Standardized End Point Definitions for Coronary Intervention Trials

The Academic Research Consortium-2 Consensus Document

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The Academic Research Consortium (ARC)-2 initiative revisited the clinical and angiographic end point definitions in coronary device trials, proposed in 2007, to make them more suitable for use in clinical trials that include increasingly complex lesion and patient populations and incorporate novel devices such as bioresorbable vascular scaffolds. In addition, recommendations for the incorporation of patient-related outcomes in clinical trials are proposed. Academic Research Consortium-2 is a collaborative effort between academic research organizations in the United States and Europe, device manufacturers, and European, US, and Asian regulatory bodies. Several in-person meetings were held to discuss the changes that have occurred in the device landscape and in clinical trials and regulatory pathways in the last decade. The consensus-based end point definitions in this document are endorsed by the stakeholders of this document and strongly advocated for clinical trial purposes. This Academic Research Consortium-2 document provides further standardization of end point definitions for coronary device trials, incorporating advances in technology and knowledge. Their use will aid interpretation of trial outcomes and comparison among studies, thus facilitating the evaluation of the safety and effectiveness of these devices.

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Since the first Academic Research Consortium (ARC) recommendations on standardized end point definitions in coronary device investigations, the landscape of coronary intervention has considerably evolved.[1] The technology has matured, and more-comer populations with more complex lesions are a major focus of clinical trials. Physiology-guided percutaneous coronary intervention (PCI) has been incorporated into clinical practice guidelines.[2] Bioresorbable vascular scaffolds (BRS) have been introduced that have unique failure modes compared with predicate devices. In addition, the universal definition of Myocardial Infarction (MI) was updated in 2012[3,4] (with a further revision due in 2018), and the Society for Cardiovascular Angiography and Interventions (SCAI) proposed a common definition of "clinically relevant MI" for periprocedural PCI– and coronary artery bypass graft (CABG)– related events that have been shown to have prognostic significance.[5] Finally, PCI and CABG trials have generally focused on reporting treatment failures (death, MI, and reintervention) as a measure of efficacy. The relatively low frequency of these events with contemporary drug-eluting stents (DES) makes demonstrating differences between current devices difficult and misses an opportunity to assess the impact of revascularization on other measures of patient status such as patient-centered outcomes that may affect larger numbers of patients.

The ARC definitions have been widely used in clinical and research settings and have provided a standard for consistency in reporting clinical outcomes that has been replicated by subsequent ARC initiatives. The current initiative reconsidered the end point definitions in device studies to make them more suitable to the present and future needs of clinical trials in more complex settings. Table 1 shows the salient differences between ARC-1 and ARC-2 in terms of the definitions of end points common to both documents.

Similar to the ARC-1 process, in-person meetings involving ARC study group members, independent experts, including surgeons and interventional cardiologists, the US Food and Drug Administration, and industry representatives provided much of the substantive discussion from which this ARC-2 consensus document was derived (Appendix A in the online-only Data Supplement provides a full list of participants).

Patient-oriented (Global) Cardiovascular End Points: General Considerations

The basis for coronary device evaluation should be overall cardiovascular outcomes from the patient perspective, including death, MI, stroke, and repeat revascularization procedures, but may also consider myocardial ischemia and objective, validated measures of quality of life (Figure 1 and Table 2).

Composite End Points

The ARC-2 consensus suggests the composite end points for device trials listed in Table 2. Composites generated by the combination of individual end points provide additional statistical power to detect potentially meaningful differences between treatments. The individual components should represent clinically meaningful events, should be linked by common elements of pathophysiology, and should be reported individually.

Table 1 Salient Differences Between ARC-1 and ARC-2 in Terms of the Definitions of End Points

End Point	ARC-1	ARC-2	Additional Comments
Death (see also Table 3)	3 Categories: cardiac, vascular, and noncardiovascular	3 Categories: cardiovascular, noncardiovascular, and undetermined	ARC-2 recommends subclassification using CDISC criteria
Myocardial infarction (see also Table 4)	(1) Different definitions of PMI for PCI and CABG (2) PMI criteria considered cTn/CK-MB	(1) A single definition for both PCI and CABG trials (2) PMI incorporates hs-cTn	Specific ancillary angiographic and imaging criteria are provided (Table 5)
Repeat revascularization (see also Tables 6 and 7)	Addressed only simple lesion scenarios	Designed to accommodate all-comer–based clinical trials and complex anatomy	ARC-2 prioritizes functional evaluation for adjudication of repeated revascularizations as clinically indicated (Table 7)
Stent thrombosis (see also Tables 6 and 7)	(1) Considered only stent trials (2) 3 Categories: definite, probable, and possible	(1) Considers stent and BRS studies (2) 2 Categories: definite and probable	ARC-2 incorporates definitions for silent occlusion and intraprocedural device thrombosis
Patient-reported outcomes	Not included	Detailed description, including blinding, quality control, handling of missing data, frequency of assessments, and duration of clinical trials	

ARC indicates Academic Research Consortium; BRS, bioresorbable scaffold; CABG, coronary artery bypass grafting surgery; CDISC, Clinical Data Interchange Standards Consortium; CK-MB, creatine kinase-MB; cTn, cardiac troponin; hs-cTn, high-sensitivity cardiac troponin; MI, myocardial infarction; PCI, percutaneous coronary intervention; and PMI, periprocedural myocardial infarction.

