NICE National Institute for Health and Care Excellence

External Assessment Centre correspondence log

MT550 DyeVert

The purpose of this log is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the company's original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the company;
b) needs to check "real world" assumptions with NICE's expert advisers, or;
c) needs to ask the company for additional information or data not included in the original submission, or;
d) needs to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is captured. The table is shared with the NICE medical technologies advisory committee (MTAC) as part of the committee documentation, and is published on the NICE website at public consultation.

#	Date	Who / Purpose	Question/request	Response received
1.	01/02/2021	**Company** Initial questions	Three previous versions are listed in the submission. Would you be able to list which versions of the systems were used in each of the studies named in section 4? • Are the only versions currently in use the Plus EZ and the Power XT? • Improvements between the generations are generally described as improving Ease of Use; in your opinion, is this likely to have an effect on clinical outcomes? Given that the	See appendix 1 • Osprey Medical Response: Yes, the current versions available in the UK are the DyeVert Plus EZ and the DyeVert Power XT systems. • Osprey Medical Response: The ease of improvements for the DyeVert Plus EZ were in regards to priming in one direction versus in a closed circuit. The ease is strictly from a time to prep perspective and the removal of the closed circuit tubing does not impact the performance of the device in any way once set up. The connections and mechanism of action in the contrast

			standard of care for minimisation of contrast volume is dependent on clinician skill, attention, and awareness? • In Corcione et al. 2017, the device investigated is described as the DyeVert NG contrast reduction system – is this the second generation DyeVert Plus System?	minimization are identical. The Power XT improvements were the addition of monitoring contrast diverted similar to the DyeVert Plus EZ and cosmetic improvements (e.g. molded housing added) • Osprey Medical Response: The DyeVert NG was prior to the DyeVert Plus System. It is identical except the DyeVert NG did not have monitoring capability. It was just the module. The user supplied their own control syringe. • Please note that the mechanism of action for all devices are identical and that the studies of the mechanism in the previous versions are applicable to the current device. This approach has been reviewed and cleared by the FDA as well.
2.			It is mentioned in section 3 that no formal training is usually required. Does this include Cath Lab staff? • How frequently do clinics request training? • Is training free if requested? • How long does training typically take if requested?	Osprey Medical Response: There is no formal training of Cath Lab staff. Osprey Medical does provide on-site personnel during product evaluations when allowed. These evaluation with Cath Lab staff are performed typically as part of the purchasing decision-making process and includes review of the instructions for use. • There have been no requests for training to date. • If additional evaluation review is requested, Osprey Medical personnel provide the evaluation free. • Typical product evaluation is performed before final decision of purchasing and is usually a 1-2 day process. The extent of staff involvement is determined by the Cath Lab.

3.			There is an IFU for a Smart Monitor and one for a Display. The monitor allows access to an app interface. Are both the Smart Monitor and Display required to use the system?	[redacted]
4.			There are 2 IFUs for the DyeVert Plus Disposable Kit (one for the EU and for the US). Does the technology differ between the EU and the US, or just the contents of the IFU? • Similarly, for the Plus EZ Disposable Kit (one for the US and one for OUS)?	Osprey Medical Response: They are the identical technology. See below. • Osprey Medical Response: They are the identical technology – in both cases, the FDA requires an indications for use statement that is not required in the EU/UK; and the FDA preferred the compatible contrast names that reflected the presented test data set to be listed in the IFU rather than the contrast viscosity ranges.
5.			Is it correct to assume that the primary difference between the Plus EZ and Power XT systems is their compatibility with manual and power injectors, respectively? • Do clinics/cath labs generally only require 1 of the 2 systems? • If they only generally require one system or the other, is the decision based on the preference of the clinicians, what kit they already have available or any other factors? • Which system is more commonly used?	Osprey Medical Response: Yes, that is the primary difference. • Osprey Medical Response: Though Cath Labs generally have a power injector available for large volume injections of the atrium (i.e. LV gram), a lab is typically self-assigned to performing diagnostic and interventional coronary angiogram by either manual or power injection; not both. In general, a Cath Lab would only require 1 of the available systems. • Osprey Medical Response: Yes, the decision is strictly a clinician preference and based on their preferred method of injection. Osprey Medical believes the UK clinicians tend to prefer manual injection in most cases.

6.			Do you have any information on how CI-AKI risk is defined outside the UK (particularly the US, Germany, Italy, Australia and the Netherlands, given that evidence has been generated in these healthcare settings)?	Osprey Medical Response: CI-AKI risk factors defined outside the UK are very similar to those risk factors identified in the countries from which the DyeVert clinical trial evidence for CI-AKI outcomes is derived based on our experience. For example, chronic kidney disease, diabetes, advanced age, and heart failure are included in the most current CI-AKI risk models derived from real-world US registry study data. European guidelines note chronic kidney disease among other comorbidities as a risk factors. CI-AKI risk factor distribution for each study is noted in Table 1.
7.			Economic analyses were excluded from your search strategy – can we assume that you will be performing a separate search for the economic submission?	Osprey Medical Response: Yes, a separate search strategy was completed for economic analyses and will be provided in the economic evidence submission.
8.			The document titled "AIC_Hospital CI-AKI Prevention Program_Draft Manuscript_Dec 2020.pdf" in the submission appears to be damaged and won't open – would you be able to provide another copy of this to NICE? It can then be securely shared to KiTEC as Academic in Confidence. Thank you.	Osprey Medical Response: Osprey Medical has emailed the document to NICE personnel in hopes that it remains workable. Note: there are some redacted sections.
9.	22/02/2021	**Expert – Dr Yahya Al-Najjar Consultant Interventional Cardiologist**	How do different contrast media affect risk of CK-AKI? • Does the choice of CM affect which other equipment is used? For example,	The data points towards lower osmolality contrasts being associated with less contrast induced nephropathy. In practice for coronary procedures we tend to use low osmolality non-ionic contrast. Of note is that contrast choice is not just due to CIN but also higher allergic reaction occurrence with ionic contrast. I am not aware

		Additional questions	does the size of catheter limit the type of CM?	that size of catheter has any impact on choice from the coronary prespective
10			Is the French catheter scale used in the UK? • What size catheters are used in your clinics?	Yes it is very much used. We use 4F up to 8F but the vast majority of coronary interventions are through 6F systems
11			Does the DyeVert device have an impact on image quality or lead to increased procedure or imaging times?	Not if trained and gone through the learning curve
12			What impact does CI-AKI have on a patient? • What type of treatment would they have? • How long would they stay in hospital on average (in addition to the primary procedure recovery time) and what type of ward? • Are there longer-term side effects? How are these managed?	There is an association with increased morbidity and mortality (which does not equate to causality). Patients will get hydration mostly and may have some of their medication omitted that can worsen renal function. Renal injury is usually reversible. The worry in patients with significant CKD is permanently causing a worsening of renal function and potentially in some cases patients needing dialysis (or bringing this forward to a time sooner than it would have been needed). Patients can stay in hospital to observe their renal function and get iv hydration. How long they stay is variable but can be up to 3 days with facility to recheck renal function as out patient

13			In your experience, is training required for using the DyeVert system? • Is there likely to be a training curve of impact dependent upon clinician experience and if yes, how long before a clinician is expert in using the device.	Yes and Yes with a learning curve of between 25 and 30 cases (in my opinion)
14			How often do patients require more than 1 catheter per procedure? • How might a radial or femoral access site affect clinical outcomes? • How is an access site chosen? • What is the approximate ratio of radial:femoral access points in the UK?	Lots cases require 2-3 catheters. A diagnostic angiogram usually requires 2 catheters with a further 3rd catheter if an intervention is performed Data suggests that radial is safer Contemporary practice is radial as the default and converting to femoral if radial fails or you need 7F or bigger catheters upfront
15			Are men more likely to require coronary angiography? Many of the studies investigating DyeVert include 70 or 80% men.	Studies tend to have more men than women likely reflecting the higher incidence of CVD in men in the study age groups
16			The scope for this assessment listed several special considerations including equality issues. The company have suggested the removal of people with an ileostomy, alcoholism, hypoalbuminemia or other comorbidities that may increase the risk of dehydration, from consideration. Their	I don't really follow their logic! The purpose of the system is to reduce contrast so not sure why in real life practice the above groups should be excluded

			rationale for this is that the DyeVert system does not effect hydration levels. Is the removal of these groups from consideration reasonable, in your opinion?	
17		**Expert – (Dr Daniel Conroy – Consultant Radiologist)**	How do different contrast media affect risk of CK-AKI? • Does the choice of CM affect which other equipment is used? For example, does the size of catheter limit the type of CM?	There are two different types of contrast used in my department. One is Omnipaque, the other is Visipaque. GE Healthcare makes both products. In my department, Omnipaque is used in most patients but Visipaque is used in patients that are deemed to be at risk of CI-AKI. This is because Visipaque is believed to be less nephrotoxic. This is a debatable subject and the literature has found Visipaque to be both less toxic and equally as toxic. No. This does not make a difference
18			Is the French catheter scale used in the UK? • What size catheters are used in your clinics?	Yes. Routinely we would use a 5-French catheter for most diagnostic imaging tests.
19			Does the DyeVert device have an impact on image quality or lead to increased procedure or imaging times?	I have no experience of using Dyevert but I can find no reason to think that this would be the case

20			What impact does CI-AKI have on a patient? • What type of treatment would they have? • How long would they stay in hospital on average (in addition to the primary procedure recovery time) and what type of ward? • Are there longer-term side effects? How are these managed?	A nephrologist would more accurately answer these questions
21			In your experience, is training required for using the DyeVert system? • Is there likely to be a training curve of impact dependent upon clinician experience and if yes, how long before a clinician is expert in using the device.	Minimal training (1-2 hrs) is likely to be needed before use.
22			How often do patients require more than 1 catheter per procedure? • How might a radial or femoral access site affect clinical outcomes? • How is an access site chosen? • What is the approximate ratio of radial:femoral access points in the UK?	Rarely, and even if multiple access points were used; only one would be used to deliver the contrast. None in relation to CK-AKI In **radiology** the access site is often dictated by the size of the access sheath required. Any case requiring an access 6F or greater is usually performed via a femoral access. Radial access is often more likely to be used if the patient does not have a history of vascular disease. This is to avoid the risk of stroke in passing catheters across the origin of the left common carotid artery.

