Australian Government

Department of Health

RATIFIED PICO

Application 1613:

Permanent acute coronary syndrome event detector (insertion, removal or replacement of) for monitoring of the heart's electrical activity

Summary of PICO/PPICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Component	Description
Patients	Patients who have experienced within the past 6 months a high-risk acute coronary syndrome (ACS) event (e.g. unstable angina, STEMI, or N-STEMI), OR who have undergone (within the previous six months), or are scheduled to undergo (within six months), coronary artery bypass grafting and have at least one of the following conditions: • diabetes (type I or type II); • compromised renal function (plasma creatinine > 106 μmol/L or creatinine clearance < 50 mL/minute/1.73 m^2); or • Thrombolysis in Myocardial Infarction (TIMI) score ≥ 3.
Intervention	AngelMed Guardian System permanent acute coronary syndrome event detector as an adjunct to standard care
Comparator	Standard care with patient-recognised symptom detection
Outcomes	Primary effectiveness outcomes • Sensitivity and specificity *for ACS events* • Positive and negative predictive value *for ACS events* • *Reduced* symptom-to-door time for confirmed occlusive events *(goal ≤2 hours)* • *Detection rate of* new Q-wave myocardial infarction • *Reduction in* cardiac-related and all-cause mortality • Number coronary ischaemic events (reversible) and occlusive (non-reversible) events averted – e.g. for patients with stable angina, report the number of angina episodes and proportion of patients who have to have additional medical therapy added to remain stable; the proportion of patients with stable angina who become unstable and require urgent surgical intervention; number of acute myocardial infarctions; time to angioplasty or coronary artery bypass graft (CABG). Secondary effectiveness outcomes • Health-related quality of life and quality of life • Overall patient satisfaction Safety outcomes • Infection • Lead migration/dislodgement • Device malfunction • Lead malfunction • Need for additional surgery/device removal • Cardiac perforation • Erosion of subcutaneous pocket • Pain at or near the pocket site • Anxiety related to the device malfunctioning or not working correctly • Cosmetic appearance • Limitation of range of motion

Component	Description
	Healthcare system outcomes • Cost of the device and the additional resources required (e.g. consumables, staff and facilities – including anaesthesia requirement [e.g. Item 21941]) to provide the service • Additional tests or follow-up required as a result of the device *(AngelMed Guardian User's Guide:* "Patients should be seen for follow-up at 1, 3, 6, and 12 months after the implant, and every 6 months thereafter") • Rates of emergency department visits, doctor visits or hospitalisations • Cost of unnecessary tests and other resource utilisation for false positive alerts • Cost of ongoing treatment and care for patients who might live longer as a result of the implanted device Total Australian government healthcare costs • Total cost to the Medicare Benefits Schedule (MBS), Pharmaceutical Benefits Scheme (PBS) and other government health budgets.

POPULATION

The population for is:

Patients who have experienced within the past 6 months a high-risk acute coronary syndrome (ACS) event (e.g. unstable angina, STEMI, or N-STEMI), OR who have undergone (within the previous six months), or are scheduled to undergo (within six months), coronary artery bypass grafting and have at least one of the following conditions:

- diabetes (type I or type II);
- compromised renal function (plasma creatinine > 106 μmol/L or creatinine clearance < 50 mL/minute/1.73 m^2); or
- Thrombolysis in Myocardial Infarction (TIMI) score ≥ 3.

PASC confirmed the intended population as stated in the PICO, but considered the population needs to be more clearly defined. In particular, the applicant should define what constitutes a 'high-risk' ACS event.

PASC considered that the group of patients at high risk for a recurrent cardiac event would need to be defined based on specific criteria. In particular, PASC considered that the definition of 'compromised renal function' should be defined in line with the definition in ALERTS, i.e. creatinine > 1.2 mg/dL (106 μmol/L) or creatinine clearance < 50 mL/minute/1.73 m^2. This has been updated in the Summary PICO.

Acute coronary syndrome (ACS) refers to the clinical symptoms caused by a partial or complete blockage of a coronary artery as a result of coronary atherosclerosis. Abrupt reduction in blood flow to the heart (acute coronary ischaemia) results in one of the following life-threatening events (Chew et al. 2016; Hammer et al. 2018):

- Unstable angina – acute obstruction of an epicardial coronary artery without myocardial infarction (myocardial biomarkers are not elevated);
- Myocardial infarction (heart attack):
  - Non-ST-segment elevation myocardial infarction (N-STEMI) – partial blockage of an epicardial coronary artery and elevated biomarkers indicating cardiac muscle damage; or
  - ST-segment elevation myocardial infarction (STEMI) – complete blockage of an epicardial coronary artery with elevated biomarkers indicating cardiac muscle damage.

Coronary heart disease is the leading cause of death in Australia, accounting for 12 per cent of all deaths in 2017 (AIHW 2019b). The age-adjusted incidence rate of heart attacks in Australia in 2011 was 427 per 100,000 people. An estimated 78,866 Australians were hospitalised for an ACS event in 2017-18, 70 per cent of which were caused by myocardial infarction (18% were STEMI) and the remainder by unstable angina (AIHW 2014; National Heart Foundation 2018). ACS events are most common among people aged 75 to 79 years (AIHW 2019a; Deloitte Access Economics 2011). As a result of the ageing population demographic in Australia, hospital separations for ACS are expected to increase to 102,363 in 2020. Approximately one in three ACS events (34%) are repeat events, which occur most commonly among men aged between 80 and 84 years and women aged between 85 and 89 years (Deloitte Access Economics 2011). The presence of other chronic conditions (multimorbidity) doubles the risk of recurrence (Canivell et al. 2018).