Figure 1 Combined end points for clinical trials in coronary interventions. cTn, cardiac troponin; URL, upper reference limit.
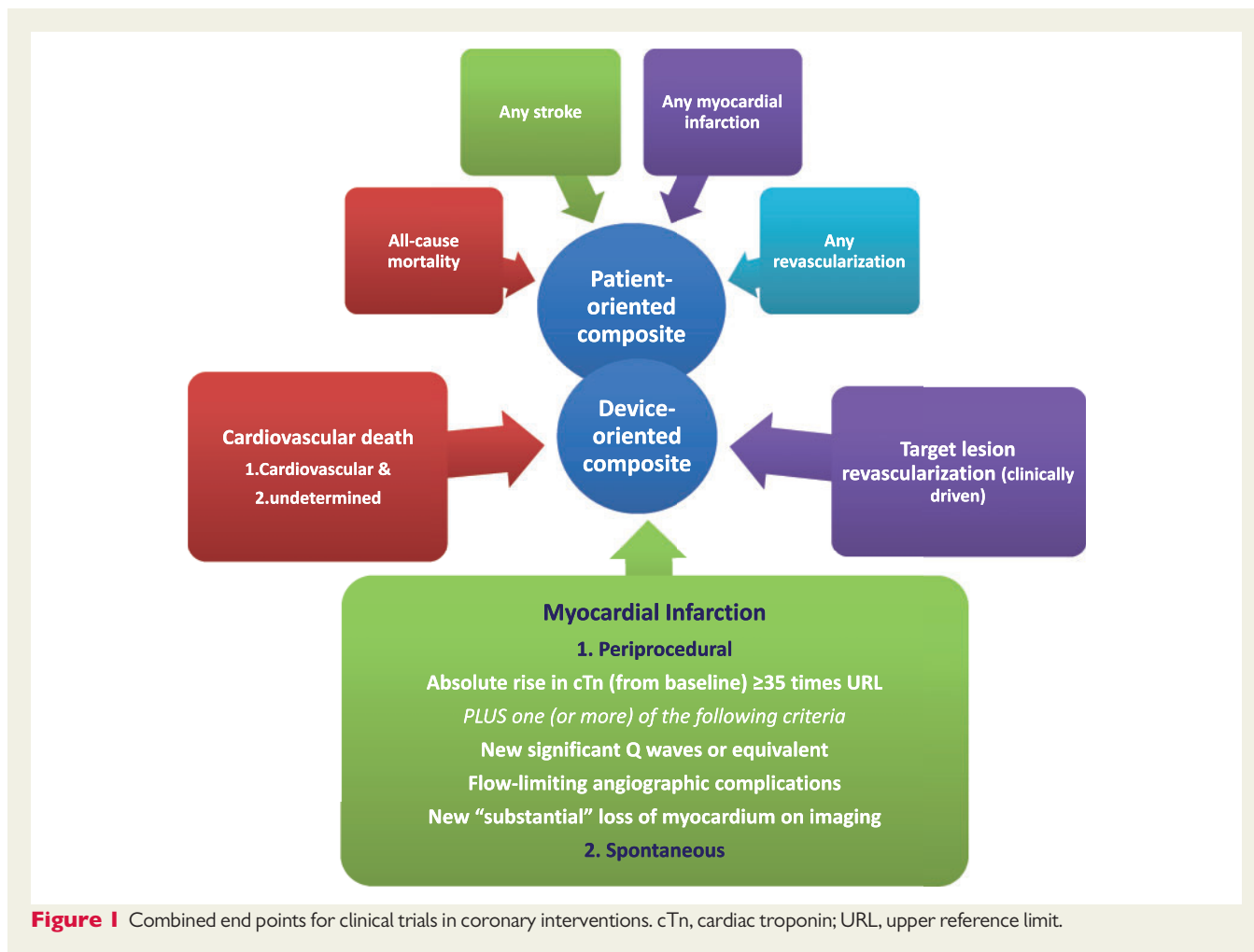
Other composites such as net clinical benefit that may incorporate safety-related events like bleeding or composites that include potential surrogate measures of device success such as patient-reported or patient-centered outcomes might have application for specific devices and clinical trials. Similarly, additional end points such as any rehospitalization either for a cardiac reason (eg, unstable angina) or for a reason related to the procedure may have application in specific trials. The ARC-2 consensus for DES and BRS end points is, in most cases, to regard such composites as secondary end points. We suggest that the terms severe recurrent ischemia and urgent target vessel revascularization, proposed as end points for some trials, be avoided, although they may serve as Clinical Events Committee (CEC) triggers to aid complete ascertainment of MI or repeat PCI.

Proposed Safety And Efficacy End Points

Death

ARC-2 considers all-cause mortality the most unbiased method to report deaths in a clinical trial or observational study, although it may be less device or procedure specific than deaths adjudicated as cardiac in origin (*Table 3*). Previously, ARC-1 recommended that death be reported as cardiac and vascular. ARC-2 proposes that the cardiac and vascular categories be merged into a single entity, cardiovascular, in order to be consistent with pharmacological studies, although in individual trials, it may be reasonable to denote more specific subcategories.

Device trials are designed primarily to reduce cardiac morbidity and mortality; thus, including noncardiac death may mask any potential signal of a device effect. Careful consideration of inclusion and exclusion criteria for specific device trials has evident merit in this context. However, we also recommend that a specific subcategory, undetermined cause, be reported for deaths for which no information is available. Deaths of undetermined cause will default to cardiovascular (but should be reported as a separate subcategory of cardiovascular death to denote this uncertainty). Deaths related to the procedure or complications of the procedure (or concomitant treatment) are always classified as cardiovascular. Adjudication issues are discussed in Appendix B in the online-only Data Supplement.

We further recommend that cardiovascular and noncardiovascular deaths be reported in tables in broad subcategories reflecting commonly occurring causes of cardiovascular and noncardiovascular

Table 2 Composite End Points

End Points	Individual Elements
Patient-oriented composite (hierarchical order)	All-cause mortality
	Any stroke
	Any MI (includes nontarget vessel territory)
	Any revascularization
Device-oriented composite (hierarchical order)	Cardiovascular death
	MI (not clearly attributable to a nontarget vessel)
	TLR (clinically driven)
Safety end points	All-cause mortality
	Cardiovascular death
	MI
	Definite/probable stent thrombosis
	Stroke (Neuro-ARC definitions)
	Bleeding (BARC-3 and -5)
Effectiveness end points	Any coronary revascularization
	Target vessel revascularization (clinically driven)
	TLR (clinically driven)
	Any hospitalization either for a cardiac reason or related to the procedure (and concomitant treatment)
	Patient-reported outcomes (ie, Seattle Angina Questionnaire)
Other composite end points	Target vessel failure
	Cardiovascular death
	MI (target vessel)
	Target vessel revascularization
	Target lesion failure
	Cardiovascular death
	MI (target vessel)
	TLR (clinically driven)

ARC indicates Academic Research Consortium; BARC, Bleeding Academic Research Consortium; MI, myocardial infarction; and TLR, target lesion revascularization.

Table 3 Classification of Death

Type of Death	Definition
Cardiovascular death	Cardiovascular death is defined as death resulting from cardiovascular causes. The following categories may be collected: 1. Death caused by acute MI 2. Death caused by sudden cardiac, including unwitnessed, death 3. Death resulting from heart failure 4. Death caused by stroke 5. Death caused by cardiovascular procedures 6. Death resulting from cardiovascular hemorrhage 7. Death resulting from other cardiovascular cause
Noncardiovascular death	Noncardiovascular death is defined as any death that is not thought to be the result of a cardiovascular cause. The following categories may be collected: 1. Death resulting from malignancy 2. Death resulting from pulmonary causes 3. Death caused by infection (includes sepsis) 4. Death resulting from gastrointestinal causes 5. Death resulting from accident/trauma 6. Death caused by other noncardiovascular organ failure 7. Death resulting from other noncardiovascular cause
Undetermined	Undetermined cause of death is defined as a death not attributable to any other category because of the absence of any relevant source documents. Such deaths will be classified as cardiovascular for end point determination.

MI indicates myocardial infarction.

death, based on the Cardiovascular Endpoints Data Standards classification,[6] as outlined in *Table 3*.

Myocardial Infarction

MI may be an entry criterion for a clinical DES/BRS trial, may occur in the periprocedural period, or may occur long after device implantation as a result of spontaneous MI or late complications of the study device.[7,8]

MI definitions include certain arbitrary assumptions and vary across PCI, CABG, structural, and cardiovascular drug trials. In particular, clinical trial definitions of periprocedural (type 4a) MI have been difficult to standardize. The complexity stems from the use of increasingly sensitive biomarkers of subtle myocardial injury balanced against a need to identify events that clearly affect clinical outcomes, including mortality. Inconsistency among definitions remains a formidable barrier to the understanding of results across clinical trials or the pooling of results for the detection of safety signals. Variability comes from the choice of different biomarkers (eg, creatine kinase-MB [CK-MB] versus cardiac troponin [cTn]), the use of different ratios for individual biomarkers, and the adoption of different thresholds (eg, manufacturer upper reference limit [URL] versus site-determined upper limit of normal) for adjudication.