				Cardiology predominantly use radial access, interventional radiology use 80% femoral and 20% radial.
23			Are men more likely to require coronary angiography? Many of the studies investigating DyeVert include 70 or 80% men.	These questions would be more accurately answered by a cardiologist
24			The scope for this assessment listed several special considerations including equality issues. The company have suggested the removal of people with an ileostomy, alcoholism, hypoalbuminemia or other comorbidities that may increase the risk of dehydration, from consideration. Their rationale for this is that the DyeVert system does not effect hydration levels. Is the removal of these groups from consideration reasonable, in your opinion?	These people would be more likely to be affected by CI-AKI and therefore I would have expected the company to be more likely to **include** these high risk patients.
25		**Expert - Professor Azfar Zaman - (Consultant Cardiologist)**	How do different contrast media affect risk of CK-AKI? • Does the choice of CM affect which other equipment is used? For example, does the size of catheter limit the type of CM?	There are two types of radiological contrast currently used for radiological procedures: iodinated and gadolinium based. In interventional cardiology, for the purpose of imaging coronary arteries, only the former is used. The standard CM used in these cases is the non-ionic, iodine based agents. The choice of CM does not affect the equipment nor the size of catheter used. However, where a simple coronary angiography is being performed in an individual with know AKI, the operator may choose to use

				a smaller French sized catheter as these will reduce the volume of contrast given to the patient. In summary, the choice of CM does not influence choice of equipment or size of catheter.
26			Is the French catheter scale used in the UK? • What size catheters are used in your clinics?	Yes. We use 4F for paediatric cases and 5F – 8F for adult cases. Smaller sizes (5-6F) are used for diagnostic cases
27			Does the DyeVert device have an impact on image quality or lead to increased procedure or imaging times?	In theory it should not as it only reduces the flux of contrast in the aortic root. However, in very large arteries, I would think there might be some diminution of image quality. On the whole, no impact on image quality, procedure or imaging times.
28			What impact does CI-AKI have on a patient? • What type of treatment would they have? • How long would they stay in hospital on average (in addition to the primary procedure recovery time) and what type of ward? • Are there longer-term side effects? How are these managed?	The risk of acute kidney injury after the administration of contrast material is influenced by patient and procedure related factors. Pre-existing chronic kidney disease is the strongest patient-related risk factor, with lower levels of kidney function associated with higher degrees of risk. Use of contrast medium at a high volume (>350 ml or >4 ml per kg) or repeated administration within 72 hours after initial administration has been shown to be associated with an increased risk. All reports of CI-AKI related adverse events are association studies. In summary: Many show that contrast-associated acute kidney injury, defined by small decrements in kidney function, is associated with increased mortality. 1-7 Contrast-associated acute kidney

				injury is also correlated with accelerated progression of underlying chronic kidney disease. Tin one study, the risk of a sustained reduction in kidney function at 90 days was greater for patients who had acute kidney injury after undergoing coronary angiography than for those who did not have acute kidney injury.8 For patients with mild acute kidney injury, the adjusted odds ratio was 4.7, and for those with more severe acute kidney injury, the adjusted OR was 17.3 supporting a graded relationship between severity of acute kidney injury and risk of sustained kidney impairment. Accordingly, deteriorating kidney function after angiography or angioplasty has been characterized as a major procedural complication in the National Cardiovascular Data Registry. 9. [1. Am J Cardiol 2004;93:1515-9, 2. JAMA 1996;275:1489-94, 3. Mayo Clin Proc 2008;83:1095-100, 4. J Am Soc Nephrol 2006;17:2871-7, 5. J Am Coll Cardiol 2000;36: 1542-8, 6. Circulation 2002;105:2259-64, 7. Isr Med Assoc J 2009;11:460-4, 8. Kidney Int 2010;78:803-9, JACC Cardiovasc Interv 2014;7:1-9..] Pre-procedure, patients identified as at risk of CI-AKI will likely be admitted the day before procedure, have nephrotoxic drugs adjusted and hydration protocols implemented. Unless they require dialysis (those with end stage renal failure destabilised by contrast) most patients will go home after procedure. Established (rather than reversible) CI-AKI is often manifest 7-10 post procedure. Once

				diagnosed and noted to be permanent, most will be dealt with on an outpatient basis. As above, studies are associational. CM are nephrotoxic so renal damage will occur but only a small number are likely to have a lasting impact on renal function.
29			In your experience, is training required for using the DyeVert system? • Is there likely to be a training curve of impact dependent upon clinician experience and if yes, how long before a clinician is expert in using the device.	No. Once the device is connected to the contrast injection apparatus, then the operator continues as usual. No.
30			How often do patients require more than 1 catheter per procedure? • How might a radial or femoral access site affect clinical outcomes? • How is an access site chosen? • What is the approximate ratio of radial:femoral access points in the UK?	Some centres perform a diagnostic procedure first and then, if indicated, revascularisation as a staged procedure. Some patients with complex disease undergo staged PCI procedures. Patients admitted with ST Elevation MI will have the culprit vessel treated during the acute admission and other obstructive lesions addressed at a later data. My best guess is that 30-40% of patients will have repeat CM procedures In terms of CM – no impact. Generally, radial access procedures are associated with a vascular complication rate of <0.4% whereas with femoral access, it is 2-3%. The preferred access site is radial for the reasons above. However, in complex cases some operators choose

				femoral access as it is easier to introduce larger bore catheters. In the UK radial access is used in over 80% of PCI procedures. 80:20 radial:femoral.
31			Are men more likely to require coronary angiography? Many of the studies investigating DyeVert include 70 or 80% men.	The incidence of significant coronary artery disease in the population is found predominantly in the male population). The studies reflect the ratio seen in most studies and national databases.
32			The scope for this assessment listed several special considerations including equality issues. The company have suggested the removal of people with an ileostomy, alcoholism, hypoalbuminemia or other comorbidities that may increase the risk of dehydration, from consideration. Their rationale for this is that the DyeVert system does not effect hydration levels. Is the removal of these groups from consideration reasonable, in your opinion?	No. These patients are also susceptible to AKI and, in my opinion, should not be excluded if they are deemed to be at high risk.
33		**Expert – Dr Mark Devonald – (Consultant Nephrologist)**	How do different contrast media affect risk of CK-AKI? • Does the choice of CM affect which other equipment is used? For example, does the size of catheter limit the type of CM?	Historically there has probably been a difference in risk of nephrotoxicity from iodinated contrast media (the original 'high osmolar' agents were considered to be higher risk) but most modern agents are similar with respect to reported nephrotoxicity and are low risk. Not to my knowledge but better answered by an interventionist.

34			Is the French catheter scale used in the UK? • What size catheters are used in your clinics?	I believe so but again I defer to the interventionists I defer again
35			Does the DyeVert device have an impact on image quality or lead to increased procedure or imaging times?	I defer again
36			What impact does CI-AKI have on a patient? • What type of treatment would they have? • How long would they stay in hospital on average (in addition to the primary procedure recovery time) and what type of ward? • Are there longer-term side effects? How are these managed?	Any type of AKI is associated with adverse outcomes including increased mortality (short and long term), increased length of stay, increased risk of developing chronic kidney disease (or risk of worsening of existing CKD); increased risk of subsequent episodes of AKI. The risks of these adverse outcomes increase with increasing stage of AKI (KDIGO stages 1-3) being worst for AKI stage 3 requiring renal replacement therapy. Usually none other than standard medical support, monitoring of renal function, adequate hydration, avoidance of other 'high risk' (nephrotoxic) drugs, appropriate follow-up to ensure recovery of serum creatinine. It depends on the severity of AKI and how soon there is evidence of recovery of kidney function (e.g. from serum creatinine). Quite often hospital admission or prolonged

				stay would not be required; the serum creatinine could be monitored as an outpatient. Sometimes the 'CI-AKI' would be detected only after the patient has gone home after the procedure because the serum creatinine might start to rise a day or two after the procedure, classically it peaks after 4-5 days, then usually improves. So in many cases the change in serum creatinine might not even be seen if blood tests aren't done; if a transient increase in serum creatinine were seen but the patient remains well then the SCr would usually be monitored as an outpatient. However, there is a clear association between AKI and prolonged hospital stay e.g. in a study that we did in Nottingham, median stay for all admissions was about 3 nights whereas for patients with AKI stage 1-3 it was about 9 nights and for those requiring renal replacement therapy it was more than 20 nights. Other published data support this increased length of stay with AKI. There are long term consequences of AKI (mentioned above) – this is becoming increasingly apparent and is an active area of research
37			The scope for this assessment listed several special considerations including equality issues. The company have suggested the removal of people with an ileostomy, alcoholism, hypoalbuminemia or other comorbidities that may increase the risk of dehydration, from consideration. Their rationale for this is that the DyeVert system does not effect hydration levels. Is the removal	I don't understand the rationale for this. Groups at risk of dehydration would in theory have a greater risk of CI-AKI (particularly those with co-existing CKD), in which case you might want to minimise the amount of contrast given in addition to ensuring that they are adequately hydrated before and after the procedure.

			of these groups from consideration reasonable, in your opinion?	
38		**Expert – Dr Sudhir Rathore – (Consultant Cardiologist)**	How do different contrast media affect risk of CK-AKI? Does the choice of CM affect which other equipment is used? For example, does the size of catheter limit the type of CM? For example, does the size of catheter limit the type of CM?	Very little effect of the different contrast media used. Up to some extent but for PCI we need 6F or above and the choice is driven by coronary anatomy and lesions. Dyvert usage will have additional impact on reducing the contrast volume.
39			Is the French catheter scale used in the UK? What size catheters are used in your clinics?	Yes. For diagnostic 5F are used and for PCI 6F or above
40			Does the DyeVert device have an impact on image quality or lead to increased procedure or imaging times?	Not really in majority of the cases.
41			What impact does CI-AKI have on a patient? What type of treatment would they have? How long would they stay in hospital on average (in addition to the primary procedure recovery time) and what type of ward?	They may need IV Fluids and supportive treatment. Renal replacement therapy in some cases. Some patients may have to stay extra days in hospital and some may need high dependency unit Some patients may have long term effect and need dialysis and could have effect on their quality of life.

			Are there longer-term side effects? How are these managed?	
42			In your experience, is training required for using the DyeVert system? Is there likely to be a training curve of impact dependent upon clinician experience and if yes, how long before a clinician is expert in using the device.	Catheter lab staff need to be trained for the device set up and clinician could be up to speed after few assisted cases.
43			How often do patients require more than 1 catheter per procedure? How might a radial or femoral access site affect clinical outcomes? How is an access site chosen? What is the approximate ratio of radial:femoral access points in the UK?	Very often and up to 30% of the cases. No significant effect on contrast volume and or CKD Majority of cases in UK are now done via Radial and sometimes Femoral depending on case complexity. Approximately 8:1
44			Are men more likely to require coronary angiography? Many of the studies investigating DyeVert include 70 or 80% men.	Majority of studies show similar gender ration of patients have treatment of CAD.

45			The scope for this assessment listed several special considerations including equality issues. The company have suggested the removal of people with an ileostomy, alcoholism, hypoalbuminemia or other comorbidities that may increase the risk of dehydration, from consideration. Their rationale for this is that the DyeVert system does not effect hydration levels. Is the removal of these groups from consideration reasonable, in your opinion?	I am not sure about the clinical data.
46	04/03/2021	**Company** Additional questions	Is the French catheter scale used in the UK? • What size catheters are used in your clinics?	The Gurm 2019a is our DyeVert Observational study, and the Gurm 2019b is study from the BMC2 (Blue Shield Blue Cross of Michigan Cardiovascular Consortium) Registry out of Michigan USA. Unfortunately, the BMC2 does not track DyeVert use in their registry. We included only the Gurm 2019a as part of the summary of published literature. The Gurm 2019b paper was referenced for the association of lower contrast volumes with lower CI-AKI risk and the increase in CI-AKI risk with contrast media doses that exceed three times the patients baseline kidney function. We have attached the Gurm 2019b paper for your reference.
47			Does the DyeVert device have an impact on image quality or lead to increased procedure or imaging times?	As discussed, Osprey identified data from presentation posters that were complimentary to published abstracts. Osprey has included those in this response for your review. We do not plan to publish the Market Acceptance Evaluation report. Osprey Medical continues to maintain post-market surveillance activities; such as the ongoing DyeVert DyeMinish Registry referenced in the submission

				but the market acceptance evaluation is complete. In terms of overlaps in population between the larger retrospective studies, Cameron et al. 2020, Tucker et al. 2020, Bunney et al 2019, and Kutschman 2019 are all single-center studies. The studies used in the CI-AKI meta-analysis were also all single-center studies.
48			What impact does CI-AKI have on a patient? • What type of treatment would they have? • How long would they stay in hospital on average (in addition to the primary procedure recovery time) and what type of ward? • Are there longer-term side effects? How are these managed?	The model patient age was based on NHS current data leveraged in HES and aligns with current NICE Guideline patient population selection. The data summary is provided in the supplementary PowerPoint provided.
49			The scope for this assessment listed several special considerations including equality issues. The company have suggested the removal of people with an ileostomy, alcoholism, hypoalbuminemia or other comorbidities that may increase the risk of dehydration, from consideration. Their rationale for this is that the DyeVert system does not effect hydration levels. Is the removal of these groups from consideration reasonable, in your opinion?	See below.