Although most recurrent cardiac events occur within the first six months after an ACS diagnosis, the timeframe for repeat ACS events may extend to many years. Between 25 and 30 per cent of patients discharged from hospital after an ACS event will experience acute myocardial infarction, stroke or cardiovascular-related death within the following five years (Abu-Assi et al. 2016; Deloitte Access Economics 2011; Jia et al. 2005; Kazmi et al. 2020). In a Swedish study of over 100,000 patients who had been admitted to hospital for a myocardial infarction, 56 per cent experienced a recurrent non-fatal myocardial infarction and 31 per cent died from cardiovascular causes within one year of the index event (Jernberg et al. 2015). In Australia, 35 per cent of patients admitted for coronary heart disease are readmitted within 24 months; nearly two-thirds of these admissions are emergent (Atkins et al. 2014). The risk of death is greater after a repeat cardiac event than for the initial ACS event. In one Australian population sample, 36 per cent of non-fatal myocardial infarctions and 55 per cent of deaths due to ACS occurred in patients suffering repeat events (Briffa et al. 2010).

The proposed AngelMed Guardian® System (Angel Medical Systems, Inc., USA) is for patients who have experienced an index ACS event and remain at high risk for a recurrent cardiac event. According to Australian clinical practice guidelines, the risk of patients with confirmed ACS experiencing recurrent ischaemic events or death is stratified with respect to the clinical features listed in Table 1.

Table 1: Markers of increased risk of mortality and recurrent ischaemic events in patients with confirmed ACS (Chew et al. 2016)

Risk classification	Clinical characteristic
Very high	• Haemodynamic instability, heart failure, cardiogenic shock or mechanical complications of myocardial infarction • Life-threatening arrhythmias or cardiac arrest • Recurrent or ongoing ischaemia (i.e., chest pain refractory to medical treatment), or recurrent dynamic ST-segment and/or T-wave changes, particularly with intermittent ST-segment elevation, de Winter T-wave changes or Wellens' syndrome, or widespread ST-segment elevation in two coronary territories
High	• Rise and/or fall in troponin level consistent with myocardial infarction • Dynamic ST-segment and/or T-wave changes with or without symptoms • GRACE score > 140
Intermediate	• Diabetes mellitus • Renal insufficiency (glomerular filtration rate < 60 mL/minute/1.73m^2) • Left ventricular ejection fraction < 40% • Prior revascularisation (percutaneous coronary intervention or coronary artery bypass grafting) • GRACE score > 109 and < 140

GRACE: Global Registry of Acute Cardiac Events (Eagle et al. 2004; Fox et al. 2006)

Rationale

Ischaemic cardiovascular causes of chest pain include ACS, stable angina, severe aortic stenosis and tachyarrhythmia. Over 500,000 patients in Australia seek medical treatment each year for acute chest pain. Of these, fewer than 20 per cent are diagnosed with ACS: 2 to 5 per cent are diagnosed with STEMI, 5 to 10 per cent with N-STEMI and 5 to 10 per cent with unstable angina (Chew et al. 2016). Evaluation of patients with suspected ACS includes 12-lead electrocardiography, risk stratification using history and physical examination findings and measurement of serum cardiac

markers (e.g., cardiac troponins or the myocardial band isoenzyme of creatine kinase). The subsequent treatment path for patients with confirmed ACS depends on the underlying cause (Barstow, Rice & McDivitt 2017; Chew et al. 2016).

Initial treatment for patients with STEMI entails emergency reperfusion with either a percutaneous coronary intervention (PCI) or fibrinolytic therapy to restore coronary blood flow. PCI is preferred if it can be performed within 90 minutes of first medical contact, otherwise fibrinolytic therapy is the procedure of choice. Patients with N-STEMI or unstable angina are stratified according to their risk of experiencing a myocardial infarction. High- and very high-risk patients undergo angiography and either PCI or coronary artery bypass graft surgery. Low-risk patients generally receive conservative treatment with antiplatelet (aspirin, a P2Y12 inhibitor or glycoprotein IIb/IIIa inhibition in combination with heparin) and anticoagulant (heparin and enoxaparin or bivalirudin) therapy (Amsterdam et al. 2014; Chew et al. 2016).

The evidence base in the application comprises data from the ALERTS (AngeLmed Early Recognition and Treatment of STEMI) randomised controlled trial, which was conducted to support an investigational device exemption submission to the United States Food and Drug Administration. The criteria for selecting patients for this trial are listed in Table 2 (Gibson et al. 2019; Holmes et al. 2019). The basis for the proposed population appears to align with the majority of the inclusion criteria for the pivotal trial (excluding the geographical constraint, age threshold and pregnancy status). In addition, these criteria are in accordance with the intermediate- to very high- risk stratification recommended in Australian guidelines (Table 1), although there may be scope to expand the proposed population to include those with reduced left ventricular fraction (<40%) and a Global Registry of Acute Cardiac Events (GRACE) score higher than 109 given Australian guidelines identify components of these criteria as intermediate risk markers for increased risk of mortality and recurrent ischaemic events in patients with confirmed ACS (Chew et al. 2016).

PASC noted the differences between the population stated in the PICO with the population in the pivotal trial on which the application was based (ALERTS), which had more proscriptive exclusion criteria. PASC also noted that a 'revascularisation procedure' as specified in the intended population could include a coronary artery bypass graft (CABG) or a percutaneous coronary intervention (PCI) compared with the ALERTS trial including only patients who had undergone or are scheduled to undergo CABG within six months of implantation.

Table 2: Patient inclusion criteria for the ALERTS pivotal trial (Gibson et al. 2014; Gibson et al. 2019; Holmes et al. 2019)

Inclusion criteria (all must be met)

• Presence of at least one of the following conditions:
  - Diabetes (type I or type II)
  - Compromised renal function (creatinine > 1.2 mg/dL or creatinine clearance < 50 mL/minute)
  - TIMI risk score ≥ 3[a]
• Patient has experienced (within the past 6 months) a high-risk ACS event (e.g., unstable angina, STEMI or N-STEMI) or has undergone or is scheduled to undergo coronary artery bypass grafting within 6 months of implantation
• Patient has already undergone coronary angiography and revascularisation, unless the physician determines it is appropriate to implant before or during the planned procedure
• Lives in a geographic area within 60 minutes of a hospital that can treat acute myocardial infarction
• Aged ≥ 21 years
• Women of childbearing age must have confirmation that they are not pregnant

[a] Using the appropriate UA/NSTEMI score or STEMI score matched to the syndrome

ACS: acute coronary syndrome; N-STEMI: Non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; TIMI: Thrombolysis in Myocardial Infarction; UA: unstable angina (Antman et al. 2000)

From the estimated 78,866 Australians hospitalised for an ACS event in 2017-18, the applicant calculated an incidence of 23,660 per annum (30%) for the target population of patients at high risk of experiencing a repeat ACS event. There are no data available on the proportion of patients from this group who would meet the additional eligibility criteria, that is: they have undergone (within the previous six months) or are scheduled to undergo a revascularisation procedure (e.g. CABG or PCI) and have at least one of the following conditions: diabetes, compromised renal function or a Thrombolysis in Myocardial Infarction score[1] (TIMI) of at least three.