The use of CK-MB versus cTn has been especially controversial in the classification of periprocedural MI. On the basis of a wealth of historical data, the SCAI suggested a CK-MB threshold of 10 times the upper limit of normal (or 5 times in the presence of new Q waves) as a determinant of clinically relevant MI.[5] In the last 2 decades, however, cTn has progressively replaced CK-MB as the preferred biomarker of myocardial injury in all other clinical settings. Thus, CK-MB assays are no longer available at many centers. Both the added clinical value of cTn assays in the triage of patients with suspected acute coronary syndrome and the prognostic

implications of background cTn levels regardless of the clinical setting are clearly established.

However, cTn assays pose several challenges from a clinical trial perspective. The analytic sensitivity among marketed cTn assays varies over several orders of magnitude. Therefore, the absolute values from 1 assay are not interchangeable with those from another. Furthermore, a several-fold increase (eg, 5 URL) with a high-sensitivity cTn (hs-cTn) assay may not be associated with a detectable increase with a less sensitive earlier-generation assay, leading to significant differences in the event frequency based solely on the assay used.

The term high sensitivity reflects the characteristics of the assay, not a difference in the form of measured cTn. Specific criteria have been proposed by the International Federation of Clinical Chemistry and Laboratory Medicine to define hs-cTn assays.[9] Briefly, such assays should detect measurable levels of cTn in many (>50%) normal subjects and reliably detect changes (total imprecision, ie, percent coefficient of variation <10%) at the 99th percentile URL.

Spontaneous MI

ARC-2 endorses the classification of spontaneous MI and MI related to complications of the study device (types 1, 2, 3, 4b, and 4c) proposed by the 2012 universal definition of MI. We note that it can be difficult for an event committee to distinguish type 1 MI from type 2 MI or nonischemic myocardial injury with necrosis when additional investigations that might provide further clarification were judged inappropriate from a clinical perspective or when complete source documentation is missing. ARC-2 recommends that suspected spontaneous MI triggers, for which a biomarker rise is documented without clear evidence of a type 1 or 2 MI, should be adjudicated and reported as "myocardial injury not meeting MI criteria" in clinical trials. As noted, the use of multiple cTn assays in a trial, such as may occur when different assays are used in referring and study centers, is problematic. Adjudication issues are discussed in Appendix B in the online-only Data Supplement.

Periprocedural PCI and CABG MI or Significant Myocardial Injury

A threshold of significance for postprocedural cTn elevation has not been determined for periprocedural MI. The initial common 2007 ARC and universal definition of periprocedural MI proposed a very low (>3 URL) biomarker threshold for PCI with a preference for cTn and did not require ancillary criteria. The ARC noted its concern that the >3 cTn stand-alone threshold would be overly sensitive as a discriminator of clinically meaningful differences among devices and recommended collection, in parallel, of CK-MB data. These concerns were validated, and the subsequent 2012 universal definition of MI both increased the cTn threshold and required additional criteria (1 or more of the following: ischemic chest pain, angiographic complications, or imaging evidence of new loss of myocardium) for PCI-related MI.

On the basis of the recognition that CK-MB data are less commonly available, there have been efforts to correlate cTn

Comment Box

- ARC proposes a definition of periprocedural MI for PCI and CABG with a common time frame, an identical biomarker threshold, and clearly defined ancillary criteria.
- ARC recommends that MI triggers be adjudicated with the use of the manufacturer-recommended URL (with sex-specific values when relevant) to facilitate comparisons between trials.
- Ideally, a single cTn assay should be used, but if not feasible, the use of the same cTn assay for the assessment of serial changes in individual trial subjects is critically important. Only cTn assays that comply with the minimum requirements of the 2012 universal definition of MI are acceptable.
- Systematic assessment of serial (timing assay specific, generally 3–6 hours) cTn values, before intervention, to ascertain whether the baseline levels are less than URL, elevated and stable or falling, or elevated and potentially rising is critical both for MI adjudication and for subsequent stratified analyses in clinical trials. In most PCI trials, cTn may be measured when informed consent is obtained and at the start of the procedure (eg, after arterial sheath placement but before intervention).
- Given the potential for ascertainment bias, we strongly advocate that the percentage of patients in whom biomarkers were actually measured at protocol-mandated time points before and after the procedure be reported in all trials and considered as a quality metric.
- Hs-cTn values must be reported as whole numbers in nanograms per liter as recommended by the International Federation of Clinical Chemistry and Laboratory Medicine.
- All data for cTn and CK-MB should be tabulated for each classification to include at least the following multiples of the URL by treatment groups: >1, ≥5, ≥10, ≥35, ≥70, ≥100, and ≥250. Cumulative frequency distributions for cTn and CK-MB by treatment group should be provided.

elevations with CK-MB values and clinical outcomes.[10] Although the correlations are imperfect, the SCAI authors suggested an alternative of cTn (≥70 the local laboratory upper limit of normal) as a replacement for CK-MB (≥10 the local laboratory upper limit of normal) on the basis of these calculations. Finally, the SCAI specifically excluded the use of hs-cTn assays for the cTn threshold because of the absence of data. Analytical data have demonstrated that at higher levels (100–10 000 ng/L), values obtained with the fifth-generation hs-cTnT assay are highly correlated with values obtained with the fourth-generation assay. As a result of the greater precision of the hs-cTnT assay, there are significant differences at low (<100 ng/L) levels.[11]

The ARC acknowledges that CK-MB data will be available only in certain situations such as when a central laboratory is funded by the clinical investigation. Recognizing that cTn or hs-cTn has or will become the standard, we propose alternative thresholds that approximate the CK-MB historical evidence. We acknowledge that, for specific comparisons, the SCAI CK-MB, the 2012 universal definition of MI, and/or the 2007 ARC-based thresholds may still be incorporated in ongoing trials. This includes those for which historical comparisons are critical or for specific trial designs such as comparisons

between PCI and CABG. However, when this is the case, we recommend that the ARC-2 definitions, described below, also be reported.

On the basis of the CK-MB historical evidence, ARC-2 proposes a common ≥35 URL threshold for cTn for both PCI- and CABG-related periprocedural MI as a reasonable threshold (*Table 4*). This

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Table 4   Periprocedural Myocardial Infarction Percutaneous Coronary Intervention and Coronary Artery Bypass Grafting (Within 48 Hours)

Myocardial infarction

    Absolute rise in cardiac troponin (from baseline) ≥35 times upper reference limit

    Plus 1 (or more) of the following criteria

        New significant* Q waves or equivalent

        Flow-limiting angiographic complications

        New "substantial" loss of myocardium on imaging

Significant periprocedural myocardial injury

    Absolute rise in cardiac troponin (from baseline) ≥70 times upper reference limit

Definitions applicable in patients with normal (or elevated and stable or falling) baseline biomarkers. For specific trials, the Society for Cardiovascular Angiography and Interventions, the 2012 universal definition of myocardial infarction, or the 2007 Academic Research Consortium criteria may be preferred. When this is the case, we recommend the Academic Research Consortium-2 criteria also be reported.

*Q-wave criteria requires the development of new Q waves ≥40 ms in duration and ≥1 mm deep in voltage in ≥2 contiguous leads.

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absolute rise applies both to patients with baseline cTn levels <URL and to those in whom baseline cTn levels are elevated and stable or falling. The ARC is concerned that the 20% rise compared with baseline, proposed by the Universal Definition Taskforce in patients with elevated and stable or falling cTn levels at baseline, may be overly sensitive in those with modest and insufficiently sensitive in those with marked elevation in baseline cTn for use as a discriminator in clinical trials.