50			On the worksheet Decision Tree! cell K22 the formula should link to Distributions!F35 instead of Distributions!F25	See below.
51			Likewise, on the worksheet Decision Tree! cell K51 the formula should link to Distributions!F35 instead of Distributions!F25	See below.
52			On the worksheet TPS! cells in the column AK refer to MI risk (Distributions!F30) when this should be AKI risk?	See below.
53			We also note some slight misrepresentations in the Markov model diagram. The model does not allow transition from the health state MI initial to the same health state (another MI next cycle) as the arrow in the diagram suggests. The model diagram should include an arrow from CKD3-4 to MI initial as the model allows this.	See below.

			a. What data informed the decision to run the model for patients aged 65?	
54			Finally, does the company have evidence to differentiate parameters according to whether patients are CKD3 or CKD4?	See below.
55	05/03/2021	**Company** Additional questions	In the clinical evidence submission, there are 2 studies named as Gurm 2019 (2019a and 2019b). Gurm 2019b is listed as supporting evidence for "More likely to experience contrast administration at or below the maximum contrast media dose" (amongst others), however it is not included in Table 1 (Summary of all relevant published studies). Can you explain why? o We don't have a copy of the 2019b paper – could you provide it?	Osprey Response: The Gurm 2019a is our DyeVert Observational study, and the Gurm 2019b is study from the BMC2 (Blue Shield Blue Cross of Michigan Cardiovascular Consortium) Registry out of Michigan USA. Unfortunately, the BMC2 does not track DyeVert use in their registry. We included only the Gurm 2019a as part of the summary of published literature. The Gurm 2019b paper was referenced for the association of lower contrast volumes with lower CI-AKI risk and the increase in CI-AKI risk with contrast media doses that exceed three times the patients baseline kidney function. We have attached the Gurm 2019b paper for your reference.
56			Several studies reported as abstracts in table 1 have extra information included in the table that is not included in the abstracts (such as patientdemographics) – are there unpublished full text manuscripts including these details that you could share with us as academic in confidence?	As discussed, Osprey identified data from presentation posters that were complimentary to published abstracts. Osprey has included those in this response for your review. We do not plan to publish the Market Acceptance Evaluation report. Osprey Medical continues to maintain post-market surveillance activities; such as the ongoing

			• Do you plan to publish the market acceptance evaluation summary report provided to us as an unpublished manuscript? Is this considered ongoing? • Are you aware of any overlaps in population between the studies, particularly the larger retrospective studies (Cameron et al. 2020, for example)?	DyeVert DyeMinish Registry referenced in the submission but the market acceptance evaluation is complete. In terms of overlaps in population between the larger retrospective studies, Cameron et al. 2020, Tucker et al. 2020, Bunney et al 2019, and Kutschman 2019 are all single-center studies. The studies used in the CI-AKI meta-analysis were also all single-center studies.
57			What data informed the decision to run the model for patients aged 65?	The model patient age was based on NHS current data leveraged in HES and aligns with current NICE Guideline patient population selection. The data summary is provided in the supplementary PowerPoint provided.
58			Does the company have evidence to differentiate parameters according towhether patients are in CKD stage 3 or CKD stage 4?	Stage 3 and Stage 4 CKD is part of the cohort presented in the Osprey submission. Regarding clinical evidence on how risk factor reduction with DyeVert translates to AKI reduction in patients with lower eGFRs, this patient population is included among the outcomes presented: • In the Gurm, et al., 2019a study of DyeVert use in a single-arm study, mean baseline eGFR was 43 ± 11 mL/min/1.73m^2 with 16% of subjects having a baseline eGFR of 20-30 mL. • In the Bunney, et al., 2019 study of DyeVert use vs a control group without DyeVert use, 31% of patients had a baseline eGFR <44 mL/min/1.73m^2

				• In the Sattar, et al., 2019 study of DyeVert use vs a control group without DyeVert use, mean baseline eGFR was 43.6 mL/min/1.73m^2 • In the Rao, et al., 2019 study of DyeVert use in a single-arm study, mean baseline eGFR was 45.7 ± 29.2 mL/min/1.73m^2 • In the Kutschman, et al., 2019a study of DyeVert use vs a control group without DyeVert use, mean baseline eGFR was 43 ± 13 mL/min/1.73m^2 Please note patients presenting with Stage 5 (eGFR <15) or on dialysis would typically not have DyeVert used as part of their procedure. In real-world clinical practice, eGFR is not the only CI-AKI risk factor of consideration. For example, in the validated CI-AKI risk model developed by Tsai, et al., (publication included in this response) from a large registry database and intended for real-world clinical application, a patient presenting with a severe GFR (defined as <30 in this paper) has a similar CI-AKI risk as a patient presenting with mild GFR (defined as 45-60 in this paper) and STEMI. Further, a patient presenting with STEMI and diabetes would be at an even higher CI-AKI risk. The table below from the paper illustrates this point and speaks to the real-world complexity of assessing patient CI-AKI risk.

59			Peripheral and coronary procedures have been included in the same economic model. Are they considered equivalent in their risk of developing CI-AKI? Is there evidence to support this?	In clinical practice today, the most common use of DyeVert for peripheral angiography is in cases combined with coronary angiography (as a combined procedure). However, some physicians are using DyeVert for peripheral vascular angiography and/or interventions as stand-alone procedures as well. Similar to CI-AKI rates in coronary angiography patients, CI-AKI rates in patients with critical limb ischemia are also rising (Prasad, 2019) with the overall rate during the analysis period being 10.4% based on the National Inpatient Sample of >273,624 patients from 2003 to 2012. The authors noted the strongest risk factors for developing AKI in this population were age, CKD, diabetes, and heart failure. Similar to the Tsai et al CI-AKI risk model for coronary angiography, Safley, et al., evaluated >27,000 procedures between 2014 and 2017. The overall CI-AKI rate was 7.4% (defined as an increase in serum creatinine of ≥0.3 mg/dL or 50% increase). The authors presented data on a peripheral vascular intervention AKI risk model and also found independent risk factors for CI-AKI were kidney function, hypertension, diabetes, anemia, heart failure, chronic limb ischemia and acute limb ischemia. Next to pre-existing severe chronic kidney disease, acute limb ischemia was the second strongest risk factor for AKI – similar to coronary studies such as Tsai et al where acute presentation was found to be a major driver of CI-AKI risk.

				Grossman, et al., analysed data from 13,126 patients in the Blue Cross Blue Shield of Michigan registry. AKI in this registry is defined as an increase in serum creatinine of ≥0.5 mg/dL. The overall AKI rate was 3% and among the significant predicators were baseline renal function, anaemia, heart failure, diabetes, acute presentation and receiving a contrast volume >3x baseline creatinine clearance.
60			Could you explain the key differences between the submitted model and the published Javanbakht et al. (2020) paper?	The key differences between the published model and the submitted models are as below: 1- The relative risk of CI-AKI has been updated. The estimated risk reduction was 21.4% in the paper but in the new model it is 41% as per results from the meta-analysis. 2- All unit costs have been updated. 3- The baseline risk of CI-AKI is also updated (only in scenario analyses)
61			Do the Power XT and PLUS EZ devices lead to an equivalent reduction inrisk of developing CI-AKI? Is there evidence to support this?	Yes, both devices have equivalent reduction in risk of developing CI-AKI as it relates to contrast reduction as both devices use the same mechanism to reduce contrast and achieve equivalent contrast reduction as demonstrated in the clinical submission (Bruno et al, 2019, Amoroso et al, 2020, Market acceptance evaluation) and internal bench testing. Below is a brief description of how the mechanism works, how contrast volume diversion is determined and

				how the user adjusts injections for more or less contrast to be delivered to the patient. Both the DyeVert Power XT and DyeVert Plus EZ devices connect to an injection source, through a sterile, single-use disposable module that diverts contrast solution through a mechanical Diversion Valve and transfer the contrast to a disposable waste bag preventing its reuse. Neither device controls contrast injection nor are they able to administer or determine contrast dosing without user determination and assessment of live imaging. In addition, both devices are designed to allow the user to maintain current contrast administration use interface of their preferred contrast injection source (manual injection for the predicate device and power injection for the subject device). The devices rely upon the fundamental physics of Ohm's Law translated to fluid flow, where the pressure difference between any two points along the path equals flow times resistance. Adding the parallel fluid path modifies the total resistance (R) in the system to be the sum of 1/R1 + 1/R2 thereby decreasing the resistance. Ohm's Law is Pressure=Flow*(1/R1+1/R2) for two resistances in parallel. 

				[redacted]  The following figures represent the contrast flow at the beginning of injection (resting state) (figure 1) and during injection (figure 2). The green arrow represents contrast flow. The modulation of the fluid pathway approximates the ideal patient flow rate at the injection site, through a mechanism of action by which the physical displacement of a portion of injection volume associated with reflux and diverts it from the patient's vasculature to an external reservoir. The systems are not intended to prevent under-injection as defined by physician chosen injection volume and/or physician manual speed being too low. Similar to current manual injection, physicians may inject at a speed and volume that is too slow/low and require a repeat injection.

				Likewise if a physician wants more contrast to go to the patient, the physician would inject at a higher speed/volume as is practiced in today's current set-up without the subject devices.
62			On the worksheet Decision Tree! cell K22 the formula should link toDistributions!F35 instead of Distributions!F25 • Likewise, on the worksheet Decision Tree! cell K51 the formula shouldlink to Distributions!F35 instead of Distributions!F25	Thank you for noting this error, please amend this. Osprey Medical has amended this internally and the cost savings improves.
63			On the worksheet TPS! cells in the column AK refer to MI risk (Distributions!F30) when this should be AKI risk?	Thank you for noting this error. This should refer to cell Distributions!F28. However, this will have very minor impact on the results.
64			We also note some slight misrepresentations in the Markov model diagram. The model does not allow transition from the health state MI initial to the same health state (another MI next cycle) as the arrow in the diagram suggests. The model diagram should include an arrow from CKD3-4 to MI initial as the model allows this.	The arrow in MI health state indicates that the patients can move to post MI health state not to initial MI health state. In regards to the second point, Osprey has amended the diagram. This will not have any impact on the results of course.

65			In the calculation of CKD 5 costs, we are unable to figure out how the final cost of 6749 was estimated. The cell in the cost sheet' B71 does not have a formula included. Can you please clarify the same? Also, we found that the NHS reference cost 2018 -19 has been used in the estimates, if so, why were the cycle 1 and subsequent cycle cost further inflated from 2017 to 2019?	The costs are taken from CG169 (appendix file-Table 99: CKD Stage 5 Costs) we inflated to 2017 price for the paper that we have published and then we also inflated to 2018-19 price when we were preparing the model for the NICE submission.
66			CI AKI index admission cost of 2834 does not reconcile with the NHS reference cost 2018-19. Could you let us know which year's NHS reference cost has been used?	We have used NHS reference cost 2018-19. The value is calculated based on the weighted average of Non-elective Long Stay. Please see table below.
67			What support for setting up and using the device is currently available, given that it's not feasible to enter hospitals right now? Do you have anyonline videos or virtual support tools?	There is no formal training of Cath Lab staff. Osprey Medical does provide on-site personnel during product evaluations (sales process) when allowed. These evaluation with Cath Lab staff are performed typically as part of the purchasing decision-making process and includes review of the instructions for use. Osprey Medical does have additional tools such as YouTube videos demonstrating priming of the device. In addition, the DyeVert Plus EZ system has a priming video that is part of the display software that the user can select and watch in real time during device set up. The user interface during the procedure (user and injection device – manual control syringe or power injector) does not change from the current user interface without the subject devices. The product evaluation usually is 1-2 days and does not