PASC considered the potential for leakage outside the intended population would likely be high for this device with such a broad range of applicable populations. PASC noted the applicant did not justify the expected utilisation per year (500 in year 1, rising to 3,100 in year 3), which would need to be rectified during the assessment phase.

INTERVENTION

The intervention is AngelMed Guardian System permanent acute coronary syndrome event detector as an adjunct to standard care.

PASC confirmed the intervention as stated in the PICO.

The AngelMed Guardian System is an implantable intracardiac monitor for detecting ischaemic coronary events in patients who are at high risk of experiencing a repeat ACS event. The Guardian System consists of an implantable device, a programmer and an external pager-sized device that is designed to augment patient notification. The implantable device, which is similar in size to a single-chamber pacemaker, is placed under the skin above the left pectoral muscle and connected to a lead that is positioned in the right ventricular apex. The device continuously monitors and collects the patient's real-time electrocardiograms (ECGs) and compares them with the patient's baseline data, which is updated daily. If a sustained (> 2 minutes) ST-segment shift of more than three standard deviations from baseline values occurs within the patient's normal resting heart rate range, the implantable device vibrates and the external device flashes and sounds an alarm prompting the patient to call an ambulance. Other abnormalities, such as tachycardia, bradycardia or arrhythmia, trigger a non-urgent alert for patients to see their doctor. The implantable device stores ECG data from up to 24 hours before and 8 hours after an alert, which can be downloaded when the patient seeks treatment to aid diagnosis. The programmer is a specially configured portable computer used by the physician to program operational parameters of the implanted device, such as patient-specific ischemia detection thresholds, and retrieve ECG data via wireless telemetry. During routine follow-up, ST-segment deviation trend data collected by the implantable device over the preceding weeks or months can be downloaded by the physician and used to determine whether additional diagnostic tests are needed (Hopenfeld et al. 2009; Kazmi et al. 2020; Rogers et al. 2016a; U.S. FDA 2018).

[1] TIMI is a risk score originally derived from ACS cohorts. For late mortality and recurrent myocardial infarction, the GRACE risk score appears to perform better than the TIMI score and thus may be preferred for clinical decision making and communication with patients and families (Australian clinical practice guidelines Chew et al. 2016).

The applicant advised that the implant is permanent until the patient requires further treatment, such as the implantation of a pacemaker. Patients should be seen for follow-up at one, three, six and 12 months after the Guardian System is implanted, and every six months thereafter. The battery longevity of the implantable device is about 3.2 years (assuming typical use), after which time an indicator will flag the need for battery replacement. Battery replacement requires an additional surgery to replace the system (e.g. explant and replace), which must occur within a month of the alert being activated (Angel Medical Systems 2018; Hopenfeld et al. 2009).

The applicant indicated that patients eligible to receive the device would be referred by an interventional cardiologist to a cardiac electrophysiologist or other accredited pacemaker implanter.

PASC considered that referrals would not be limited to just interventional cardiologists, as claimed by the applicant. Rather, PASC considered that eligible patients could be referred by any specialist or consultant physician.

The training required to implant the Guardian System is identical to that required to implant a pacemaker. The applicant estimated the proposed medical service would take approximately one hour; however, they did not provide a detailed breakdown of the procedural steps, imaging technique and anaesthesia used. The procedure is performed in a cardiac catheter laboratory as an inpatient procedure and requires a one- to two-night hospital stay, although the applicant notes that there may be instances where the device is implanted during a planned revascularisation procedure.

The device is not currently available in Australia. However, an application for inclusion in the Australian Register of Therapeutic Goods was submitted on 6 November 2019 (TRG Application ID DV-2019-DA-18301-1), with an expected notification date of August 2020.

PASC noted that the intervention is not currently registered on the ARTG and that the applicant expects TGA approval in August 2020.

PASC also noted that the device is not eligible for listing on the Prostheses List.

The Applicant did not agree with PASC's assertion that the device is not eligible for listing on the Prostheses List, noting that currently, a very similar prosthesis, Billing Code MI141 - Insertable Cardiac Monitor, is listed. The Applicant stated they intend to resolve this issue if an application is lodged for listing of the device on the Prostheses List.

Contraindications

Based on the exclusion criteria used in the ALERTS pivotal trial (Gibson et al. 2014; Gibson et al. 2019; Holmes et al. 2019), the presence of any of the following is a contraindication for implanting the Guardian System:

- Atrial fibrillation, bundle branch block or left ventricular hypertrophy.
- Occurrence of haemorrhagic stroke, transient ischaemic attack, or gastrointestinal haemorrhage in the past 6 months.
- History of bleeding disorders or severe coagulopathy.
- Epilepsy, severe allergies, unresolved infection or cancer or other severe disease.
- Inability to respond to alarms properly or to feel the vibration of the implanted device.
- Localised scar tissue and high thresholds at the lead implantation site.
- Presence of an implanted cardioverter-defibrillator, cardiac resynchronisation device or pacemaker.