ARC proposes that 1 ancillary criterion be required in addition to the ≥35 cTn rise to fulfill the definition of periprocedural MI. The ancillary criteria are 1 or more of the following: "flow-limiting" angiographic complications in a major epicardial vessel or >1.5-mm-diameter branch, new significant Q waves (or equivalent) related to the procedure, or a "substantial" new wall motion abnormality on echocardiography related to the procedure. The ancillary angiographic and electrocardiographic criteria should be adjudicated, ideally after core laboratory assessment, by an independent CEC. The CEC should review the angiographic images and the 12-lead electrocardiographic tracings (*Table 5*). Chest pain is not considered a criterion with sufficient specificity to be a useful discriminator in this setting.

While acknowledging that no evidence-based prognostic threshold for periprocedural injury exists for hs-cTn, we accept a rise in cTn ≥70 times the URL (when baseline levels are less than the URL or elevated and stable or falling) as a reasonable threshold for a stand-alone definition of significant periprocedural injury. We recommend that these isolated biomarker elevations also be reported. Although a perfect definition is not possible, this allows discrimination between therapies such as novel DES or scaffolds at a level that is

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Table 5   Angiographic Complications/Imaging Criteria

Complications	Criteria
Loss of patency of major vessel, graft, or side branch	Abrupt main vessel closure
	1. When TIMI grade 3 or 2 flow at baseline; TIMI grade 0 or 1 flow after the procedure
	2. When TIMI grade 1 flow at baseline; TIMI grade 0 flow after the procedure
	3. When TIMI grade 0 flow at baseline and vessel patency (TIMI grade 2 or 3 flow) established during procedure; TIMI grade 0 flow after procedure
	Side branch (≥1.5 mm) occlusion after the procedure: TIMI grade 0 or 1 flow in a side branch initially patent with TIMI grade 2 or 3 flow
Embolization	The appearance of an abrupt cutoff in the distal vessel (or in a side branch ≥1.5 mm) after percutaneous coronary intervention
Disruption of collateral flow	Reduction in collateral flow by ≥1 grades (Rentrop classification)
Persistent slow flow or no reflow	Markedly delayed flow (TIMI grade 2 for slow flow, TIMI 0 or 1 for no reflow) in a target vessel with minimal (<30%) residual stenosis at the stented/scaffolded segment and no evidence of flow-limiting dissection
Major dissection	Dissection in the target vessel greater than type B from National Heart, Lung, and Blood Institute classification
Coronary artery bypass graft surgery specific	Angiographically documented new occlusion or flow-limiting stenosis in the graft or new native coronary artery occlusion
New regional wall motion abnormality	Ideally, prospectively predefined imaging protocol or, in its absence, core laboratory or CEC adjudicated
Imaging evidence of loss of viable myocardium	Ideally, prospectively predefined imaging protocol or, in its absence, core laboratory or CEC adjudicated

CEC indicates Clinical Events Committee; and TIMI, Thrombolysis in Myocardial Infarction.

Table 6   Repeat Revascularization

Classification	Definition
Target lesion	The target lesion is defined as the treated segment including the 5-mm margin proximal and distal to the stent/scaffold.*
Target lesion revascularization	Target lesion revascularization is defined as a repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion.
Target vessel	The target vessel is defined as the entire major intervened coronary vessel, including side branches.
Target vessel revascularization	Target vessel revascularization is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel including the target lesion.
Target vessel non–target lesion revascularization	Target vessel non-target lesion revascularization is defined as any repeat percutaneous intervention or surgical bypass of the target vessel for pre-existing disease, disease progression or other reasons unrelated to the target lesion as defined above.

*The Clinical Events Committee may ask for the help of a quantitative coronary analysis core laboratory for the identification of target lesion and adjudication of TLR.

potentially meaningful. For completeness, we strongly urge complete reporting of biomarker data at various thresholds for a qualitative comparison.

A recent American College of Cardiology/American Heart Association consensus document states:

> When data elements and definitions are standardized across studies, comparison, pooled analysis, and meta-analysis are enabled, thus deepening our understanding of individual studies. Although end point definitions may evolve over time, a period in which definitions remain static is needed for terms to be used successfully to conduct a meta-analysis.[6]

The ARC recognizes that the advent of hs-cTn assays with precisely defined, objective, and reproducible parameters for the various elements of the definition could serve as a benchmark to provide the data set for such a meta-analysis.

When the baseline cTn is elevated and rising or when a second determination is superfluous (eg, ST-segment–elevation MI), the ARC considers that it is not possible to reliably distinguish whether a subsequent biomarker rise results from the index MI or is a new MI related to a periprocedural complication. Research protocols in such populations may adopt study-specific end points such as those proposed by SCAI to adjudicate events related to the procedure that may inform a future revision of this document.

Silent MI

The term silent MI, as defined by the Universal Definition Taskforce, refers to new significant Q waves that develop during follow-up outside the periprocedural period. ARC-2 suggests that such events be reported as a separate end point, typically not as a component of the primary end point, in the absence of a clinical event with documented biomarker elevation. ARC-2 suggests that the same Q-wave criteria (development of new Q waves ≥40 ms in duration and ≥1 mm deep in voltage in ≥2 contiguous leads) as for PMI may be used. Alternatively, the methodology used to detect silent MI should be prespecified in detail in the protocol.

Regulatory Considerations

For a study intended for review by a regulatory authority, sponsors may propose a periprocedural MI definition for the primary analysis

Table 7   Fractional Flow Reserve and Quantitative Coronary Analysis for Event Adjudication of Clinically Indicated Repeat Revascularizations

Hierarchically

1. Core laboratory–reported fractional flow reserve ≤0.80 or instant wave-free ratio ≤0.89
2. Site-reported fractional flow reserve ≤0.80 or instant wave-free ratio ≤0.89
3. Quantitative coronary analysis* diameter stenosis >50% (based on the average of multiple views) with either recurrent symptoms or positive noninvasive functional test
4. Quantitative coronary analysis* diameter stenosis >70% (based on the average of multiple views) regardless of other criteria
5. Quantitative coronary analysis diameter stenosis >70% (based on the worst view) regardless of other criteria

*Three-dimensional analysis is preferred when available.

that is most appropriate for the trial design. This is of particular relevance for studies that use historical control data, taking into account the definition used in the control data sets. Although the universal definition of MI and SCAI periprocedural MI definitions have advantages and limitations, ARC acknowledges that they are reasonable, and we suggest, when possible, an additional analysis of periprocedural MI rates with alternative definitions used as a secondary end point to assess the consistency of study outcomes. It is recommended that the selected definition be discussed with regulators before the initiation of patient enrollment. Regardless of the periprocedural MI definition, the most important issue in the assessment of periprocedural events is a complete as possible ascertainment of the necessary data (ie, measurement of cardiac biomarkers and ancillary clinical criteria).

MI Adjudication in the Absence of Minimum Prespecified Protocol Data

As noted above, the failure to measure protocol-specified criteria, generally biomarker levels, may result in underreporting and

potentially introduce bias. Ideally, such scenarios should be addressed upfront in the protocol and CEC charter. However, this is often not the case. We propose (Appendices B and C in the online-only Data Supplement) broadly applicable criteria for CEC adjudication when specific elements for periprocedural or spontaneous MI are permanently missing.