				involve additional training. Osprey personnel review the instructions for use. If a request is made for additional instructions for use review due to staff turnover, Osprey would provide this free of charge. However, Osprey is not aware of any such requests to date. The interface with the device is identical to current luer and tubing interfaces of common cath lab devices.
68			Could you provide some additional clarity about how the diversion part ofthe device works? How is the volume of contrast diverted determined? Isit based on pressure applied to the syringe? Can a clinician intentionally inject harder to override the diversion mechanism?	See answer above.
69			In the initial section of the clinical evidence submission, there is a request to remove “consideration of people with an ileostomy, alcoholism, hypoalbuminemia or other comorbidities that may increase the risk of dehydration” from the special considerations, including issues related to equality. We were not sure about the reasons behind this – these patients would be considered higher risk and should be considered as equality issues due to their potential inability to receive hydration. What are your thoughts on this?	Similar to the Osprey statement in the clinical submission (p. 4 of 128), the subject system is not intended to be a substitute to hydration as the guidelines recommend hydration along with contrast minimization as part of standard modifiable risk reduction strategies for CI-AKI. Osprey Medical notes that those that are not able to benefit from hydration (due to access limitations or other reasons) do not currently have alternative treatments; and, it is not the intent of Osprey Medical for DyeVert Systems to substitute for hydration. Osprey Medical does agree that ideally all modifiable risk reduction strategies are employed for all patients, and in some cases, uncontrollable factors may prevent a full approach. As such, it may be inferred that a preferred secondary

				approach would be the employment of partial risk reduction strategy as compared to none. However, limited data is available to support this recommendation at this time and is the reason for the request to remove "consideration of people with an ileostomy, alcoholism, hypoalbuminemia or other comorbidities that may increase the risk of dehydration" from the special considerations, including issues related to equality.
70			Further, we were wondering if you were aware of why the Bath et al. 2019 paper was only published as an abstract (given that it is an RCT) and if you're aware of any plans to publish this in full?	Our Osprey Medical clinical team has indicated that the authors for the Bath et al (2019) abstract do not have any intention to create a manuscript for publication at this time.
71	17/03/2021	**Expert - Professor Azfar Zaman - (Consultant Cardiologist)** Additional question	The recent update to the NICE guidance on avoidance of CI-AKI indicated that the most effective preventive intervention is oral sodium bicarbonate and oral fluids, and that this regime can reduce the risk of CI-AKI to 2.74% in patients at risk (CK% stages 3-4). Would you routinely use this intervention with at risk patients? Do you think the estimate of the risk of CI-AKI of 2.74% after oral fluids and oral bicarbonate is reasonable?	This practice (bicarbonate infusion) is not praciced here or routinely elsewhere. I will have to look at the data to see where they get the figure of 2.74. It seems exaggerated.

72		**Expert – (Dr Daniel Conroy – Consultant Radiologist)**	The recent update to the NICE guidance on avoidance of CI-AKI indicated that the most effective preventive intervention is oral sodium bicarbonate and oral fluids, and that this regime can reduce the risk of CI-AKI to 2.74% in patients at risk (CK% stages 3-4). Would you routinely use this intervention with at risk patients? Do you think the estimate of the risk of CI-AKI of 2.74% after oral fluids and oral bicarbonate is reasonable?	I don't use sodium bicarbonate in my practice. We just use fluids only. With regards to fluids, a lot of my patients would be fasting for 4 hours prior to a procedure which prevents the use of oral fluids. Some patients will also be unable to eat after the procedure for a few hours as well. In this scenario we may use intravenous fluids instead. It would be our routine practice to use IV fluids before and after the procedure in patients with a low GFR (glomerular filtration rate) of less than 30. Oral fluids would be more appropriate to use in an outpatient setting, for example if the patient was coming for a CT scan and needed contrast. Oral fluids before and after the scan would be recommended in this case. I would think that a 2-3% risk of AKI in managed patients would seem to be a reasonable number.
73		**Expert – Dr Sudhir Rathore – (Consultant Cardiologist)**	The recent update to the NICE guidance on avoidance of CI-AKI indicated that the most effective preventive intervention is oral sodium bicarbonate and oral fluids, and that this regime can reduce the risk of CI-AKI to 2.74% in patients at risk (CK% stages 3-4). Would you routinely use this intervention with at risk patients? Do you think the estimate of the risk of CI-AKI of 2.74% after oral fluids and oral bicarbonate is reasonable?	We routinely use IV Fluids in patients with high risk of AKI and Sodium Bicarbonate use is variable. I do not have any data to support.

Insert more rows as necessary

Appendix 1.

During correspondence with the company and experts, additional information is sometimes included as file attachments, graphics and tables. Any questions that included additional information of this kind is added below in relation to the relevant question/answer:

Three previous versions are listed in the submission. Would you be able to list which versions of the systems were used in each of the studies named in section 4?

Author	Device
Sapontis et al, 2017	**DyeVert (identical pressure compensating valve (i.e. diversion valve)**
Corcione et al, 2017	**DyeVert Plus**
Desch et al, 2018	**DyeVert**
Gurm et al, 2019a	**DyeVert Plus**
Bruno et al, 2019	**DyeVert Power XT (first version)**
Tajti et al, 2019	**DyeVert Plus**
Briguori et al, 2020	**DyeVert Plus EZ**

Zimin et al, 2020	**DyeVert Plus EZ**
Turner & Tucker 2020	**DyeVert Plus & DyeVert Plus EZ**
Bath et al, 2019	**DyeVert Plus**
Kutschman et al, 2019a	**DyeVert Plus & DyeVert Plus EZ**
Kutschman et al., 2019b	**DyeVert Plus & DyeVert Plus EZ**
Sattar et al, 2018	**DyeVert Plus**
Rao, 2019	**DyeVert Plus**
Bunney et al, 2019	**DyeVert & DyeVert Plus**
Amoroso et al, 2020	**Power XT (first version)**
Cameron et al, 2020	**DyeVert Plus & DyeVert Plus EZ**

MT550 DyeVert Company Meeting – minutes – 02.02.21

Introductions and roles:

KiTEC:

- Jamie Erskine – Health Technology Assessor - project lead
- Kate Goddard – Health Technology Assessor
- Mark Pennington – Health Economist
- Murali Kartha – Health Economist
- Farhad Shokraneh – Systematic Reviewer/Information Specialist
- Jo Boudour – Project Manager

NICE:

- Lizzy Latimer – Technical Adviser
- Charlotte Pelekanou – Technical Analyst
- Samantha Baskerville – Technical Analyst

Company:

- Melanie Hess - Vice President of Regulatory, Compliance, and Quality. Osprey Medical
- Kim Knish - Vice President of Clinical Affairs. Osprey Medical
- Michael Branagan-Harris - CEO. Device Access UK
- Mehdi Javanbakht - Senior Health Economist. Device Access UK

Discussion on questions:

1) **Three previous versions are listed in the submission. Would you be able to list which versions of the systems were used in each of the studies named in section 4?**A

   a. **Are the only versions currently in use the Plus EZ and the Power XT?**

      MH – There are three previous DyeVert Plus systems: DyeVert, DyeVert NG and then DyeVert Plus, Dyevert Plus EZ is what is available now.
      MH – there are two versions of the Power XT system. Monitoring was not available in the first version. The second version provided firmware on the waste bag and identifies how much contrast is in the bag. There are some cosmetic differences too.
      MH - the valve component is identical in all the versions. DyeVert Plus – the device is physically the same, there is a circuit board inside and a connection for a smart syringe to the system. It can wirelessly communicate to a display.

   b. **Improvements between the generations are generally described as improving Ease of Use; in your opinion, is this likely to have an effect on clinical outcomes? Given that the standard of care for minimisation of contrast volume is dependent on clinician skill, attention, and awareness?**

      MH – doesn't affect clinical outcomes. The diversion valve is identical across all of them.

   c. **In Corcione et al. 2017, the device investigated is described as the DyeVert NG contrast reduction system – is this the second generation DyeVert Plus System?**

2) **It is mentioned in section 3 that no formal training is usually required. Does this include Cath Lab staff?**

   MH – the product itself is standard where they would use it. We would do a typical product evaluation, introduction to product at hospital site when deciding if they want to purchase or not. Not aware of any formal training requested.
   JE – who at hospital would be involved?
   MH - physician would be on site as well as Cath Lab staff.

   a. **How frequently do clinics request training?**

b. **Is training free if requested?**

c. **How long does training typically take if requested?**

3) **There is an IFU for a Smart Monitor and one for a Display. The monitor allows access to an app interface. Are both the Smart Monitor and Display required to use the system?**

MH – you need either/or the Smart Monitor or the Display. Smart Monitor is not available in the UK. We have CE marked it and do anticipate it becoming available.

4) **There are 2 IFUs for the DyeVert Plus Disposable Kit (one for the EU and for the US). Does the technology differ between the EU and the US, or just the contents of the IFU?**

MH – IFUs are different for EU and US but it is just the documents that are different. Different information was required by the FDA for the US version.

a. **Similarly, for the Plus EZ Disposable Kit (one for the US and one for OUS)?**

5) **Is it correct to assume that the primary difference between the Plus EZ and Power XT systems is their compatibility with manual and power injectors, respectively?**

JE – is the difference primarily compatibility with power injectors or are there any other differences?
MH – all the diversion valves are identical. Power XT is compatible with power injectors. The valve is very slightly different on the Power XT model.
JE – do the systems only require one: power injector or manual injector?
MH – yes.
JE – do UK clinicians prefer the manual injectors? MH – don't know but can try to find out. UK tends to lean more manual than power.
ACTION: Osprey Medical to supply information on power and manual injectors for the UK.

a. **Do clinics/cath labs generally only require 1 of the 2 systems?**

b. **the preference of the clinicians, what kit they already have available or any other factors?**
   i. **Which system is more commonly used?**

6) **Do you have any information on how CI-AKI risk is defined outside the UK (particularly the US, Germany, Italy, Australia and the Netherlands, given that evidence has been generated in these healthcare settings)?**

JE – how is risk defined?
KK – it's very similar across major markets, demographics are similar and pathways for care are similar. Equipment is very similar and flow of the procedure. Guidelines are very similar. Publications referenced in the guidelines are all the same. There doesn't seem to be any kind of market specific characteristics that differentiate one from another.

7) **Economic analyses were excluded from your search strategy – can we assume that you will be performing a separate search for the economic submission?**

8) **The document titled "AIC_Hospital CI-AKI Prevention Program_Draft Manuscript_Dec 2020.pdf" in the submission appears to be damaged and won't open – would you be able to provide another copy of this to NICE? It can then be securely shared to KiTEC as Academic in Confidence. Thank you.**

AOB:

CP – Is the Smart Monitor calculated on the same cost basis as the Display?
MH – same cost structure.
CP– Would you recommend DyeVert in a more emergency setting?
MH – yes and take precaution to protect the kidneys.
CP – For the Display, how do you figure out the total contrast upper limit?
MH - our display doesn't calculate a recommended dosage. The user can enter this.

KK – in an emergency setting you would just assume patient is probably borderline.
KK – the lack of setting a dose threshold and lack of documenting the threshold bridges both of these quality gaps.
LL – the economic submission is due to NICE on 23rd February.

MT550 DyeVert Expert Engagement Meeting – minutes – 12.02.21

Introductions and roles:

KiTEC:

- Jamie Erskine – Health Technology Assessor - project lead
- Kate Goddard – Health Technology Assessor
- Mark Pennington – Health Economist
- Murali Kartha – Health Economist
- Farhad Shokraneh – Systematic Reviewer/Information Specialist
- Jo Boudour – Project Manager

NICE:

- Lizzy Latimer – Technical Adviser
- Charlotte Pelekanou – Technical Analyst
- Samantha Baskerville- Technical Analyst
- Victoria Fitton – Project Manager
- Cheryl Hookway – Health Technology Adoption Manager

Experts:

- Dr Yahya Al Najjar – Consultant Interventional Cardiologist, Manchester University NHS Foundation Trust
- Professor Azfar Zaman, Consultant Cardiologist, Freeman Hospital, Newcastle upon Tyne.

- Dr Sudhir Rathore, Consultant Cardiologist with special interest in the treatment of patients with coronary artery disease, NHS Frimley Health Foundation Trust
- Dr Bella Huasen, Interventional Radiology and Vascular Consultant, Lancashire University teaching health trusts NHS
- Dr Mark Devonald, Consultant Nephrologist, Nottingham University Hospitals (until 21/12/2020); Liverpool University Hospitals Foundation Trust (from 22/12/2020)
- Dr Daniel Conroy, Consultant Radiologist, Belfast Health and Social Care Trust

Discussion on questions:

The clinical value of DyeVert

We want to understand the value of DyeVert as non-users/non-experts

• What is the benefit of a system that diverts contrast media, as opposed to clinicians judging the amount of dye being given? Are there alternate ways in current practice of reducing contrast media to individuals?