Rationale

In Australia, the referral, attendance and completion rates for cardiac rehabilitation programs prescribed after an ACS event are low, and the patients most likely to drop out are usually those with the highest risk of recurrence (Redfern et al. 2007). In addition, many of the medications prescribed for patients with ACS are intended to be taken for an extended period of time, often for life, but 10 to 25 per cent of patients discontinue their medications after six months and 14 to 46 per cent are no longer taking them 12 months after discharge (Chen et al. 2015; Deloitte Access Economics 2011). These behaviours increase the likelihood of a repeat ACS event.

Most irreversible heart muscle damage and lethal arrhythmias occur in the first sixty minutes following vessel occlusion, so early detection and intervention are crucial for averting severe complications and death (Kazmi et al. 2020). The relative risk of death one year after an ACS event is increased by 7.5 per cent with every 30-minute delay in reperfusion therapy (Gibson 2001). Despite significant advances in reducing time to treatment once a patient reaches the hospital (door-to-balloon and door-to-needle times), the median time from symptom onset to arrival at a medical facility remains between two to three hours, despite various interventions to improve patient education and awareness (Boersma 2006; DeVon et al. 2010). Difficulties in improving symptom-to-door time stem from patient denial, anxiety and misconceptions about heart attack symptoms and clinical misdiagnosis and failure to recognise ECG findings indicating a myocardial infarction (Kazmi et al. 2020). For example, few Australians are aware that neck pain, nausea, vomiting and jaw pain are signs of a heart attack, and this lack of knowledge delays patient response to warning signs (National Heart Foundation 2018). This is compounded by the fact that myocardial infarctions are asymptomatic or “silent” in at least 50 per cent of sufferers, particularly women, diabetic or hypertensive patients and the elderly (Benjamin et al. 2017; Rogers et al. 2016b; Sheifer, Manolio & Gersh 2001). In addition, patients with chronic angina may overlook symptoms that mimic their usual level of chest discomfort (Kazmi et al. 2020). Thus, there is significant scope for reducing the time from symptom onset to presentation (symptom-to-door time) and potentially averting progression to myocardial infarction and cardiac muscle damage.

COMPARATOR

The comparator for this Application is standard care with patient-recognised symptom detection.

PASC confirmed the comparator as stated in the PICO.

There are no alternatives to the proposed device for near real-time outpatient monitoring for ACS events. Patients at risk for ACS must rely on patient-recognised symptoms to prompt them to seek medical attention. The Guardian System is designed to act as an adjunct to patient-recognised symptoms and to potentially identify asymptomatic ACS events.

In the submission prepared for the United States Food and Drug Administration, the device-related safety outcomes were contrasted with those of a single-chamber pacemaker, which could therefore be used as a benchmark comparator for acute procedural and long-term implantations risks (U.S. FDA 2018).

Rationale

The current standard of care for patients who have experienced ACS is aimed at reducing the occurrence of new vascular events through secondary prevention strategies. These include lifestyle changes such as quitting smoking and being physically active, intensive risk factor modification (e.g.,

controlling hypertension, managing diabetes mellitus), and use of cardioprotective medications such as long-term antiplatelet therapy, statins, betablockers, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (Amsterdam et al. 2014; Chew et al. 2016). In addition, Australian guidelines recommend providing patients with a written action plan for dealing with acute worsening or new unstable angina symptoms, which includes self-administration of short-acting nitrates and aspirin, and instructions on when and how to call an ambulance, or their physician if an ambulance service is not readily available (Chew et al. 2016).

OUTCOMES

Patient-relevant outcomes

The clinical claim is for superior effectiveness in predicting ACS events and for reducing the rate of false alarms, compared with patient-recognised symptoms alone. In addition, the Guardian System may detect asymptomatic ACS events and prompt patients to seek medical attention when they otherwise would not have.

PASC confirmed the outcomes as follows:

Safety:

- Infection
- Lead migration/dislodgement
- Device malfunction
- Lead malfunction
- Need for additional surgery / device removal
- Cardiac perforation
- Erosion of subcutaneous pocket
- Pain at or near the pocket site
- Anxiety related to the device malfunctioning or not working correctly
- Cosmetic appearance
- Limitation of range of motion

Primary effectiveness outcomes:

- Sensitivity and specificity for ACS events
- Positive and negative predictive value for ACS events
- Reduced symptom-to-door time for confirmed occlusive events (goal of ≤2 hours)
- Detection rate of new Q-wave myocardial infarction
- Reduction in cardiac-related and all-cause mortality
- Number of coronary ischaemic (reversible) and occlusive (non-reversible) events averted – e.g. for patients with stable angina, report the number of angina episodes and proportion of patients who have to have additional medical therapy added to remain stable; the proportion of patients with stable angina who become unstable and require urgent surgical intervention; number of acute myocardial infarctions; time to angioplasty or CABG.

Secondary effectiveness outcomes:

- Health-related quality of life and quality of life
- Overall patient satisfaction

Healthcare system:

- Cost of the device and the additional resources required (e.g. consumables, staff and facilities – including anaesthesia requirement [e.g. Item 21941]) to provide the service
- Additional tests or follow-up required as a result of the device
  (AngelMed Guardian User's Guide: "Patients should be seen for follow-up at 1, 3, 6, and 12 months after the implant, and every 6 months thereafter").
- Rates of emergency department visits, doctor visits or hospitalisations
- Cost of unnecessary tests and other resource utilisation for false positive alerts
- Cost of ongoing treatment and care for patients who might live longer as a result of the implanted device

Total Australian Government Healthcare costs:

- Total cost to the Medicare Benefits Schedule (MBS), Pharmaceutical Benefits Scheme (PBS) and other government health budgets.

Rationale

In this context, diagnostic performance is a patient relevant outcome because false negatives or missed ACS events may pose a significant risk for patients, particularly if they have symptoms but do no seek medical attention because the Guardian System has not prompted them to do so. Conversely, the ability of the Guardian System to correctly identify coronary ischaemic events earlier and to reduce false alarms will likely lead to changes in patient outcomes and prognosis. Although the majority of health expenditure for ACS is accrued during the initial event (77%), an additional 23 per cent is contributed by subsequent outcomes, such as heart failure or recurrent ACS events (National Heart Foundation 2018). Therefore, the Guardian System will have potential knock-on effects with respect to ongoing follow-up and care required for patients implanted with the device, rates of hospitalisations for recurrent ACS events and the resources required to provide the service.

