined to classify discordances in adjudication of primary endpoint events (‘major discordances’). Where any major discordance was identified, all other potential events meeting these criteria were identified by programmed queries from the Resolute-AC trial database and returned to the primary CEC for reconsideration. The GOC process described in this manuscript took place and was finalized before the 12 months Resolute-AC trial database lock, data analysis and reporting.

2.3. Events included in this analysis

For the purpose of this pre-specified analysis, we randomly identified a subset of 100 potential trial events including 5 deaths, 40 MI's, 21 repeat revascularisation and 34 cases of stent thrombosis. This breakdown was set based on the specific type of event (related to the primary endpoint of TLF) and the

prevalence of the event. After the external validation process and review by the GOC, we performed a dedicated central study base screening process to detect any events whose adjudication might be affected by the GOC recommendations

2.4. Statistical analysis

Variables were summarized as percentages for dichotomous variables or medians (25th–75th percentiles) for continuous variables. The Resolute-AC trial was powered for non-inferiority testing of the primary endpoint at 12 months on an intention-to-treat basis. (1) Based on the published statistical analysis plan we challenged the primary conclusion of the main paper implementing a worst case scenario for the R-ZES: any discrepancies in adjudication of individual components of TLF were set in favour of the EES and non-inferiority testing repeated. Analyses were performed with SAS version 8.02 by a dedicated statistician.

3. Results

A total of 2245 of 2292 patients (97.9%) completed 12-months follow up in RAC. We identified 1336 suspected events for the primary endpoint of TLF (49 deaths, 1019 non-fatal MI, 268 percutaneous coronary revascularisations), and 206 for stent thrombosis Table 1 shows the data source break down for the event triggers in the Resolute-AC trial and their relative contribution to the reported outcome.

Table 2 details the results of the cross-adjudication process on a pre-specified random sample of 100 event triggers. For the individual components of the primary endpoint of TLF (non-hierarchical), there was a final discordance between CECs for 7 out of 100 suspected events in 5 patients: 2 deaths, 3 MIs and 2 TLRs. In the context of the GOC-process, the primary CEC unilaterally reviewed all discrepancies on adjudications implicating TLF, yet maintained their initial judgement.

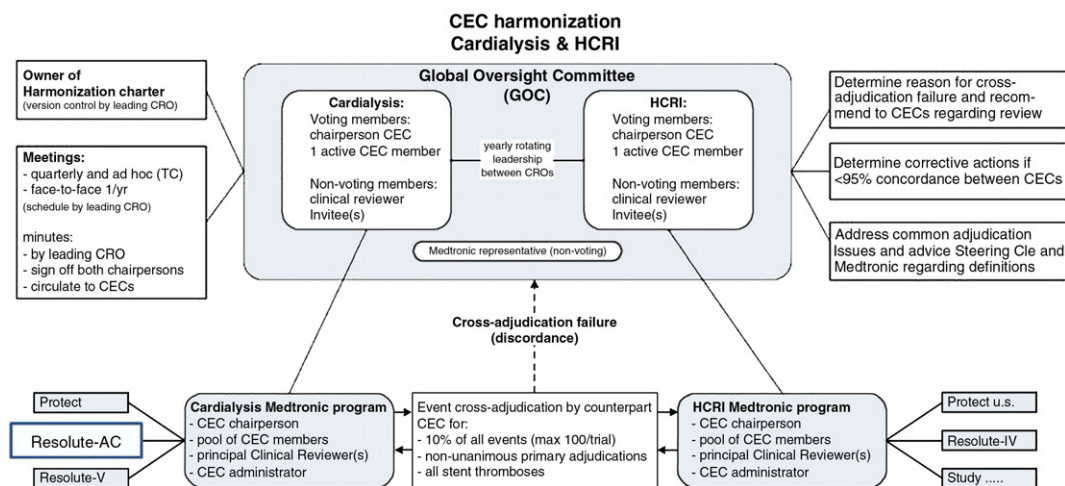


Fig. 1. The global oversight committee (GOC). This GOC provides a forum for discussion of complex clinical cases and scenario's and an instrument for CEC adjudication quality control. The GOC maintains a CEC master document according to the result of its deliberations. Their members will review trial specific elements related to event adjudication and data management. Appropriate channels of communication, lines of responsibility and authority are important prerequisites in its contribution to the smooth and effective clinical trial conduct. The Committee consists of the CEC chairperson of each aCRO (co-directors), one clinical reviewer from each aCRO (observer), one active CEC members from each aCRO (ad hoc members) and a representative of the study sponsor.

Table 1

Breakdown of the suspected primary endpoint events and primary endpoint events during the consecutive steps in data review and reporting in the resolute all-comers trial within 12 months (results on event level).