AZ: During coronary angiogram, most centres use manual injection of contrast agent. This goes into the guiding catheter that goes into coronary artery. Sometimes it's difficult to control how much goes in –too much pressure could be applied. DyeVert reduces pressure and the amount of contrast going outside of coronary artery and into patient plasma.

SR: I agree with the above. Everyone has a different force that can be applied, can be difficult to control this.

YN: Main issue is to reduce contrast and strength of injection for 2 reasons to 1) help reduce risk of contrast induced nephropathy but in 90-95% of patients it's not an issue. As a result how much contrast you inject is not on the forefront of operators' minds. 2) The sheer force of the injection can tear arteries, so DyeVert may help reduce the pressure. Some hospitals use automated systems. This system takes that into account.

DC: Can I ask cardiologists - what is the average injected volume per injection and per procedure?

AZ: 5-10ml per injection, total volume is more complicated – coronary angiogram can be as little as 20-30ml, for a complex PCI volumes as high as 1 litre.

• Are there barriers to being able to give less dye without a device like DyeVert?

LL: Are there other ways of reducing contrast media, or reducing the risk of kidney injury through contrast media?

YN: Ideal system is the next iteration of DyeVert – measures flow going through and then it's automated. This is a first step – also need to identify patient groups that need it.

AZ: Difficult question. The reflex is to say you inject less, but the onus is on operator to ensure the image is of high enough quality with enough contrast that you don't have to repeat it. So balance between minimising contrast, but keeping imaging quality. We hope that DyeVert will do this as it allows

forceful injecting for an optimal image but balances this with the least contrast necessary. Reemphasise what YN said – we are only looking at a selected few patients with moderate/severe kidney injury.
BH: We are likely to keep seeing more patients with chronic kidney injury over time. Reducing dye is a good idea but repeat that it's a problem in a select group with select procedures. In terms of what we can do in the meantime – we can reduce concentration by mixing with saline, but trade off with image quality. Sometimes you can afford to have lower quality, but for more precise procedures you can't. Fluoroscopy machine technology is evolving – there is some software you can do a single run and then based on that run continue with the rest of the procedure (possibly more for peripheral procedures rather than coronary and neuro). Can also use CO2 but this is specific to body organ parts. Software tech may be a solution but it's expensive.
DC: Use of CO2 angiography – can use if people are allergic to contrast or renal function is very poor. Image quality not as good. Renal clearance of <10 and not on dialysis may use here. In scenario of GFR<30 we would use minimum amount of contrast. Peripheral angiography setting can use less contrast, more central organs may need larger volume per injection (can be 20-30ml per injection). DyeVert may be more useful if using larger volumes per injection.
CH: I've spoken to expert users who mentioned gadolinium enhanced MRI as an alternative to iodinated contrast – do experts use this? Is this a valid alterative? Is CO2 widely available or only locally available?
YN: My understudying CO2 not recommended for coronaries – toxic. Not gadolinium – it's contraindicated in people with kidney disease.
AZ: Gadolinium not used for CA imaging.
MD: GFR question – premise of this is that contrast is bad for kidneys. I think it's a debateable premise. Recent consensus if you have a GRF>30 then the risk is minimal, and even below that is debateable. So a basic question is do you need to worry about precise amount of contrast at all?
Re gadolinium, we do use MR contrast studies in patients with CKD. What is the contraindication here? Concern about a condition called NSF.
YN: MRI or CT are not high enough resolution in interventional coronary angiography, so this is a side-track.
Agreed. There is no strong evidence of causality bw negative outcome and contrast induced nephropathy. Lots of observational studies into this. From my experience in tertiary renal centre, often patients with later stages of chronic kidney disease, there would be concerns about doing complex interventions as there are concerns about them needing dialysis. There is concern about risk of CI-nephropathy in these patients with few nephrons working in the first place.
SR: Studies link contrast volume with contrast induced nephropathy. CV is only one factor but it is a factor that can be modified and controlled. It is multifactorial e.g. age, diabetes all has to be considered.
MD: Just to add CV is alleged risk factor. Observational studies, but studies are a little outdated. Consensus is that or GFR>30 it's not a significant risk factor.
SR – Use of DyeVert depends on overall risk on CI-nephropathy. Not just about CV – also the type of patient, and procedure. Complex angioplasty requires more contrast - incidence of CI-N is 0.5% (in a large registry) get CI-nephropathy, even if renal function is normal. Risk is multifactorial.
AZ: Ask MD, are we agreed that in eGFR 15-29 (CKD 4 group) – does limiting CV here work?

MD: Current evidence might say CKD4 plus other risk factors – you could minimise contrast use here. I don't think the risk is high for that group. We did a pilot study in coronary angiography - selecting high risk patients for CI-N – didn't get enough outcomes with this to carry on with study.
AZ – It's very possible that patients weren't followed up for long enough.
MD – Contrast *induced* AKI should really be termed Contrast *associated* AKI. Any interventional procedure can cause AKI – other possible causes. Causality is not clear enough.
YN – I agree with Mark. In terms of hard clinical outcomes – how many patient end up on dialysis due to contrast – it's only really in emergency/acute settings. It's an area where there is no evidence either way, there is a signal is that it's associated with worse outcome though. I support reducing CM, as it's a safer assumption atm. Until there's enough data, better to miminise volume in this group.
AZ: Is contrast medium nephrotoxic? CM does increase circulating volumes. In certain situations (like heart failure) we may want to reduce that volume whether it's nephrotoxic or not.
MD: Yes, this is a fair point. The protocol around renal protection for contrast studies may not be helping patients at risk of volume overload. Agree there are many patients to be careful of total volume, not just contrast.

Risk and treatment of CI-AKI

We want to understand the risk of developing AKI after peripheral or coronary angiography procedures.

• How is the risk of CI-AKI primarily determined in the NHS? Do you use eGFR as a marker of kidney function? Is this measurement taken for all individuals, regardless of risk factors (no known risks), or settings (i.e. A and E).
MD: CI-AKI definition used most internationally is the KDIGO. 50% in serum creatinine over a period of time (not well defined). Usually around 24-48 hours or a 26 mM increase in 24 hours. Peaks classically after 4-5 days. Needs adequate follow up period.
There are discrepancies in definition bw studies. KDIGO has been used for around for 10 years, but there are different ways of measuring. Before that it could be quite arbitrary.
LL: EGFR mentioned already. Is this taken regardless of setting?
Experts: Yes
• The company are focusing upon CKD stage 3+ as a particularly at-risk group, is this reflective of your decision making? Are there other population groups who are at particular risk?
YN – Too loose. Needs to be stage 4. Stage 3 is not a problem generally. Complex case may be used if 3, but general policy to focus on stage 4.
AZ: I would endorse that. 4 and 5 who are not on dialysis or complex stage 3 when you need to use larger volume of contrast (>500ml).

• How may clinical outcomes related to CI-AKI be affected by co-morbidities such as diabetes or coronary artery disease?
YN: Yes generally. Pre-hydration can reduce problems (so assessment on the day can affect the decision). Anecdotally magnesium. Generally comfortable not to use in stage 3.

MD: There are various comorbidities in older studies (heart failure, diabetes, MI and solid organ transplants) that indicate associated risk factors. My opinion is to concentrate on stage 4 and risk factors. Worry about cost effectiveness. Even stage 4 may not be very high risk.
SR: Agree with 4+ . Could be considered in stage 3 with other risk factors or if high contrast volume is going to be used.
BH: In peripheral (IR, vascular and neuro side) we sometimes similar problems with volumes. Completely agree with Mark. You can put a patient through a lot and no renal problems result. And then another patient with fewer problems but lack of perfusion and dehydration, can be a problem. It's very much case-by-case basis.
If this is expensive, there will be other alternatives in the future.
AZ: I believe is that CM is nephrotoxic. The problem is do we don't have sufficiently sensitive biomarkers to detect injury. We are sensitive that patients can come back for repeat procedures (staged or same procedure). I am uncomfortable with this as I think CM is nephrotoxic, but we don't have sensitive enough tools to measure it on every occasion.
BH: Yes, and we can all agree that we shouldn't give too much of anything unnecessary.

Decision-making on the use of DyeVert and patient populations

We want to understand when DyeVert is likely to be used and of most value.

• For those who use DyeVert, how do you decide which procedures need the device?
• Are there particular clinical parameters you would use? Does the use of DyeVert change the decision-making pathway for testing kidney function before an angiography procedure?
LL: If DyeVert used with angiography, will DyeVert change clinical practise in terms of decision making?
AZ: No. If it's approved in select cases, we will use it but I won't change the clinical process. We've trialled it for 3 months but haven't used it on a regular basis as it doesn't have NICE approval, so it would be an additional cost.
AZ: We used it as a way of getting operators to get used to the process.
YN: I have used it in patients with GRF<20.
SR: We use it clinically at the hospital. Have had training. We use the manual version. Local protocol is patients EGFR<30 (group 4+). Coronary intervention (rather than coronary angiogram) in procedures with contrast volume of >100ml.
• Would this change if the procedure were elective or emergency?
LL: Does it have any particular benefits in emergency vs elective settings?
YN: Emergency may be useful in theory (as patients may have more risk factors), but in practice can't identify patients beforehand. So the question is how to predict this? Caveat is we don't always know the risk factors/history.
AZ: As Mark mentioned, ST elevation MI pathway patients may be more likely to have contrast medium injury (and low blood pressure <100). Haemodynamic compromise. We can potentially select these patients.

• Would this be different for those at risk of developing CI-AKI needing peripheral as compared to coronary angiography procedures?

DC and BH: We have not used it in peripheral. Bella uses software that reduces contrast and pump that controls contrast given. Different as it's peripheral – DyeVert probably more valuable to colleagues with more fragile organs and smaller diameter vessels.
DC – Peripheral angiography is often in bleeding patients with lower blood pressure. Difficult to conclude AKI was due to contrast use (as kidneys are very sensitive to a period of shock).
CH: Interested in patient experience. If patient does have nephropathy after a procedure – what sort of symptoms would they experience? If patient meets criteria for AKI – does it change their experience? Would it increase LOS?
MD: Any form of AKI is bad news. AKI definitely increases LOS (mentioned MD Nottingham study) – median LOS for all patients (not necessarily contrast induced/associated) with AKI was 3 days. AKI stage 1 was 9 days. AKI requiring renal replacement was median 22 days. Mortality and increase in chronic kidney disease increases with AKI. Patient POV – it's more serious than people realise.
BH: More people are getting chronic kidney injury due to general state of health e.g. more diabetes, obesity, high BP. Increase renal problems.
YN: Also aging population.

Understanding the clinical pathway and integration of DyeVert

We want to understand the impact of DyeVert on the current clinical pathway and on the decision-making for the management of patients.

• Does the use of DyeVert require more clinical judgement on the volume of contrast? How is contrast volume currently monitored for angiography procedures. Is there a trigger point where you would think the patient is at risk of CI-AKI? Are there any steps you would take in this instance?
LL: Can you tell if a patient is higher risk during contrast delivery?
YN: Not really. Predominant risk factors is EGFR and pre-existing kidney disease. People who are hypo-perfused. CV is associated (not necessarily causal) with injury.
If you've had to use high volume, it can affect decision making at the time. May have to pause if concerned that it will push patient into kidney failure or fluid overload.
• From feedback we understand that most Cath labs use the manual device, is the trend and preference in the NHS to use manual over power injectors? What is the decision-making process for use of manual or power injectors?
AZ: We use manual. Basic ones. As I understand it there are two types – recycle dye or throw away.
YN: I prefer using automatic – more hands free.
LL: In the UK, the DyeVert manual system is predominant.
Yahya: Main deciding factor is cost. Also learning curve.
BH: In peripheral, it's case by case. Depends on body part being treated e.g. aorta more likely be automatic.
• Desch et al. 2018, states that "Diagnostic coronary angiography was performed according to current best practice defined as a minimum of 6 coronary CM injections with differing angiographic projections for the left coronary artery and 2 for the right coronary artery using standard low-dose fluoroscopy protocols (15 frames per second). If clinically necessary, a higher or lower number of injections were taken."