Current and proposed clinical management algorithms

PASC advised that 'eventually' and 'immediately' should be defined (in both algorithms). PASC noted that 'immediately' was defined as ≤2 hours following the event in the ALERTS trial.

PASC advised that the outcomes in both algorithms should reflect those in the PICO.

PASC advised that 'false alarm' was redundant and should be removed under 'No investigation' in the 'current management' algorithm.

PASC advised that seeking treatment 'eventually' and a resulting 'delayed investigation' should be included in the 'proposed management algorithm' to capture patients who do not immediately seek treatment.

PASC noted that in the ALERTS trial 16.6% of emergency department visits by patients with recognised symptoms but who were not alerted by the coronary syndrome event detector were true-positive for ACS. Accordingly, PASC advised that there should be an additional pathway in the proposed management algorithm under 'patients who experience symptoms that may indicate a pending ACS event' where the patient recognises symptoms but is not alerted by the coronary syndrome event detector but seeks treatment (either 'immediately' or 'eventually').

The current and proposed clinical algorithms have been updated to reflect PASC's advice.

Current clinical management algorithm for identified population

The current clinical management algorithm for patients with a history of high-risk ACS is presented in Figure 1 below.

Proposed clinical management algorithm for identified population

The proposed clinical management algorithm for patients with a history of high-risk ACS who are eligible to receive the Guardian System implant is presented in Figure 2 below.

Figure 1: Current clinical management algorithm for patients with a history of ACS

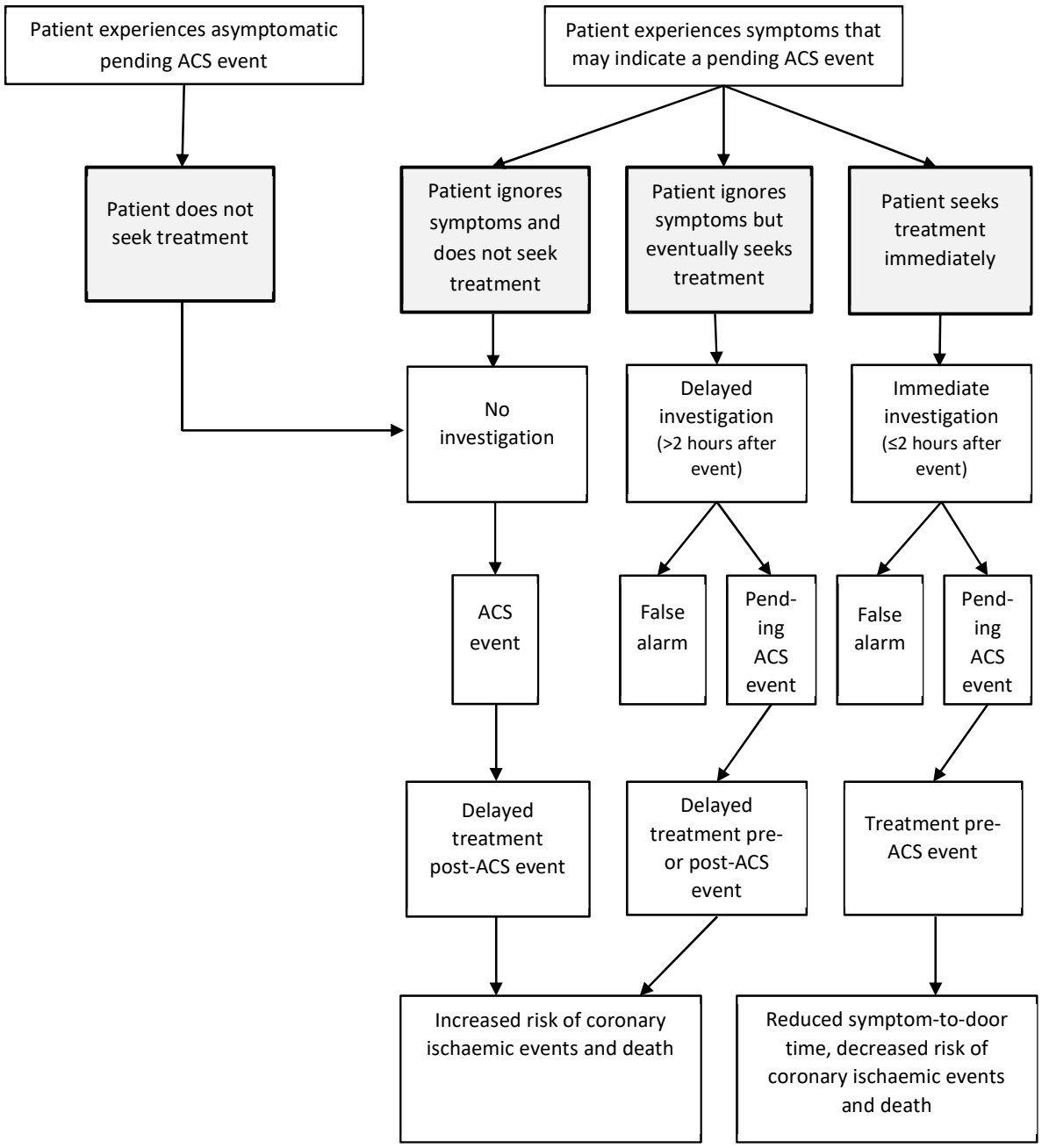
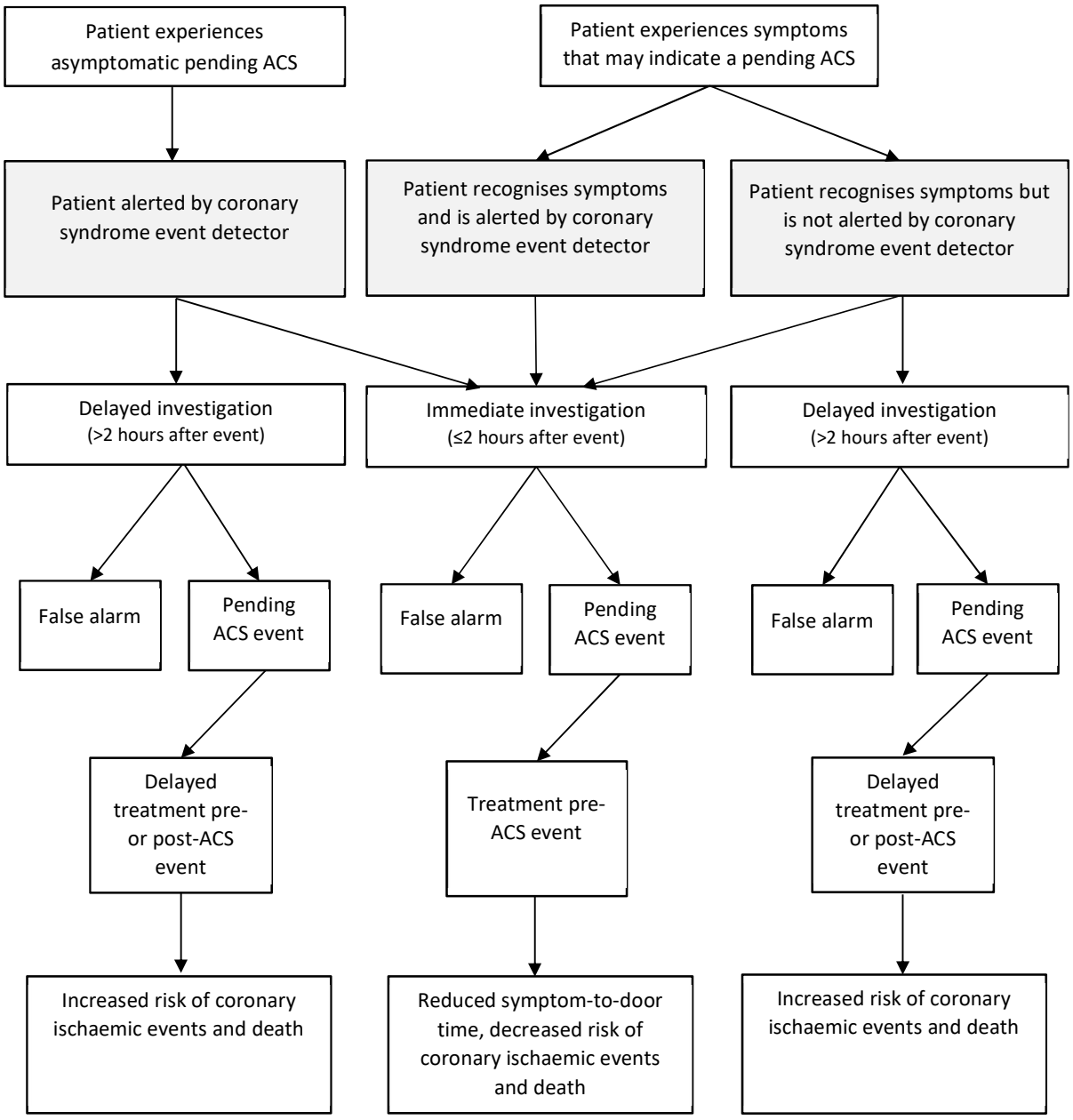