Stroke

Although stroke is rare in the context of coronary device trials, it is an important periprocedural complication of CABG and may occur during follow-up after either revascularization strategy. The ARC recommends that the recent NeuroARC classification be followed.[12] Central to these recommendations are the need for assessment at the investigational site by an independent neurologist and the inclusion in the CEC membership of a neurologist to advise on all or selected potential stroke and transient ischemic event triggers as predefined in the CEC charter.

Bleeding

The ARC recommends that bleeding complications in PCI or CABG trials be classified according to the Bleeding Academic Research Consortium criteria.[13]

Repeat Revascularization

Target lesion revascularization is defined as reintervention for clinically significant renarrowing and thus includes 2 fundamental factors: a functional component and a clinical component (Table 6). The definition of clinically indicated target lesion revascularization (TLR) or target vessel revascularization was an integral part of the 2007 ARC document. We noted that a prerequisite to designate a reintervention as clinically indicated or ischemia driven was the demonstration of a 50% to 70% stenosis on quantitative coronary angiography (QCA) at the target lesion or in the target vessel, assessed by an independent core laboratory (with additional criteria as defined in Table 7). These criteria, incorporating the role of an independent core laboratory using quantitative methods for assessment, are an industry standard that is widely accepted by investigators, trial sponsors, and regulatory authorities around the world. The field has evolved, and the current ARC consensus gives priority to functional assessment with fractional flow reserve (FFR) or equivalent techniques. However, CEC adjudication, with the aid of independent QCA assessment of baseline and reintervention angiograms at a minimum, is mandatory when functional assessments are not performed in trials in which TLR or target vessel revascularization is an end point (Table 6). Of note, in PCI versus CABG trials, the ascertainment of target lesion revascularization is challenging, if not impossible, in the CABG arm. Therefore, ARC recommends that only target vessel revascularization is considered in such trials.

On occasion, at the index procedure, attempted study stent implantation may prove unsuccessful because of technical (eg, failure to predilate a calcified lesion) or other (eg, periprocedural unanticipated hemodynamic instability) challenges, and the patient is brought back later for a second attempt. In such situations, following the intention-to-treat principle, the second procedure should be considered a target lesion revascularization unless otherwise specified in the

protocol. Thus, the time frame for repeat revascularization starts from the moment the patient is taken off the catheterization laboratory table.

Physiological assessments (either FFR or instant wave-free ratio [iFR]) may be useful to justify repeat revascularization procedures as part of the clinical end point adjudication and may serve as a criterion to validate the justification for intervention at the time of study entry in specific protocols. Many lesions with <50% diameter stenosis on QCA are FFR positive, and many with >50% diameter stenosis are FFR negative, particularly if a single view is used for QCA. In fact, a significant proportion of lesions visually >70% stenotic are FFR negative.

The most important trial design concern with incorporating FFR/iFR data into the end point adjudication process will be the assurance of uniform ascertainment. The protocol must specify clearly which suspect lesions should undergo FFR assessment. Suggested schemes for trials with and without planned angiographic follow-up are presented in Figures 2 and 3.
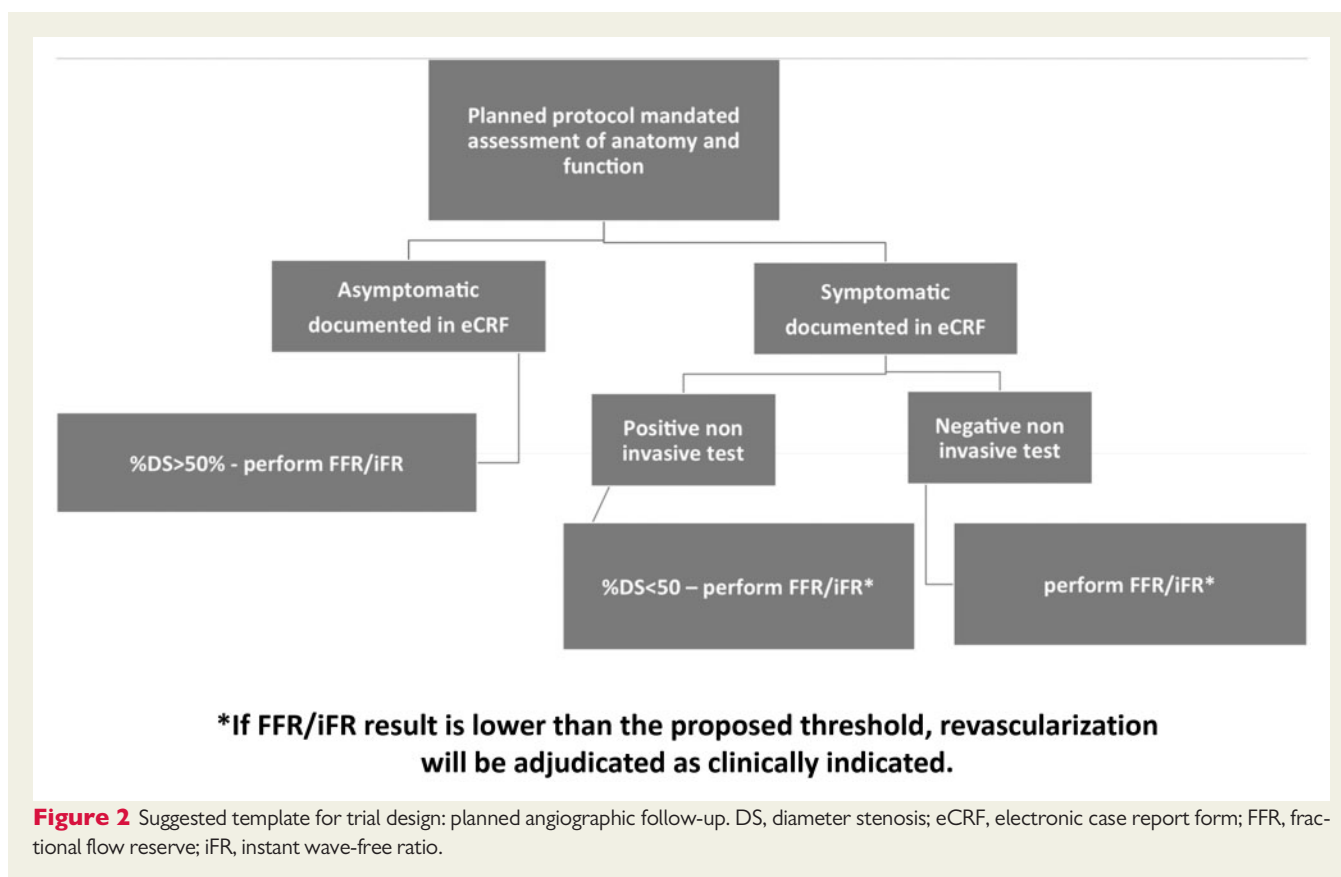
The study protocol and CEC manual of operations must also clearly outline, in advance, how FFR/iFR data will be incorporated into the adjudication process in specific scenarios. We recommend that when protocol-mandated FFR/iFR is not performed, such revascularizations should be classified as clinically indicated. We further recommend that when FFR results differ from the results of noninvasive testing or results on QCA, FFR/iFR should take precedence in the decision-making hierarchy.

ARC-2 recommends that resting distal coronary pressure to aortic pressure ratio, contrast/saline FFR, quantitative flow ratio, and FFR from computed tomography, although not yet widely available, can, within their acknowledged limitations, be used for adjudication purposes if specified in the protocol. In the near future, perfusion-based computed tomography may be validated as an additional technique to guide event adjudication.