• This study was based in Germany, does UK practice follow similar standards?
• Are you aware of differences in standards between the UK and other EU countries (or the US/Canada and Australia), either for determining the risk of CK-AKI, or for performing angiography?

AZ: KDIGO definition and contrast induced nephropathy definition – procedure is the same between countries. No concerns about studies from different countries.
DC and BH: Don't think there are significant differences internationally, BH confirmed practice was the same in New Zealand where she previously worked.
MD: No concerns.

MT550 DyeVert Company Meeting – minutes – 05.03.21

Introductions and roles:

KiTEC:

- Jamie Erskine – Health Technology Assessor - project lead
- Kate Goddard – Health Technology Assessor
- Mark Pennington – Health Economist
- Murali Kartha – Health Economist
- Khanh Ha Bui – Health Economist (Observer)
- Anna Buylova-Gola –Health Economist (Observer)

NICE:

- Lizzy Latimer – Technical Adviser
- Charlotte Pelekanou – Technical Analyst
- Samantha Baskerville – Technical Analyst
- Chris Chesters – Senior Technical Advisor
- Victoria Fitton – Project Manager

Company:

- Mike McCormick - President and CEO of Osprey Medical
- Melanie Hess - Vice President of Regulatory, Compliance, and Quality. Osprey Medical
- Kim Knish - Consultant Clinical Affairs. Osprey Medical
- Michael Branagan-Harris - CEO. Device Access UK
- Mehdi Javanbakht - Senior Health Economist. Device Access UK

Summary of the clinical evidence review and questions on the submission

JE:

- The studies consistently indicate that DyeVert reduces the amount of Contrast Media (CM) vs standard procedure and that image quality is non-inferior. One study reports reduced hospital stay (Briguori). Only 1 study includes UK patients, but NICE experts did not feel this would be a biasing issue (as procedures are similar globally). Most of the studies have a company conflict of interest, but the EAC did not feel this was a significant issue.

The EAC statistician has reviewed the meta-analysis and believes the methods are robust. However, there is a concern about the low-to-moderate quality of the studies included in the pooled estimate of relative risk of CI-AKI and the weight given to retrospective studies, as well as the 30% baseline risk figure potentially being too high. The EAC will likely complete sensitivity analysis.

NICE experts would use DyeVert (DV) in very high risk kidney disease population (CKD 4+) so the EAC would be interested in more evidence in these groups. Additionally, AKI can peak at 5 days and manifest up to 7-10 days post-procedure. Evidence base would benefit from longer follow up. Also, more information on effect on hospital Length of Stay (LOS), alongside capturing of CI-AKI severity and related morbidity and mortality. One of the ongoing studies (REMEDIAL IV) appears to be promising in fulfilling some of these requirements.

KK – Generally in our studies there is a broad range of CKD patients. Company can look into subgroup of higher risk patients. In terms of follow up, practise varies a lot. Our data reflects real-world clinical practise. Clinical guidelines recommend follow up of CKD patients within approximately a week.

Discussion on questions:

Clinical Evidence:

We wanted to clarify a few details regarding the studies included in the clinical evidence submission.

• In the clinical evidence submission, there are 2 studies named as Gurm 2019 (2019a and 2019b). Gurm 2019b is listed as supporting evidence for "More likely to experience contrast administration at or below the maximum contrast media dose" (amongst others), however it is not included in Table 1 (Summary of all relevant published studies). Can you explain why?
  o We don't have a copy of the 2019b paper – could you provide it?

KK – The first Gurm study (2019a) is the DV observational study. The second is a separate Gurm study (2019b) is a separate registry being conducted in Michigan (the start of which predates DyeVert) and this registry doesn't capture DyeVert use, unfortunately, but has published extensively on the relationship between contrast volume and CI-AKI. Second paper can be provided for information.

• Several studies reported as abstracts in table 1 have extra information included in the table that is not included in the abstracts (such as patient demographics) – are there unpublished full text manuscripts including these details that you could share with us as academic in confidence?

KK – posters and published abstracts were used to complete the data in the submission. We can provide the posters. There's generally one abstract per poster, with the exception of Kutschman 2019a which was an abstract only.

• Do you plan to publish the market acceptance evaluation summary report provided to us as an unpublished manuscript? Is this considered ongoing?

KK – The MAE report has been completed. It is part of larger post market surveillance we carry out. The projects have concluded. We currently do not plan to formally publish this.

• Are you aware of any overlaps in population between the studies, particularly the larger retrospective studies (Cameron et al. 2020, for example)?

KK – Studies used in meta-analysis for AKI (for example) are individual hospital studies, so there is no overlap in terms of participating hospitals or patients.

Economic Evidence:

We wanted to understand the population included in the model:

• What data informed the decision to run the model for patients aged 65?

MJ – HES data for all people having PCI or DCA (combined) and the mean age is from NHS HES data.

MK – In the published paper the age is 72, is it that this didn't include HES data? This is non-UK data.

MJ – The model allows exploration of different scenarios. UK based data was used to inform that parameter.

• Does the company have evidence to differentiate parameters according to whether patients are in CKD stage 3 or CKD stage 4?

MJ – Model is informed by NICE CG169. In the most recent model, stages 3-5 have been combined. We don't have data to differentiate them, but all the input is applicable to stage 3 and 4. We can share the HES data summary and how it was accessed.

LL – to clarify, we have data on 3-5, but parameters can't be separated into 4+.

MJ – correct.

• Peripheral and coronary procedures have been included in the same economic model. Are they considered equivalent in their risk of developing CI-AKI? Is there evidence to support this?

MJ – Yes, assumed equivalence for risk. Clinical evidence for peripheral is limited. Rao 2019 looks at this group of patients.
KK – from a clinical perspective, there are larger datasets (Blue Cross Blue Shield Michigan Registry) that have looked at peripheral patients and have found a lot of the same risk factors. We can share this information with you.
LL- how has the difference been accounted for in costs?
MJ – model is for PCI and DCA, we have mainly used these costs. Assumed costs are similar.
• Could you explain the key differences between the submitted model and the published Javanbakht et al. (2020) paper?
MJ – Original model was based on PCI and CA and then when working on the scope saw it was peripheral. Assumed same risk. Procedure costs may be different, but can adjust this if necessary.
The major parameter that has changed since the publication (around 2 years ago) is risk reduction. RR was main driver of change in cost saving. Risk of AKI was taken from meta-analysis. In the publication, the Mehran score, which was used alongside CM volume to infer risk of CI-AKI. In the new model, updated health unit costs were also included.
MP – submission had a baseline risk of AKI from a 2004 paper that was 30%, how was this arrived at? This seems higher than the other evidence. Why was this source used?
KK – The paper (Mehran 2004) is referenced in the NICE guideline and we felt it was a reasonable base case. The model can be altered with a drop down for other baseline risks.
• Do the Power XT and PLUS EZ devices lead to an equivalent reduction in risk of developing CI-AKI? Is there evidence to support this?
MH – The mechanism of action for contrast savings is similar between two devices and a more detailed description of the diversion valve will be provided. Clinical and bench data evidence obtained thus far demonstrates equivalence between the two devices.
We wanted to clarify a few points in the economic model. The EAC have potentially identified some small errors and would like to check to ensure they haven't misunderstood.
The possible errors are:
• On the worksheet Decision Tree! cell K22 the formula should link to Distributions!F35 instead of Distributions!F25
• Likewise, on the worksheet Decision Tree! cell K51 the formula should link to Distributions!F35 instead of Distributions!F25
• On the worksheet TPS! cells in the column AK refer to MI risk (Distributions!F30) when this should be AKI risk?
• We also note some slight misrepresentations in the Markov model diagram. The model does not allow transition from the health state MI initial to the same health state (another MI next cycle) as the arrow in the diagram suggests. The model diagram should include an arrow from CKD3-4 to MI initial as the model allows this.
All agreed that the above questions will be answered by email.
Device Adoption:
The NICE adoption team wanted to clarify a few adoption questions.

• What support for setting up and using the device is currently available, given that it's not feasible to enter hospitals right now? Do you have any online videos or virtual support tools?
MH – no formal training is required. It's a standard interface in the cath lab. We do provide product evaluation. Company can go through IFU to make sure questions are answered. There are youtube videos and on the website to review the priming of the devices. The monitor contains a real time walkthrough of the priming process. There are lot of support tools.
Evaluation process is carried out over the course of 1-2days as part of the normal sales process as physicians evaluate their interest in purchasing. Staff can do a walkthrough of priming/using the device. Device is attached to current manifold or power injector. The process for the clinician does not change once the device is primed. No additional time spent on training (because not necessary).
• Could you provide some additional clarity about how the diversion part of the device works? How is the volume of contrast diverted determined? Is it based on pressure applied to the syringe? Can a clinician intentionally inject harder to override the diversion mechanism
MH – Most simple explanation, like a fork in the river. If the pressure is equivalent on both sides, the water is split 50/50. The mechanical valve steps in on one side and manages the resistance of the flow, ensuring that on average 60% of CM goes to patient and on average 40% is diverted. Valve is strictly mechanical. If the clinician injects more slowly, there is possibility of more diversion occurring and less contrast going to the patient. Similar to the current injection process without the device. If you want to divert less (more contrast goes to the patient), then inject harder/faster. The device can be overridden by switching off the device at the manifold. We will provide additional detail of the diversion valve and how it works in a written response to these questions.

File attachments/additional information from question 58:

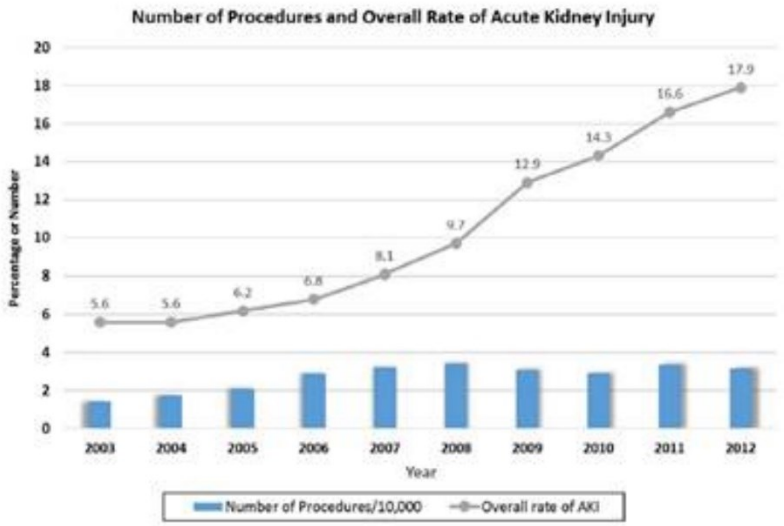
Table 4. A Simplified Integer Risk Score for Calculating the Risk of AKI and AKI-D

	Points		Converting Points to Risk			
	AKI	AKI-D	AKI	Risk (%)	AKI-D	Risk (%)
Age, y						
<50	0		0	1.9	0	0.03
50 to 59	2		5	2.6	1	0.05
60 to 69	4		10	3.6	2	0.09
70 to 79	6		15	4.9	3	0.15
80 to 89	8		20	6.7	4	0.27
>90	10		25	9.2	5	0.48
			30	12.4	6	0.84
Prior 2 weeks HF	11	2	35	16.5	7	1.5
Severe GFR	18	5	40	217	8	2.6
Moderate GFR	8	3	45	27.9	9	4.4
Mild GFR	3	1	50	35.1	10	7.6
Diabetes	7	1	55	43.0	11	12.6
Prior HF	4		>60	51.4	12	20.3
Prior CVD	4				13	31.0
NSTEMI/UA	6	1				
STEMI	15	2				
Prior card shock	16					
Prior card arrest	8	3				
Anemia	10					
IABP	11					

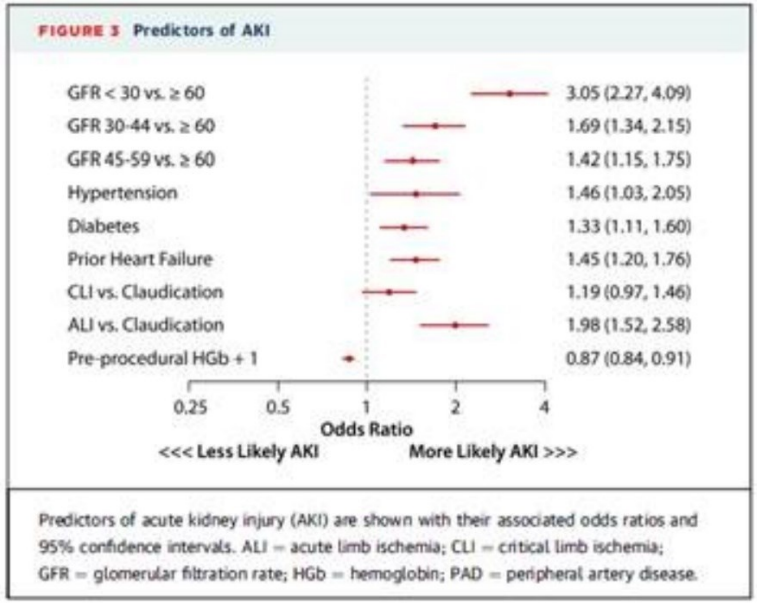
AKI indicates acute kidney injury; HF, heart failure; NSTEMI, non-ST elevation myocardial infarction.