Figure 2: <u>Proposed</u> clinical management algorithm for patients with a history of ACS



Proposed economic evaluation

The applicant claimed that the Guardian System is expected to be superior in comparative effectiveness to standard care in predicting ACS events and reducing the rate of false alarms. Therefore, the most appropriate economic evaluation is a cost-effectiveness (or cost-utility analysis) to determine the costs relative to the effectiveness of the intervention in reducing symptom-to-door time and averting myocardial infarctions (relative to the comparator).

PASC confirmed that a cost-effectiveness or cost-utility analysis is appropriate because of the claim of superior comparative effectiveness.

Proposed MBS item descriptor and MBS fee

The MBS fees for the proposed items were estimated by the applicant, based on those listed for implantation of a single-chamber permanent pacemaker: Items 38350 and 38353 on the Medicare Benefits Schedule (MBS). The applicant stated that the AngelMed Guardian System is implanted in exactly the same way as a cardiac pacemaker and lead are implanted.

PASC confirmed the proposed item descriptor and fees are based on existing items for single-chamber permanent pacemakers.

Category 2 – DIAGNOSTIC PROCEDURES AND INVESTIGATIONS
Proposed item descriptor: Permanent acute coronary syndrome event detector, insertion, removal or replacement of for patients who have experienced a previous acute coronary syndrome event Multiple Operations Rule (Anaes.) MBS Fee: $259.55 Benefit: 75% = $194.70 (In-hospital/admitted patient only procedure)

Category 2 – DIAGNOSTIC PROCEDURES AND INVESTIGATIONS
Proposed item descriptor: Single chamber permanent transvenous electrode, insertion, removal or replacement of Multiple Operations Rule (Anaes.) MBS Fee: $648.85 Benefit: 75% = $486.65 (In-hospital/admitted patient only procedure)

PASC advised that consideration should be given to the need for a 'bolt-on' item (i.e. an item that has a lesser fee compared to the fee when the device insertion is completed as a standalone procedure) for when the device is inserted at the time of a 'revascularisation procedure'

PASC also noted that high out-of-pocket costs for patients would be likely given that bulk billing of this service is unlikely, the device is not eligible for listing on the Prostheses List and the battery would require replacement after around 3.2 years of typical usage.

Consultation feedback

PASC noted that a consumer organisation was generally supportive of the intervention, claiming that it would ensure that patients receive medical attention in a timely manner. However the organisation also noted there could be a disadvantage if the patient would require a pacemaker or defibrillator at a later date.