	Initial adjudication	After GOC database review	Confirmed pre-validation process	Confirmed post-validation process
Target lesion failure ^a	1318	1336	275	272
Cardiac death	49	49	34	34
Target vessel MI	1019	1019	99	95
Clinical TLR	250	268	92	95
Stent thrombosis	205	206	48	48

^a Non hierarchical.

3.1. Death

Of 5 deaths, the primary CEC adjudicated 5 as cardiac death, implementing a conservative ('worst case') view unless a clear non-cardiac cause, with independent confirmation by source documentation, was evident. The option "unexplained" was generally used to indicate that additional source documentation would potentially alter the initial decision but that, in its absence, cardiac death would be the default. In accordance with the ARC recommendations unexplained death defaulted to cardiac death. Whilst the external CEC adjudicated 2 cases of cardiac death by the primary CEC as non-cardiac death, the GOC endorsed the position taken by the primary CEC, based on the worst case scenario.

Table 2

Results for cross adjudication (expressed as counts and percentages).

Suspected event	Primary CEC	Cross CEC	
		Concordant	Discordant
Death	5/5 (100.0)	5/5 (100.0)	0 (0.0)
Cardiac death	5/5 (100.0)	3/5 (60.0)	2/5 (40.0)
Non-cardiac death	0/5 (0.0)	2/5 (40.0)	3/5 (60.0)
Myocardial Infarction ^a	12/40 (30.0)	9/40 (22.5)	3/40 (7.5)
Target vessel MI	7/40 (17.5)	6/40 (15.0)	1/40 (2.5)
Non target vessel MI	3/40 (7.5)	1/40 (2.5)	2/40 (5.0)
Unknown ^b	2/40 (5.0)	0/40 (0.0)	2/40 (5.0)
Q-wave-MI	1/40 (2.5)	0/40 (0.0)	1/40 (2.5)
Non-Q wave MI	7/40 (17.5)	7/40 (17.5)	0/40 (0.0)
Undetermined ^c	4/40 (10.0)	0/40 (0.0)	4/40 (10.0)
Revascularisation	21/21 (100.0)	21/21 (100.0)	0/21 (0.0)
Clinical signs and/or symptoms of myocardial ischemia	18/21 (85.7)	17/21 (81.0)	1/21 (2.0)
CI-TLR	6/21 (28.6)	6/21 (28.6)	0/21 (0.0)
CI-TVR	12/21 (57.1)	11/21 (52.3)	1/21 (4.8)

CEC denotes clinical events committee, CI-TLR denotes clinical indicated target lesion revascularization, CI-TVR denotes clinical indicated target vessel revascularization.

^a Extended historical (World Health Organization)-MI-definition.

^b Target vessel cannot be attributed.

^c The presence of a Q-wave could not be determined.

3.2. Myocardial Infarction

Of 40 suspect MI events, the primary CEC confirmed 12 MI events. One was a Q wave and 7 were non-Q wave MIs according to the extended historical definition. In 4 patients the MI could not be unequivocally classified as Q or non-Q with the source documentation provided. Cross-adjudication resulted in 4 discrepancies. The external CEC did not confirm 3 MI events (1 was not clearly attributable to a non-target vessel and thereby potentially contributed to the primary endpoint of TLF). One (1/3) discordance between CECs was based on interpretation of the ECG-readings; 2 were based on interpretation of the biomarker data (both patients had primary PCI at index).

3.2.1. MI (extended historical) not clearly attributable to a non-target vessel

Discrepancies in this category were 2. Both were related to differences in the attribution of the MI to the target vessel ('in the territory of the implanted stent'). However, as 'Target vessel location unknown' defaults to target vessel, one discrepancy was resolved.

3.2.2. Qversus non-Q-MI

In 7 cases both CECs agreed on a non-q-wave MI. Q-wave versus non-Q-wave discrepancies were all driven by missing or poor quality follow-up ECG recordings and new (or pre-existing) bundle branch block. In the absence of ECG data (i.e., missing baseline or follow up ECG), or when Q-wave could not be determined (e.g. left bundle branch block, poor ECG quality) the primary CEC took a conservative approach resulting in all such MIs being classified as Q. After review by the GOC, the option "cannot be determined" and "no ECG available" defaults to "non-Q-wave MI," unless the CEC felt (on review of all other available data) that it should be classified, on clinical grounds, as a Q-wave MI. After readjudication by the Primary CEC, two discrepancies were resolved.

3.3. Clinical indicated TLR-TVR

For clinically indicated-TLR, no discrepancies were identified. There was one discrepancy in clinical indicated TVR, based on difference in appreciation of the clinical justification for re-intervention between CECs.