Tsai TT, et al. Validated contemporary risk model of acute kidney injury in patients undergoing percutaneous coronary interventions: insights from the National Cardiovascular Data Registry Cath-PCI Registry. J Am Heart Assoc. 2014 Dec;3(6):e001380. doi: 10.1161/JAHA.114.001380. PMID: 25516439; PMCID: PMC4338731.

File attachments/additional information from question 59:



Prasad A, Hughston H, Michalek J, Trevino A, Gupta K, Martinez JP, Hoang DT, Wu PB, Banerjee S, Masoomi R. Acute kidney injury in patients undergoing endovascular therapy for critical limb ischemia. Catheter Cardiovasc Interv. 2019 Oct 1;94(4):636-641. doi: 10.1002/ccd.28415. Epub 2019 Aug 16. PMID: 31419029.



Safley DM, et. al. Acute Kidney Injury Following In-Patient Lower Extremity Vascular Intervention: From the National Cardiovascular Data Registry. JACC Cardiovasc Interv. 2021 Feb 8;14(3):333-341. doi: 10.1016/j.jcin.2020.10.028. PMID: 33541543.

TABLE 2 Pre-PVI predictors for the development of post-PVI CIN by stepwise logistic regression

Name	Odds ratio (95% CI)	*P*-value[1]
Creatinine clearance < 30 mL/min[a]	3.1 (2.1, 4.4)	<0.001
Creatinine clearance 30-60 mL/min[a]	1.2 (1, 1.6)	0.112
Low BMI < 18[b]	3.3 (1.2, 9)	0.024
High BMI > 30[b]	4.3 (1.5, 12.2)	0.006
Pre anemia	2 (1.6, 2.6)	<0.001
Hyperlipidemia	0.8 (0.6, 1.1)	0.126
Diabetes	1.8 (1.4, 2.3)	<0.001
Prior CHF	1.7 (1.3, 2.1)	<0.001
COPD	0.7 (0.5, 0.9)	0.002
CVD or TIA	1.2 (1, 1.5)	0.123
Prior PCI	1.4 (1.1, 1.7)	0.013
Prior MI	1.3 (1, 1.6)	0.06
Prior CABG	0.7 (0.5, 0.9)	0.012
Aspirin (Pre procedure)	0.8 (0.6, 1)	0.101
Ace inhibitor (Pre procedure)	0.8 (0.7, 1)	0.096
Critical limb ischemia	1.6 (1.2, 2.1)	<0.001
Renal	1.8 (1.2, 2.7)	0.006
Status—urgent[c]	3 (2.4, 3.9)	<0.001
Status—emergent[c]	7.7 (4.9, 12.2)	<0.001
Contrast/CCC ratio > 3[d]	1.4 (1.1, 1.8)	0.003

Model Assessment Measure (Hosmer-Lemeshow *P*-value: 0.487; Area under the ROC curve (AUC): 0.786).
[a]Reference is creatinine clearance > 60 mL/min.
[b]Reference is normal BMI (18 ≤ BMI ≤ 30).
[c]Reference is elective.
[d]Reference is contrast/CCC ratio ≤ 3.
[1]$P < 0.05$ is significant.

Grossman PM, et al. Contrast-induced nephropathy in patients undergoing endovascular peripheral vascular intervention: Incidence, risk factors, and outcomes as observed in the Blue Cross Blue Shield of Michigan Cardiovascular Consortium. J Interv Cardiol. 2017 Jun;30(3):274-280. doi: 10.1111/joic.12379. Epub 2017 Apr 3. PMID: 28370487.

File attachments/additional information from question 61:

Figure 1: Beginning of injection (resting state)

Figure 2: During Injection

File attachments/additional information from question 65:

Table 99: CKD Stage 5 Costs

Resource	frequency	Cost per cycle	Distribution & Parameters	Source of cost
Patients on RRT - Cycle 1				
Nephrologist appointment	2 per cycle	£374	Gamma α = 7.86; β = 27.62	NHS reference costs 2010/11[107]
eGFR	12 per cycle	£56	Table 96	NHS reference costs 2010/11[107] & PSSRU 2012[103]
Epoetin alpha	1788 units per week (£0.005 per unit)	£39	Table 96	BNF 62[198] & CG114[287]
Access procedure	1	£1,323	Table 98	NHS reference costs 2010/11[107]
RRT		£5,460	Pooled average of RRT modalities (Table 97)	
Sub Total		***£7,252***		
Patients on Conservative Management (CM) – Cycle 1 and subsequent cycles				
Nephrologist appointment	2 per month	£374	Gamma α = 6.63; β = 23.69	NHS reference costs 2010/11[107]
Phone call	12 per cycle	£64	Fixed	PSSRU 2012[103]
Home visits	3 per cycle	£66	Fixed	PSSRU 2012[103]
eGFR	12 per cycle	£56	Table 96	NHS reference costs 2010/11[107] & PSSRU 2012[103]
Diuretics	80mg per day	£43	Table 96	BNF 62[198] +GDG assumption
Epoetin alpha	1788 units per week	£39	Table 96	BNF 62[198] & CG114[287]
Sub Total		***£642***		
Patients on RRT cycle 2 onwards				
Nephrologist appointment (no initial consultation)	2 per cycle	£314	Gamma α = 6.63; β = 23.69	NHS reference costs 2010/11[107]
eGFR	12 per cycle	£59	Table 96	NHS reference costs 2010/11[107] & PSSRU 2012[103]
Epoetin alpha	1788 units per week	£39	Table 96	BNF 62[198] & CG114[287]
Access procedure	0.15 per cycle	£199	Table 98	NHS reference costs 2010/11[107]
RRT		£5,460	Pooled average of RRT modalities (Table 97)	
Sub Total		***£6,284***		
Totals				
Cycle 1	90% RRT/10% CM	£6,585		
Cycle 2 onwards	90% RRT/10% CM	£5,512		

EA(

File attachments/additional information from question 66:

		Total			Elective			Non-elective Long Stay		
Currency	Currency Description	Activity	Unit Cost £	Total Cost £	Activity	Unit Cost £	Total Cost £	Activity	Unit Cost	Total Cost
LA07H	Acute Kidney Injury with Interventions, with CC Score 11+	2,113	5,601	11,835,657	41	9,190	376,775	2,015	5,656	11,395,848
LA07J	Acute Kidney Injury with Interventions, with CC Score 6-10	3,744	4,618	17,288,894	95	5,820	552,937	3,533	4,695	16,588,259
LA07K	Acute Kidney Injury with Interventions, with CC Score 0-5	3,019	3,636	£10,975,624	216	3,879	837,958	2,724	3,693	10,059,668
LA07L	Acute Kidney Injury without Interventions, with CC Score 12+	8,238	2,633	21,691,645	50	5,638	281,879	5,666	3,513	19,901,842
LA07M	Acute Kidney Injury without Interventions, with CC Score 8-11	20,733	1,947	40,373,702	227	3,285	745,657	12,380	2,854	35,336,485
LA07N	Acute Kidney Injury without Interventions, with CC Score 4-7	36,747	1,456	53,493,110	527	1,880	990,529	18,948	2,313	43,834,582

LA07P	Acute Kidney Injury without Interventions, with CC Score 0-3	2 6,741	1,037	27,737,170	673	1,477	993,943	10,071	1,956	19,694,441	
			1,810			2,613			2,834		

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology consultation: DyeVert for reducing contrast media in coronary and peripheral angiograph

Supporting documentation – Committee papers

The enclosed documents were considered by the NICE medical technologies advisory committee (MTAC) when making their draft recommendations:

1. **EAC assessment report** – an independent report produced by an external assessment centre who have reviewed and critiqued the available evidence.
2. **Assessment report overview** – an overview produced by the NICE technical lead which highlights the key issues and uncertainties in the company's submission and assessment report.
3. **Scope of evaluation** – the framework for assessing the technology, taking into account how it works, its comparator(s), the relevant patient population(s), and its effect on clinical and system outcomes. The scope is based on the sponsor's case for adoption.
4. **Adoption scoping report** – produced by the adoption team at NICE to provide a summary of levers and barriers to adoption of the technology within the NHS in England.
5. **Sponsor submission of evidence** – the evidence submitted to NICE by the notifying company.
6. **Expert questionnaires** – expert commentary gathered by the NICE team on the technology.
7. **EAC correspondence log** – a log of all correspondence between the external assessment centre (EAC) and the company and/or experts during the course of the development of the assessment report.
8. **Company fact check comments** – the manufacturer's response following a factual accuracy check of the assessment report.

Please use the above links and bookmarks included in this PDF file to navigate to each of the above documents.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

GID- MT550 - DyeVert for reducing contrast media in coronary and peripheral angiography

External Assessment Centre report

Produced by: King's Technology Evaluation Centre (KiTEC)

Authors:

Jamie Erskine, Health Technology Assessor, KiTEC

Kate Goddard, Health Technology Assessor, KiTEC

Farhad Shokraneh, Information Specialist and Systematic Reviewer, KiTEC

Murali Kartha, Senior Health Economist, KiTEC

Mark Pennington, Senior Health Economist, KiTEC

Khanh Ha Bui, Research Associate in Health Economics

Anna Buylova Gola, Research Fellow in Health Economics, KiTEC

Steve Keevil, Director, KiTEC

Correspondence to: Joanne Boudour, joanne.boudour@kcl.ac.uk

Date completed: 30/03/2021

Contains confidential information: Yes

Number of attached appendices: 4

Purpose of the assessment report

The purpose of this External Assessment Centre (EAC) report is to review and critically evaluate the company's clinical and economic evidence presented in the submission to support their case for adoption in the NHS. The report may also include additional analysis of the submitted evidence or new clinical and/or economic evidence. NICE has commissioned this work and provided the template for the report. The report forms part of the papers considered by the Medical Technologies Advisory Committee when it is making decisions about the guidance.

Declared interests of the authors

Description of any declared interests with related companies, and the matter under consideration. See NICE's Policy on managing interests for board members and employees.

None.

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Copyright belongs to King's Technology Evaluation Centre.

Dr Yahya al-Najjar is a Consultant Interventional Cardiologist at Manchester University NHS Foundation Trust, no conflict declared.

Professor Azfar Zaman is a Consultant Cardiologist at Freeman Hospital, Newcastle upon Tyne, no conflict declared.

Dr Sudhir Rathore is a Consultant Cardiologist with special interest in the treatment of patients with coronary artery disease at NHS Frimley Health Foundation Trust, no conflict declared.