PASC also noted concern from the peak organisation for funders that the trial was funded by the manufacturer, that several authors had conflicts of interest, and that the trial did not meet its primary efficacy endpoint. The organisation also noted that there are no cost-effectiveness data and that the application's estimate of the eligible population was likely to be too low.

Next steps

PASC advised that, upon ratification of the post-PASC PICO, the application can proceed to the Evaluation Sub-Committee (ESC) stage of the MSAC process.

PASC noted the applicant has elected to progress its application as an ADAR (applicant-developed assessment report).

References

Abu-Assi, E, López-López, A, González-Salvado, V, Redondo-Diéguez, A, Peña-Gil, C, Bouzas-Cruz, N, Raposeiras-Roubín, S, Riziq-Yousef Abumuaileq, R, García-Acuña, JM & González-Juanatey, JR 2016, 'The risk of cardiovascular events after an acute coronary event remains high, especially during the first year, despite revascularization', *Rev Esp Cardiol (English ed.)*, vol. 69, no. 1, pp. 11-8.

Amsterdam, EA, Wenger, NK, Brindis, RG, Casey, DE, Jr., Ganiats, TG, Holmes, DR, Jr., Jaffe, AS, Jneid, H, Kelly, RF, Kontos, MC, Levine, GN, Liebson, PR, Mukherjee, D, Peterson, ED, Sabatine, MS, Smalling, RW & Zieman, SJ 2014, '2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines', *J Am Coll Cardiol*, vol. 64, no. 24, pp. e139-e228.

Angel Medical Systems 2018, *AngelMed Guardian® implantable medical device (IMD) model AMSG3 Users guide*, viewed 4 March 2020, <http://www.angel-med.com/wp-content/uploads/2019/01/AngelMed_IMD_Manual.pdf>.

Antman, EM, Cohen, M, Bernink, PJ, McCabe, CH, Horacek, T, Papuchis, G, Mautner, B, Corbalan, R, Radley, D & Braunwald, E 2000, 'The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making', *JAMA*, vol. 284, no. 7, pp. 835-42.

Atkins, ER, Geelhoed, EA, Knuiman, M & Briffa, TG 2014, 'One third of hospital costs for atherothrombotic disease are attributable to readmissions: a linked data analysis', *BMC Health Serv Res*, vol. 14, p. 338.

Australian Institute of Health and Welfare (AIHW) 2014, *Acute coronary syndrome: validation of the method used to monitor incidence in Australia. A working paper using linked hospitalisation and deaths data from Western Australia and New South Wales. CVD 68*, AIHW, viewed 28 February 2020, <https://www.aihw.gov.au/getmedia/5d9bc18b-582a-4d7e-ade8-f67852307db9/17013.pdf.aspx?inline=true>.

Australian Institute of Health and Welfare (AIHW) 2019a, *Cardiovascular disease. Cat. no. CVD 83*, AIHW, viewed 28 February 2020, <https://www.aihw.gov.au/reports/heart-stroke-vascular-diseases/cardiovascular-health-compendium>.

Australian Institute of Health and Welfare (AIHW) 2019b, *Deaths in Australia*, AIHW, viewed 28 February 2020, <https://www.aihw.gov.au/reports/life-expectancy-death/deaths-in-australia/contents/summary>.

Barstow, C, Rice, M & McDivitt, JD 2017, 'Acute coronary syndrome: diagnostic evaluation', *Am Fam Physician*, vol. 95, no. 3, pp. 170-7.

Benjamin, EJ, Blaha, MJ, Chiuve, SE, Cushman, M, Das, SR, Deo, R, de Ferranti, SD, Floyd, J, Fornage, M, Gillespie, C, Isasi, CR, Jimenez, MC, Jordan, LC, Judd, SE, Lackland, D, Lichtman, JH, Lisabeth, L, Liu, S, Longenecker, CT, Mackey, RH, Matsushita, K, Mozaffarian, D, Mussolino, ME, Nasir, K, Neumar, RW, Palaniappan, L, Pandey, DK, Thiagarajan, RR, Reeves, MJ, Ritchey, M, Rodriguez, CJ, Roth, GA, Rosamond, WD, Sasson, C, Towfighi, A, Tsao, CW, Turner, MB, Virani, SS, Voeks, JH, Willey, JZ,

Wilkins, JT, Wu, JH, Alger, HM, Wong, SS & Muntner, P; American Heart Association Statistics Committee, Stroke Statistics Subcommittee 2017, 'Heart disease and stroke statistics-2017 update: A Report from the American Heart Association', *Circulation*, vol. 135, no. 10, pp. e146-e603.

Boersma, E; Primary Coronary Angioplasty vs. Thrombolysis Group 2006, 'Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients', *Eur Heart J*, vol. 27, no. 7, pp. 779-88.

Briffa, TG, Hobbs, M, Tonkin, A, Sanfilippo, F, Hickling, S, Ridout, S & Knuiman, M 2010, 'Population trends of recurrent coronary heart disease event rates remain high', *Circ Cardiovasc Qual Outcomes*, vol. 4, no. 1, pp. 107-13.

Canivell, S, Muller, O, Gencer, B, Heg, D, Klingenberg, R, Räber, L, Carballo, D, Matter, C, Lüscher, T, Windecker, S, Mach, F, Rodondi, N & Nanchen, D 2018, 'Prognosis of cardiovascular and non-cardiovascular multimorbidity after acute coronary syndrome', *PloS One*, vol. 13, no. 4, e0195174.

Chen, HY, Saczynski, JS, Lapane, KL, Kiefe, CI & Goldberg, RJ 2015, 'Adherence to evidence-based secondary prevention pharmacotherapy in patients after an acute coronary syndrome: A systematic review', *Heart Lung*, vol. 44, no. 4, pp. 299-308.

Chew, DP, Scott, IA, Cullen, L, French, JK, Briffa, TG, Tideman, PA, Woodruffe, S, Kerr, A, Branagan, M & Aylward, PE; NHFA/CSANZ ACS Guideline 2016 Executive Working Group 2016, 'National Heart Foundation of Australia & Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the management of acute coronary syndromes 2016', *Heart Lung Circ*, vol. 25, no. 9, pp. 895-951.