3.4. Stent thrombosis

There was no discordance for stent thrombosis events: the primary CEC changed their initial decision on 3 events in the interim based on additional source documents, not available at the time of the initial adjudication but provided to the external CEC for the cross-adjudication. These readjudications, by the primary CEC, were automatically triggered by the availability of the new source documents independent of the current study.

3.5. Implementation of oversight committee recommendations: effect on event rates

As shown in Table 3, after the initial adjudication by the primary CEC, the primary endpoint of TLF (hierarchical) at 12-months was positively adjudicated in 184 patients. Stent

Table 3
Resolute all-comers trial outcomes at 12 months (entire patient cohort).

Outcome	Final adjudication	Changes during GOC review ^a		Index CEC adjudication
		Added	Removed	
Target lesion failure ^b	186	2	0	184
Death				
All cause	49	–	–	49
Cardiac	34	–	–	34
Noncardiac	15	–	–	15
Myocardial infarction ^c				
All	100	0	2	102
Target-vessel	93	0	3	96
Non-target-vessel	8	1	0	7
Q-wave	16	1	12	27
Non-Q-wave	85	12	3	76
TLR ^d	82	3	0	79
TVR ^d	109	6	0	103
Stent thrombosis				
ARC definite or probable	26	–	–	26
ARC definite	16	–	–	16
ARC probable	11	–	–	11
ARC possible	18	–	–	18

ARC denotes Academic Research Consortium.

^a Changes on per patient base.

^b Target Lesion Failure is defined as a composite of death from cardiac causes, any myocardial infarction (not clearly attributable to a nontarget vessel), or clinically indicated target-lesion revascularization. Results for TLF are hierarchical.

^c Extended historical (World Health Organization)-MI-definition.

^d TLR denotes clinical indicated target lesion revascularization, TVR denotes clinical indicated target vessel revascularization, these events represents ischemia-driven events.

thrombosis, either definite or probable, was adjudicated in 26 patients. Following the GOC validation process, but before data base closure, TLF (hierarchical) was positively adjudicated in two more patients based on removal of 1 MI event (one out of 4 additional MI events in 3 patients was censored, 2 MI events occurred in patients that also died from a cardiac cause and were counted as cardiac death), and 3 added clinical TLRs (Table 1, 12 month outcome on a per event level). The total count for stent thrombosis cases did not change. Of notice, during the GOC-process specific queries on this item were performed on all 1019 (100%) of the MI-triggers. There were no unreported new ischemic events, and therefore no probable stent thrombosis cases (6), from the time the guiding catheter was removed and the patient left the catheterisation suite up to 48 h. By protocol, the CEC could adjudicate a Q-wave MI in the context of an appropriate clinical scenario and cardiac enzyme data (supplementary appendix). The RAC database was

interrogated to identify all MIs, previously adjudicated as 'Q-wave cannot be determined' or 'no ECG available' to determine whether the default to non-Q-MI was appropriate considering the clinical scenario and/or cardiac biomarker elevations. As a result, two more MIs were adjudicated as Q-wave based on the cardiac enzyme data. One non-target vessel MI was no longer considered an event upon review (Data not shown).

Table 4 shows the primary endpoint analysis in Resolute-AC biased against the study stent (R-ZES) stent by adding 3 clinically indicated TLR to R-ZES and removing 4 target vessel MI from EES. In this worst case scenario, the one-sided 95% confidence interval for the difference between the two stents remained on the positive side of the pre-specified non-inferiority margin of 0.035 (3.5%).

4. Discussion

The principal findings and potential consequences of the Resolute Clinical Program GOC external CEC validation process described in this manuscript are the following:

- The cross-adjudication of a predefined subset of 100 potential primary endpoint events and/or stent thrombosis resulted in 6 discrepancies between 2 different and independent CECs. They were mainly related to the adjudication of target-vessel MI and revascularisation events and explained by a difference in clinical judgement and/or interpretation of angiographic source data.
- The primary CEC reconsidered all individual discordant events and maintained its initial judgement for all adjudications related to TLF.
- In total seven primary outcome events in 5 patients were reclassified based on the harmonization procedures. The (hierarchical) primary endpoint of TLF increased by two events.

This is the first report on an external CEC-process validation in a coronary stent program. It reflects the ongoing effort of 3 AROs, experienced in the field, to improve the quality of the CEC adjudication process. The aim is to identify and address factors related to human error or misjudgement, and to identify complex clinical scenarios where a harmonized approach will facilitate consistency across AROs. This should allow meaningful comparisons between trials and pooling of trial results. It is important to recognize that this validation was performed after robust, pre-specified, internal checks, by the primary ARO. Thus, while the discrepancies in the present study were limited, much greater differences would be expected in studies

Table 4
Modelling the primary endpoint analysis biased against the zotarolimus eluting study stent. A comparison with the parent resolute-AC trial results.