ARC-2 recognizes that all trial protocols may not incorporate the mandatory use of FFR (or any other functional assessment). When this is the case, we recommend the use of independent core laboratory–verified QCA analysis using the hierarchical approach outlined in Table 7. These measurements, in conjunction with symptom status and the results of noninvasive testing, will form the basis for event adjudication. A report of the European Society of Cardiology–European Association of Percutaneous Cardiovascular Interventions Task Force on the Evaluation of Coronary Stents in Europe[14] endorsed the role of independent QCA analysis, stating, "Offline quantitative coronary analysis in a centralized core laboratory with blinded outcome assessors in case of comparative studies is mandatory." Similarly, the US Food and Drug Administration[15] emphasizes the role of independent quantitative angiographic assessment.

The QCA analysis should be provided to the CEC team to assist its assessment in conjunction with the clinical data with access to the original angiograms on request.

ARC-2 recommends that all DES/BRS study designs require completion of clinical evaluations before any protocol-mandated invasive procedures are performed. This approach will avoid the bias observed in several studies in which an increase in TLR related to protocol-mandated catheterization was documented.

Figure 2 Suggested template for trial design: planned angiographic follow-up. DS, diameter stenosis; eCRF, electronic case report form; FFR, fractional flow reserve; iFR, instant wave-free ratio.

Staged Procedures

Staged procedures are frequently performed in complex multivessel cases to decrease the risk of contrast-induced nephropathy and to increase the likelihood of complete revascularization. All staged procedures should be completed with the assigned study stent.

The decision to stage and the reason(s) along with the specific lesions to be treated during the staged procedure should be documented at the end of the index procedure in the electronic case report form. Latitude is allowed when the index procedure is performed in an acute setting and the local heart team may guide subsequent management. In studies in which chronic total occlusions are index lesions, subsequent procedures may be undertaken to achieve final angiographic success.

Planned documented staged procedures are not considered TLRs. However, the recommended time interval within which planned elective staged PCI procedures should be completed must be defined in the protocol. When a staged procedure is performed earlier (or later) than planned, it should be adjudicated, taking into account the circumstances. For example, when a culprit lesion was treated at index and a staged intervention is performed earlier than planned because of unscheduled readmission with symptoms, the procedure should be classified as an unplanned PCI. When a staged procedure is performed outside the time window for valid logistical or medical reasons, it may be classified as a protocol violation and not an unplanned PCI. However, when a decision was made that a planned

staged procedure was no longer indicated, subsequent treatment of such lesions will be considered an unplanned PCI. All of these scenarios should be described in the protocol and CEC charter.
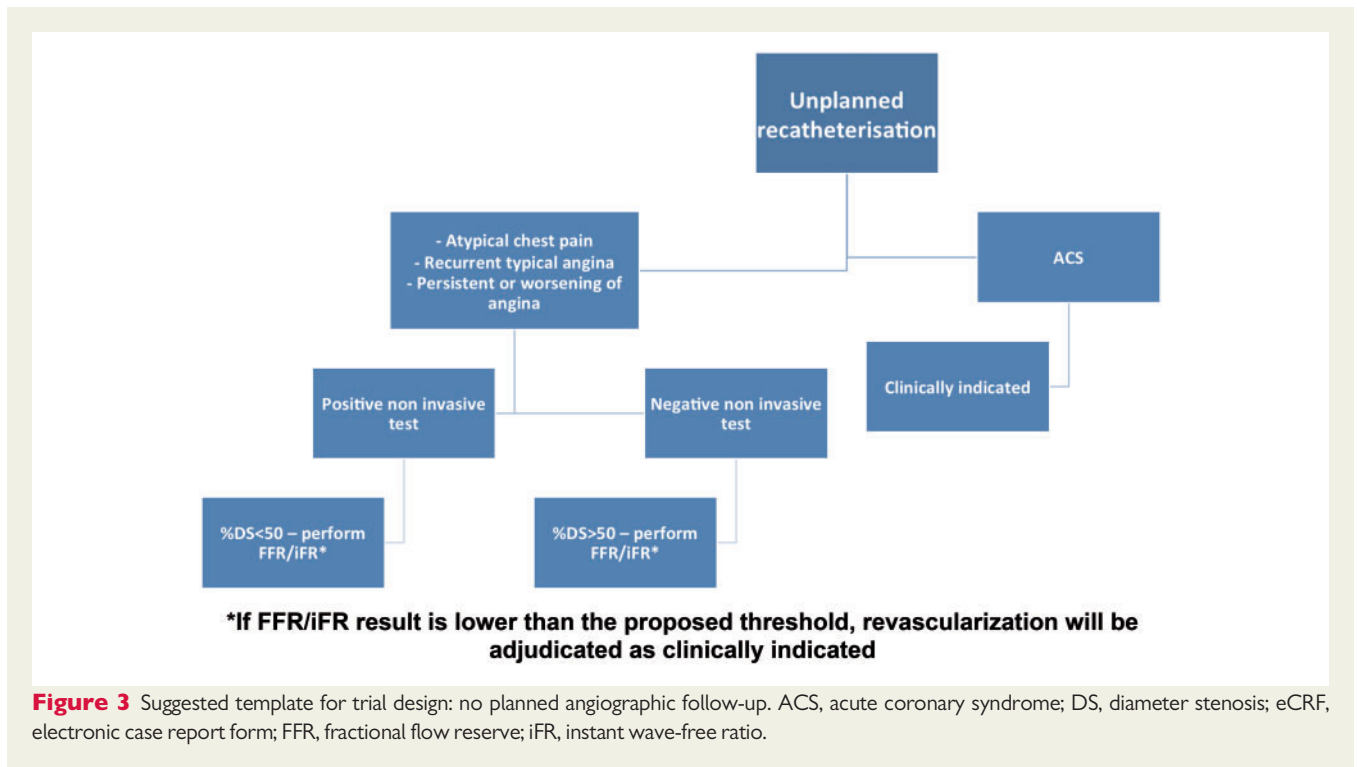
ARC-2 strongly recommends that staged procedures be allowed only in vessels not treated at the index procedure to avoid potential disruption of the index lesions.

Bifurcation Lesions

The Medina classification has gained general acceptance as a simple, relevant clinical and research tool, and we recommend that dedicated bifurcation trials adopt this classification. If another classification is used, it should be prespecified in the protocol.

Core laboratory analysis using dedicated QCA bifurcation software has documented that patients included in bifurcation trials often have less complex disease compared with the visually assessed parameters that led to inclusion in the trial. The ARC recommends that criteria be verified before trial inclusion. If preprocedural independent verification of inclusion criteria is not performed, a retrospective analysis (prespecified in the protocol) may provide supplemental information to the intention-to-treat population. ARC-2 recommends that in such a scenario, both per-protocol independent core laboratory–verified and intention-to-treat populations be reported.

Other issues concerning the adjudication of revascularization are discussed in Appendix B in the online-only Data Supplement.

Figure 3 Suggested template for trial design: no planned angiographic follow-up. ACS, acute coronary syndrome; DS, diameter stenosis; eCRF, electronic case report form; FFR, fractional flow reserve; iFR, instant wave-free ratio.

Stent/Scaffold Thrombosis

The first ARC document proposed a standardized classification based on a consensus that both levels of evidence and timing of events could be stratified to define varying degrees of certainty and to imply different pathophysiological mechanisms. This classification required evidence of a clinical event and did not include silent late occlusions as manifestations of stent thrombosis. The time frame for stent thrombosis starts when the patient has been undraped and taken off the catheterization laboratory table (*Table 8*).