Deloitte Access Economics Pty Ltd 2011, *ACS in perspective: The importance of secondary prevention*, Deloitte Access Economics Pty Ltd, viewed 28 February 2020, <https://www2.deloitte.com/content/dam/Deloitte/au/Documents/Economics/deloitte-au-economics-acs-perspective-importance-secondary-prevention-011111.pdf>.

DeVon, HA, Hogan, N, Ochs, AL & Shapiro, M 2010, 'Time to treatment for acute coronary syndromes: the cost of indecision', *J Cardiovasc Nurs*, vol. 25, no. 2, pp. 106-14.

Eagle, KA, Lim, MJ, Dabbous, OH, Pieper, KS, Goldberg, RJ, Van de Werf, F, Goodman, SG, Granger, CB, Steg, PG, Gore, JM, Budaj, A, Avezum, A, Flather, MD & Fox, KA; GRACE Investigators 2004, 'A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry', *JAMA*, vol. 291, no. 22, pp. 2727-33.

Fox, KA, Dabbous, OH, Goldberg, RJ, Pieper, KS, Eagle, KA, Van de Werf, F, Avezum, A, Goodman, SG, Flather, MD, Anderson, FA, Jr. & Granger, CB 2006, 'Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE)', *BMJ*, vol. 333, no. 7578, p. 1091-4.

Gibson, CM 2001, 'Time is myocardium and time is outcomes', *Circulation*, vol. 104, no. 22, pp. 2632-4.

Gibson, CM, Holmes, D, Mikdadi, G, Presser, D, Wohns, D, Yee, MK, Kaplan, A, Ciuffo, A, Eberly, AL, 3rd, Iteld, B & Krucoff, MW 2019, 'Implantable cardiac alert system for early recognition of ST-segment elevation myocardial infarction', *J Am Coll Cardiol*, vol. 73, no. 15, pp. 1919-27.

Gibson, MC, Krucoff, M, Fischell, D, Fischell, TA, Keenan, D, Abueg, C, Patel, C & Holmes, D 2014, 'Rationale and design of the AngeLmed for Early Recognition and Treatment of STEMI trial: a randomized, prospective clinical investigation', *Am Heart J*, vol. 168, no. 2, pp. 168-74.

Hammer, Y, Iakobishvili, Z, Hasdai, D, Goldenberg, I, Shlomo, N, Einhorn, M, Bental, T, Witberg, G, Kornowski, R & Eisen, A 2018, 'guideline-recommended therapies and clinical outcomes according to the risk for recurrent cardiovascular events after an acute coronary syndrome', *J Am Heart Assoc*, vol. 7, no. 18, e009885.

Holmes, DR, Jr., Krucoff, MW, Mullin, C, Mikdadi, G, Presser, D, Wohns, D, Kaplan, A, Ciuffo, A, Eberly, AL, 3rd, Iteld, B, Fischell, DR, Fischell, T, Keenan, D, John, MS & Gibson, CM 2019, 'Implanted monitor alerting to reduce treatment delay in patients with acute coronary syndrome events', *J Am Coll Cardiol*, vol. 74, no. 16, pp. 2047-55.

Hopenfeld, B, John, MS, Fischell, DR, Medeiros, P, Guimarães, HP & Piegas, LS 2009, 'The Guardian: an implantable system for chronic ambulatory monitoring of acute myocardial infarction', *J Electrocardiol*, vol. 42, no. 6, pp. 481-6.

Jernberg, T, Hasvold, P, Henriksson, M, Hjelm, H, Thuresson, M & Janzon, M 2015, 'Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective', *Eur Heart J*, vol. 36, no. 19, pp. 1163-70.

Jia, YH, Yang, YJ, Wei, YZ, Yao, M & Hu, SS 2005, 'Coronary angiographies of patients with recurrent acute coronary syndrome following coronary artery bypass grafting', *Chin Med J (Engl)*, vol. 118, no. 7, pp. 612-4.

Kazmi, SHA, Datta, S, Chi, G, Nafee, T, Yee, M, Kalia, A, Sharfaei, S, Shojaei, F, Mirwais, S & Gibson, CM 2020, 'The AngelMed Guardian(®) System in the detection of coronary artery occlusion: current perspectives', *Med Devices (Auckl)*, vol. 13, pp. 1-12.

National Heart Foundation of Australia 2018, *Economic cost of acute coronary syndrome in Australia: The cost to governments*, National Heart Foundation of Australia, viewed 4 March 2020, <https://www.heartfoundation.org.au/images/uploads/publications/Economic_cost_of_ACS_in_Australia__the_cost_to_governments.pdf>.

Redfern, J, Ellis, ER, Briffa, T & Freedman, SB 2007, 'High risk-factor level and low risk-factor knowledge in patients not accessing cardiac rehabilitation after acute coronary syndrome', *Med J Aust*, vol. 186, no. 1, pp. 21-5.

Rogers, T, Steinvil, A, Torguson, R & Waksman, R 2016a, 'The AngelMed Guardian system: Is there a role for implantable devices for early detection of coronary artery occlusion?', *Cardiovasc Revasc Med*, vol. 17, no. 8, pp. 522-7.

Rogers, T, Steinvil, A, Torguson, R & Waksman, R 2016b, 'Overview of the 2016 US Food and Drug Administration Circulatory System Devices Panel meeting on the AngelMed Guardian System', *Circulation*, vol. 134, no. 3, pp. 262-4.

Sheifer, SE, Manolio, TA & Gersh, BJ 2001, 'Unrecognized myocardial infarction', *Ann Intern Med*, vol. 135, no. 9, pp. 801-11.

U.S. Food and Drug Administration (U.S. FDA) 2018, *AngelMed Guardian System - P150009. Summary of safety and effectiveness data.*, U.S. FDA, viewed 4 March 2020, <https://www.accessdata.fda.gov/cdrh_docs/pdf15/P150009B.pdf>.