	Primary endpoint	Resolute (ZES) N = 1140 patients	Xience-V (EES) N = 1152 patients	Difference (%)	One sided 95% upper confidence bound (%)	Delta (%)	P-Value
RAC-III	TLF 360 days	8.2% (92/1119)	8.3% (94/1126)	–0.1	1.8	3.5	<0.001
Worst case scenario considering the GOC-process	TLF 360 days	8.5% (95/1119)	8.0 (90/1126)	0.5	2.4	3.5	0.005

TLF denotes target-lesion failure a composite of death from cardiac causes, any myocardial infarction (not clearly attributable to a non-target vessel), or clinically indicated target-lesion revascularization within 12 months.

where less stringent monitoring of source documents occurred and where less robust procedures were in place to ensure internal consistency in event adjudication. This external CEC-process validation involved reassessment of a substantial proportion of all suspected events in RAC. Based on the initial identification of potential discrepancies in a limited subset of one hundred events, up to 70% of all suspected primary endpoint events were reassessed. In the end, 7 out of 224 (3.0%) primary outcome events were reclassified, with only two additional patients identified as having a TLF. The current CEC-process validation contributed to a more correct outcome reporting without challenging the main Resolute-AC trial results or conclusions.

The RAC was open label for the stent component with a risk for systematic 'differential' misclassification of events (i.e. periprocedural MI) by the investigators. With this in mind and provided the non-inferiority design of RAC, protection against non-differential misclassification of events, by the use of an independent CEC –blinded to treatment assignment–, may be most important [9]. Ideally the clinical adjudication process by itself should be highly specific, based on a uniform application of pre-specified criteria for event definitions. In the Resolute-AC, the primary-device oriented- endpoint was aligned with the ARC consensus definitions for stent investigations in stable coronary disease patients with de novo lesions. [6] A specific challenge was the implementation of the ARC definitions in an all-comer study design. The inclusion of patients with ACS and/or more complex lesion morphology (e.g. left main lesions, bifurcations or trifurcations) may jeopardize uniform clinical endpoint adjudication. We emphasize the importance of process guidance and rules with an effort to anticipate complex adjudication scenarios especially in contemporary large, near real world studies with relatively long-term clinical endpoints. We call for an on-going effort to codify, and document the rationale for, adjudication decisions for complex scenarios in order to maintain consistency throughout a trial.

The available ARC-definitions had evident limitations when addressing re-infarction/MI extension due to PCI in patients with an on-going spontaneous MI. As discussed in the recent literature, adjudication of an MI due to PCI in patients with an ongoing spontaneous MI using the 2007 Universal MI definitions may be problematic [10,11]. Unless there is a clear indication that the cardiac biomarker sample values were falling following the index event and rising again, there would otherwise be insufficient biomarker data to adjudicate a PMI based on the biomarker data. For Resolute-AC, the steering committee considered MI events adjudicated according to the modified historical definitions of MI [1–8]. While it was anticipated that MI adjudication might prove problematic as nearly one third of the all-comers patient population presented with an ACS, no major discordance between CECs was noted while implementing these pre-specified MI adjudication rules. However, attributing the MI event to the target vessel implicated clinical judgment and caused divergence in opinion between CECs.

With this external validation, all aspects of clinical endpoint adjudication, from data collection to final CEC judgement, were addressed. Relevant with respect to the interpretation of a specific clinical trial is the percentage of permanently missing minimal required data for event adjudication and the way these were handled. Permanently

missing data can potentially impact the power of a trial and introduce bias in the outcome analysis [12].

The impact of an external validation process on the final Resolute-AC outcome reporting may be considered important. Currently much published trial data is not based on adjudication and data analysis by a truly independent CEC. In that context, the potential for error is a source of major concern and its potential impact on the reliability of published data is not something that is widely appreciated by the general medical community.

External validation of the CEC process to judge accuracy and consistency in event adjudication should be considered as a factor in the assessment of the quality of a trial and in the relative weight given to published data.

There are limitations to our analysis. Only a limited subset of suspected events was cross-adjudicated in this process so the potential impact on the trial outcome reporting may have been underestimated. However, as already indicated, up to 70% of all event triggers, including all MI event triggers were re-examined, and re-adjudicated where necessary, based on specific issues identified by the GOC.

5. Conclusions

CECs must be rigorous and consistent in their analysis of data to maximize the clinical and research value of clinical trial data. The quality of the CEC-process should be assessed on an on-going basis throughout the clinical trial and/or trial program via internal and/or external validation. Pooling of data within a coronary stent trial program is possible if uniform endpoint definitions are used and the CEC- adjudication process harmonised.

6. Disclosures

The authors have no conflicts of interest to report related to the content of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.cct.2012.08.012>.

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