This classification included unexplained death within 30 days after the procedure as a criterion for probable stent thrombosis. Given the uncertain specificity of this criterion after ST-segment–elevation MI, the updated ARC-2 classification recommends no longer including unexplained death within 30 days as a criterion for probable stent thrombosis when the index procedure was performed in the context of ST-segment–elevation MI, albeit with evident implications for historical comparisons.

In line with the nomenclature target lesion/vessel revascularization, investigators may consider the term target lesion thrombosis to refer to definite stent/scaffold thrombosis and target vessel thrombosis to refer to probable stent/scaffold thrombosis. This new nomenclature can accommodate late thrombotic events occurring in BRS studies when is not certain whether the device is still present in the coronary artery.

The initial ARC stent thrombosis classification included possible stent thrombosis to capture potential stent thrombosis events occurring beyond 1 year that may present as unexplained death. However, it has become apparent that an increasing proportion of deaths remain unexplained over time, leading to a potential exaggeration of the rates of very late stent thrombosis and possible dilution of a signal for differences between groups resulting from noise created by inclusion of events unrelated to stent thrombosis. A recent autopsy study suggested that the possible stent thrombosis category be refined, through the use of additional criteria, to define a "modified possible" stent thrombosis category that offered improved diagnostic accuracy in this setting.[16] ARC-2 feels that this modest improvement in diagnostic accuracy, however, does not justify its adoption and recommends that the possible stent thrombosis category be removed altogether (*Table 7*). Nevertheless, we emphasize again the importance of careful clinical follow-up and complete ascertainment of clinical data for the duration of any clinical study to minimize the uncertainty in determining cause of death and thus to help identify potential late or very late stent thrombosis events.

Reporting of late or very late stent thrombosis may be complex to interpret when events occur secondary to an intervening TLR, but censorship may bias reporting in favor of devices with higher restenosis risk. ARC-2 favors reporting of such events as secondary stent thrombosis.

The initial ARC consensus considered that the incidental documentation of stent occlusion, without the required ancillary criteria, should be classified as silent stent occlusion. While maintaining this view, ARC-2 recommends that the numbers of such cases be reported in studies in which angiographic follow-up is prespecified in the protocol. Such reporting offers the potential to enhance the understanding of the frequency and implications of this phenomenon.

Table 8   **Definition and Timing of Stent/Scaffold Thrombosis**

Classification	Criteria

Definite stent/scaffold thrombosis	Angiographic confirmation of stent/scaffold thrombosis*
	 The presence of a thrombus† that originates in the stent/scaffold or in the segment 5 mm proximal or distal to the stent/scaffold or in a side branch originating from the stented/scaffolded segment and the presence of at least 1 of the following criteria:
	     Acute onset of ischemic symptoms at rest
	     New electrocardiographic changes suggestive of acute ischemia
	     Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous myocardial infarction)
	 Or
	 Pathological confirmation of stent/scaffold thrombosis
	     Evidence of recent thrombus within the stent/scaffold determined at autopsy
	     Examination of tissue retrieved following thrombectomy (visual/histology)

Probable stent/scaffold thrombosis	Regardless of the time after the index procedure, any myocardial infarction that is related to documented acute ischemia in the territory of the implanted stent/scaffold without angiographic confirmation of stent/scaffold thrombosis and in the absence of any other obvious cause.‡
Silent stent/scaffold occlusion	The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered stent thrombosis.
Timing of ST (duration after stent implantation)	
Acute	0§–24 h
Subacute	>24 h–30 d
Late	>30 d–1 y
Very late	>1 y

Early stent thrombosis is 0 to 30 days (acute plus subacute stent thrombosis). MI indicates myocardial infarction.
*Definite stent/scaffold thrombosis is considered to have occurred by either angiographic or pathological confirmation.
†Occlusive thrombus: Thrombolysis in Myocardial Infarction grade 0 or 1 flow within or proximal to a stent/scaffold segment. Nonocclusive thrombus: intracoronary thrombus is defined as a (spherical, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, persistence of contrast material within the lumen, or visible embolization of intraluminal material downstream.
‡When the stented/scaffolded segment is in the left circumflex coronary artery or in the presence of preexisting electrocardiographic abnormalities (eg, left bundle branch block, paced rhythms), definitive evidence of localization may be absent and Clinical Events Committee adjudication is based on review of all available evidence).
§Defined as the moment the patient is undraped and taken off the catheterization table.

Intraprocedural stent thrombosis has been recognized for some time, but a prognostic role for this rare event has only recently been suggested. The definition is based on masked independent core laboratory frame-by-frame analysis of the angiogram.[17,18] No studies on variability among core laboratories have been reported. Furthermore, such events may not be recorded on angiography, thus raising the issue of ascertainment bias. ARC-2 recommends intraprocedural stent thrombosis as an additional, optional classification but does not include it as a subcategory of stent thrombosis, the timing of which begins when the patient has been taken off the catheterization laboratory table.

First-generation BRS platforms are now approved in many countries, and many novel platforms are undergoing clinical trials. ARC-2 recommends long-term follow-up, beyond the anticipated resorption phase, to capture any potentially unexpected safety signals.

While acknowledging the semantic difficulty of classifying stent thrombosis as being related to a BRS when resorption of the BRS is theoretically complete, the ARC feels it is important to identify such potential safety issues. The occurrence of definite stent thrombosis, as defined in *Table 8*, within the 2 radiopaque markers or the 5-mm proximal and distal margins will be regarded as scaffold site thrombosis. Stent thrombosis events, after BRS reintervention even years after complete scaffold resorption, should also be reported as secondary stent thrombosis.

Bioresorbable Scaffolds

BRS are a novel technology based on polymeric or metallic platforms, which have been developed to behave in a fashion similar to traditional metallic DES in the short term but are then completely resorbed over a variable time frame. The ARC recommends that, in all such trials, patients should be followed up beyond the anticipated bioresorption phase to capture any potentially unexpected safety signals.

The lack of radiopacity of most BRS devices may be an issue when the patient returns for protocol-mandated or clinically indicated angiography. Acute unrecognized malapposition may result in scaffold disruption during instrumentation of the vessel for protocol-mandated invasive imaging. ARC-2 recommends that such TLRs in

asymptomatic patients without restenosis be classified as nonclinically indicated TLR.

Patient-reported Outcomes

Coronary device trials have generally considered treatment failure (eg, target lesion failure) as the key parameter of efficacy and safety. Although important, such outcomes are relatively rare. From the patient perspective, the key indications and benefits of coronary revascularization often relate to improved health status measured in terms of symptoms, function, and quality of life.[19,20] Quantifying health status is therefore a critical requirement for more completely defining the benefits of treatment.[21,22] Patient-reported outcomes systematically measure health status directly from the patient, without amendment or interpretation of the response by a clinician or anyone else. A patient-reported outcome can be captured by self-report or interview, provided that the interviewer is trained to record only the patient's response. The outcome can be measured in absolute terms (eg, severity of a symptom, sign, or state of a disease) or as a change from a previous measure to more clearly define treatment benefit.

Although it is true that, in contemporary practice, fewer than 40% of patients are treated with PCI for stable ischemic heart disease as opposed to an acute coronary syndrome, all patients have coronary artery disease. According to the guidelines, the principal goals of treating patients with coronary disease are secondary prevention (avoiding death and MI) and optimizing patients' symptoms, function, and quality of life. Among patients treated for acute MI or unstable angina, a substantial proportion have angina and health status limitations during follow-up, and baseline angina (angina before their acute MI) is a strong predictor of longer-term angina.[23] Accordingly, we feel that the use of patient-reported outcomes should be routinely considered in the design of clinical trials to provide important information for subsequent medical decision making and shared medical decision making with patients.

The US Food and Drug Administration has produced detailed guidance on the use of patient-reported outcomes to make a claim and to obtain product labeling.[24] Generally, findings measured by a well-defined and reliable patient-reported outcome instrument in appropriately designed investigations can be used to support a claim in medical product labeling if the claim is consistent with the documented measurement capability of the instrument. However, there are certain challenges and requirements to accomplish patient-reported outcome–based labeling, most notably the fact that no patient-reported outcome has been qualified for the purpose of labeling claims in coronary artery disease despite the availability of well-validated measures.[25–28] This represents a significant challenge for researchers and industry in the quest to gain approval for treatments that alleviate symptoms and improve function and quality of life.

Assuming that a patient-reported outcome measure was qualified by ≥1 regulatory bodies, there are important considerations in designing a trial to demonstrate treatment benefits from patients' perspectives. If a patient-reported outcome is to be used as a trial outcome, it is ideal to mask patients (and investigators performing follow-up evaluations) to their randomized treatment to minimize bias. Patient blinding is feasible in many device versus device studies and is strongly recommended if possible. Patient blinding is rarely feasible, however, in studies comparing strategies such as PCI and medical or surgical treatment, with ORBITA (Objective Randomised Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina) being a rare exception. In device versus device trials, techniques that may minimize the effects of unblinding are useful. In strategy trials, longer-term follow-up, during which patients' perceptions of the immediate benefits of 1 treatment versus another (eg, the placebo effect) may diminish, is important to show sustained health status benefits over time. In open-label device trials, it is important to minimize bias by having patient-reported outcomes administered by staff who are unaware of treatment assignment or study hypotheses. Simple blinding and perception questionnaires may be administered to evaluate the success of early and late patient masking. Supplementing clinical trial data with future observational registries can provide additional confidence in the benefits of therapy. However, despite their importance to patients, it remains unclear whether regulatory authorities will allow patient-reported outcomes to be used as primary outcomes or if they will be relegated to only secondary end points. In the current regulatory environment, we suggest using patient-reported outcomes as supportive or secondary end points unless discussions with the regulators indicate support for their use as primary outcomes.

Regulatory qualification of a patient-reported outcome could simplify selection of a measure to quantify the experiences of patients with their disease and treatment. In the absence of guidance, researchers need to select tools that will quantify the domains of health most likely to be affected by treatment. Tool selection should consider issues of sensitivity to clinical change, recall period, patient burden (to minimize missing data), and the timing of patient-reported outcome assessments. In general, disease-specific measures are much more sensitive to treatment than generic tools.[27] Any patient-reported outcome instrument (eg, a questionnaire) to measure treatment benefit or risk should have proven psychometric properties (eg, validity, reliability, responsiveness, and interpretability) to measure the claimed concept.[24] The recall period (ie, the time period patients are asked to consider in response to a patient-reported outcome item or questionnaire) can be momentary (real time) or retrospective and of varying length. In the setting of coronary disease, in which angina typically occurs with exertion, recall periods are important so that patients can reflect on their recent symptoms across a range of usual activities. It is important, however, to consider the ability of patients to reliably recall the information requested. Different instruments use different recall times. For example, the Seattle Angina Questionnaire uses a 4-week recall period, which has been shown to be highly correlated with patient-reported angina frequency on daily diaries, thus suggesting that 4 weeks is not too long a recall period for patients.[25] Instruments vary in the number of questions they ask,[29] and investigators need to explicitly consider what domains of patient experience are most relevant in identifying the optimal measures while seeking to minimize the burden of data collection. At a minimum, patient-reported outcome assessments should be administered before randomization and at a clinically relevant follow-up interval. This not only ensures balanced randomization but also enables absolute and relative changes in health status to be

Table 9   **Patient-Reported Outcomes in Clinical Trials**

General Protocol Considerations	Description
Blinding	Patients should (if feasible) be blinded to treatment assignment throughout the trial.
	Investigators, research coordinators, and assistants during the follow-up period should be blinded throughout the trial.
	A blinding or perception questionnaire at hospital discharge and at the time of the primary end point may be administered to assess the success of patient blinding.
Quality control	Training and instructions to patients for self-administered patient-reported outcome instruments.
	Interviewer training and interview format for patient-reported outcome instruments administered in an interview format.
	Instructions for the clinical investigators for patient supervision, timing, and order of questionnaire administration during or outside the office visit, processes and rules for questionnaire review for completeness, and documentation of how and when data are filed, stored, and transmitted to or from the clinical trial site.
	Plans for confirmation of the measurement properties of the instrument using clinical trial data.
Handling missing data	Patients should remain in the clinical trial, even if they have discontinued treatment, and they should continue to provide patient-reported outcome data. The protocol should also establish a process by which patient-reported outcome measurement is obtained before or shortly after patient withdrawal from treatment should early withdrawal be unpreventable.
Frequency of assessments	The timing of assessments should correspond to the specific research questions being addressed, the length of recall asked by the response options of the instrument, demonstrated instrument measurement properties, the natural history of the disease or condition, the nature of the treatment, and planned data analysis.
Clinical trial duration	Duration of follow-up with a patient-reported outcome assessment should be the same as for other measures of effectiveness. However, the clinical trial duration appropriate for the patient-reported outcomes–related objective may not be the same duration as for other end points.

measured. Statistical analyses should explicitly describe how multiple end points and missing data are handled and how the data will be analyzed to maximize interpretability of the results (eg, responder analyses that can be converted in numbers needed to treat; *Table 9*).

In summary, a primary goal of coronary revascularization is to alleviate symptoms and functional limitations and to optimize quality of life. Valid, sensitive, practical instruments exist to capture a range of patients' experiences. Clinical trial designs need to carefully consider how alternative treatments might affect the health status of patients and capture changes in these domains. Once available, these outcomes can improve the understanding of treatment benefits and support the ability of doctors to communicate these benefits to their patients.

Summary and Conclusions

The ARC-2 initiative has updated the widely used ARC-1 pragmatic consensus definitions for coronary device trials to incorporate experience gained with the initial definitions, interim recommendations from professional societies, and the expansion of clinical trials to include more complex patient/lesion subsets and novel devices. Consistent application of these definitions in clinical trials may result in more efficient regulatory evaluation. Consistent with the ARC charter, this process and the definitions provided rely heavily on consensus and highlight the role of key clinical trial processes such as independent adjudication by event committees and evaluation of angiographic outcomes by core laboratories.

In cases in which historical comparisons are important and for specific study designs, we recommend reporting ARC-1 and -2 definitions, particularly with regard to death and stent/scaffold thrombosis.

Recommendations for the integration of patient-reported outcomes reflect the increasing focus on patient-centered outcomes in addition to traditional hard clinical end points. The central priority was the recognition that the application of consistent definitions across clinical trials of devices or strategies for revascularization with transparent reporting is ultimately more informative for the accrual of knowledge than are multiple individual studies with varying, continually evolving definitions.

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