Dr Bella Hausen is an Interventional Radiology and Vascular Consultant at Lancashire University Teaching Health Trusts NHS, no conflicts declared.

Dr Daniel Conroy is a Consultant Radiologist at Belfast Health and Social Care Trust, no conflict declared.

Dr Mark Devonald is a Consultant Nephrologist, Liverpool University Hospitals Foundation Trust, no conflicts declared.

Responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Contents

Abbreviations

Term	Definition
AKI	Acute Kidney Injury
AUC	Area-Under-the-Curve
CA	Coronary Artery
CAD	Coronary Artery Disease
CAG	Coronary Angiography
CI-AKI	Contrast-Induced Acute Kidney Injury
CI	Confidence interval
CIN	Contrast Induced Nephropathy
CKD	Chronic Kidney Disease
CM	Contrast Media
CMV	Contrast Media Volume
CTO	Chronic Total Occlusion
DAG	Diagnostic Angiography
DCA	Diagnostic Coronary Angiography
DHSC	Department of Health and Social Care
EAC	External Assessment Centre
eGFR	Estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
ICA	Interventional Coronary Angiography
IQR	Interquartile range
KDIGO	Kidney Disease: Improving Global Outcomes
MAUDE	Manufacturer and User Facility Device Experience
MDRD	Modification of Diet in Renal Disease
MHRA	Medicines & Healthcare products Regulatory Agency
MTEP	Medical Technologies Evaluation Programme
NCDR	National Cardiovascular Data Registry
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICE CG	NICE clinical guideline
NICE MTG	NICE medical technology guidance
NICE QS	NICE quality standard
NMB	Net Monetary Benefit
OCT	Optical Coherence Tomography
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUORUM	Quality of Reporting of Meta-analyses
RCT	Randomised controlled trial
ROC	Receiver Operating Characteristic
SCr	Serum Creatinine

SD	Standard deviation
STEMI	ST-Elevation Myocardial Infarction
VAS	Visual analogue scale
Vs	Versus

Executive summary

The company included 8 studies published in full text, 9 published as abstracts and 2 unpublished manuscripts in their submission. The EAC included all of these studies and did not identify any further evidence. Overall, the EAC believes the clinical evidence to be of moderate quality.

Two RCTs are reported in the literature, 1 in full text (Desch et al. 2018) and 1 as an abstract (Bath et al. 2019). The EAC judged (Desch et al. 2018) to be the highest quality evidence and found it to be at a low risk of bias. The remaining evidence comprised 4 other prospective studies (Gurm et al. 2019a, Sapontis et al. 2017 and Zimin et al. 2020, Anon., Unpublished), 12 retrospective studies and an unpublished Market Access Evaluation. These remaining studies vary in quality from low to moderate.

Study populations were largely homogeneous in age (mean 61 – 72 years), sex (up to 82% men: men almost always more common) and mean baseline eGFR (43 – 74 ml/min/1.73m^2). The EAC were advised that, in the UK, the DyeVert system would only be considered for use in patients with eGFR<30, so it is possible that the study populations are at a lower risk of developing CI-AKI on average. Only 1 abstract (Amoroso et al. 2020) reported results for a small number participants from the UK. However, experts suggest that practice is very consistent throughout developed countries, so the EAC believes the evidence to be generalisable to the UK. A vast majority of the evidence focused on coronary angiography; only a total of 9 participants undergoing peripheral angiography were included (Corcione et al. 2017 and Rao 2019). This is not unexpected; experts suggested that the DyeVert system would be much less likely to be used in peripheral angiography. Further, there is limited evidence on the DyeVert Power XT system (Bruno et al, 2019; Amoroso et al. 2020 and DyeVert, Unpublished), in comparison to the DyeVert (Plus and Plus EZ) manual injection system.

Results from the literature consistently shows that using DyeVert reduces the contrast media volume injected, either in comparison to a standard manual manifold or in comparison to the attempted volume. Mean volume was between 17 – 41% in the DyeVert groups in the comparative studies (EAC calculated). Image quality was also consistently reported to be non-inferior or acceptable, although this measure

was not always made by an independent, blinded reader and is a subjective judgement. One study (Briguori et al. 2020) showed using DyeVert significantly reduced hospital stay (8 ± 4 vs. 6 ± 2 days; p = 0.003). There is a lack of follow-up in the studies, however, which may be reflective of practice as most participants were only followed until discharge (often only a couple of days post-procedure). Experts suggested that CI-AKI symptoms peak after 4-5 days and may not even manifest until 7-10 days post-procedure.

The company performed 6 separate fixed and random effects meta-analyses looking at different outcomes, including 4 to 8 studies each. The EAC felt that the meta-analyses were well performed and statistically robust. However, many of the included studies were of low quality and retrospective studies were often given over 50% weight for results. The EAC, therefore, is not confident in the validity of the results of these meta-analyses.

The company identified 9 relevant economic studies; 5 were excluded as they contained no cost analysis, resulting in the inclusion of 4 studies. Javanbakht et al. (2020) presents a decision tree followed by a Markov Model, which the EAC considers to be well constructed. Further, the EAC believes the company's deterministic and probabilistic sensitivity and scenario analysis to have been appropriately implemented. Economic analysis undertaken by the EAC indicates DyeVert is cost saving for patients with stage 3-4 CKD, representing a population at risk of CI-AKI. However, there is considerable uncertainty on both the baseline risk of CI-AKI and the effectiveness of hydration measures to reduce this risk. The cost analysis indicates that DyeVert begins to save money as the risk of CI-AKI climbs above 8%.

The EAC notes that the evidence on which the analysis rests does not distinguish the risk for stage 3 versus stage 4 CKD or the risk for peripheral versus coronary angiography. It seems probable that the risk of CI-AKI in some patients with well managed CKD disease, and no other risk factors undergoing peripheral angiography may be below 8%. In these patients DyeVert is unlikely to be cost saving and may not be cost-effective. Further evidence on the absolute risk of CI-AKI would be required to identify this subgroup with confidence.

1 Decision problem

The company suggested 1 change to the scope.

Decision problem	Scope	Proposed variation in company submission	EAC comment
Population	People at risk of contrast-induced acute kidney injury (CI-AKI) who need coronary and peripheral angiography with contrast media	None	
Intervention	DyeVert™ Contrast Reduction Systems used as an adjunct to standard NHS clinical practice	None	
Comparator(s)	Conventional hand or automated injection of contrast media	None	
Outcomes	CI-AKI incidence CI-AKI severity Measures of renal function, such as serum creatinine concentration, estimated glomerular filtration rate and urine output. Volume of contrast agent received and diverted. Image quality. Length of hospital stay and rates of re-admission as a	None	

	result of CI-AKI or acute heart failure (suspected cause by contrast agent). Rate of acute heart failure with suspected cause by contrast agent. Rate of renal replacement therapy, intensive care transfer or mortality as a result of CI-AKI. Device-related adverse events.		
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which can include scenarios in which different numbers and combinations of devices are needed.	None	
Subgroups	Other identifiable subgroups who may be at particularly	None	

	high risk for developing CI-AKI		
Special Considerations, including issues related to equality	People with chronic kidney disease, heart failure, diabetes, and renal transplant would be more at risk of CI-AKI. Kidney disease occurs more frequently in males, people over the age of 60, and those of African-Caribbean, African or South-Asian family origin. People who have an ileostomy or older people are at an increased risk of becoming dehydrated and may need special consideration. Conditions including alcoholism and hypoalbuminemia may also affect the ability to have pre- and post-scan hydration.	Removed consideration of people with an ileostomy, alcoholism, hypoalbuminemia or other comorbidities that may increase the risk of dehydration.	The company suggest that the DyeVert system is not recommended as a replacement or substitute for hydration.

2 Overview of the technology

DyeVert (Osprey Medical Inc) is a non-invasive system that aims to minimise the volume of contrast media injected to patients during coronary or peripheral angiography, while maintaining adequate image quality. Reducing contrast media volume (CMV) may benefit patients at risk of acute kidney injury (AKI), including those with chronic kidney disease (CKD), diabetes, heart failure and organ transplants by decreasing the risk of contrast induced AKI (CI-AKI).

The primary mechanism used by DyeVert is a proprietary valve that diverts excess CM into a collection bag by providing flow resistance that increases with increased injection pressure. There are 2 DyeVert systems currently available in the UK, the DyeVert Plus EZ and the DyeVert Power XT. The primary difference between the systems is their compatibility with manual and power injectors, respectively. The Power XT system diversion valve mechanism is almost identical to that on the Plus EZ system, but due to the difference in injector, a minor adjustment is present to allow for the difference in dye flow rate.

The DyeVert Plus EZ system comprises 3 main components: a disposable module, a disposable smart syringe, and a reusable monitor. The module is a single-use, EO (Ethylene Oxide) sterile system. It consists of the DyeVert valve, which diverts excess CM into the DyeVert collection bag and allows the remaining volume to be injected into the patient's vasculature through standard Cath Lab components. The smart syringe connects to a standard manifold system and is manually operated by the clinician to aspirate dye into the syringe and then inject the dye into the module. The monitor displays the total administered volume and total diverted volume (as a percentage of total volume) of CM in real-time. These factors are measured using a Hall Effect sensor and are communicated from the smart syringe and module to the monitor via Bluetooth Low Energy.

The DyeVert Power XT System consists of 2 components: the DyeVert Power XT assembly and the contrast collection bag. The assembly performs the same function as the smart syringe and module on the manual version of the

system. There is no reusable monitor on the power system, however, the (disposable) contrast collection bag includes a digital display that shows the diverted volume of dye.

The Plus EZ and Power XT Systems are both class I CE marked devices as of July 2018 and August 2020, respectively. There have been 2 previous versions of the DyeVert Plus EZ: the DyeVert (launched in 2015) and the DyeVert Plus (launched in October 2016). All versions of this system use the same diversion valve; the earliest version did not have any monitoring capability and subsequent iterations have improved 'ease of use'. The Power XT system has 1 previous version (also named the Power XT System), launched in June 2018. This version was identical to the current one but had no monitoring capability.

3 Clinical context

Acute Kidney Injury (AKI) is often a complication of other serious illnesses. The NICE guideline on Acute kidney injury: prevention, detection and management (NG148) states that the use of iodine-based contrast media (CM) is a risk factor for AKI and that this risk increases with volume. It is therefore recommended that risk of AKI should be assessed prior to the use of CM and that the volume used should be as low as reasonably achievable. The guideline states that eGFR should be measured to assess for CKD before iodine-based CM is offered to adults for non-emergency imaging. In cases of emergency imaging, risk of AKI should be assessed without delaying imaging. Increased risk is associated with:

- chronic kidney disease (adults with an eGFR < 40 ml/min/1.73 m^2 are at particular risk)
- diabetes but only with chronic kidney disease (adults with an eGFR < 40 ml/min/1.73 m2 are at particular risk)
- heart failure
- renal transplant
- age 75 years or over
- hypovolaemia

- increasing volume of contrast agent
- intra-arterial administration of contrast medium with first-pass renal exposure.

NICE define CKD as "abnormal kidney function and/or structure" in CG182 – Chronic kidney disease in adults: assessment and management. Various stages of CKD are defined based on Glomerular Filtration Rate (GFR); NICE use the same thresholds as the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines:

Table 1 - Kidney Disease Improving Global Outcomes GFR categories. (From NICE CG182 - copyright belongs to the KDIGO CKD Work Group).

GFR category	GFR (ml/min/1.73 m ^{2})	Terms
G1	>90	Normal or high
G2	60–89	Mildly decreased*
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

Iodine-based CM are administered for use in x-ray based imaging modalities such as angiography, where they are used to visualise the blood vessels. Coronary angiography may be indicated to investigate recent-onset chest pain (NICE CG95), stable angina (NICE QS21) and other acute coronary syndromes (NICE QS68) amongst others. Peripheral angiography also has several indications, such as in people with peripheral arterial disease who need extra imaging after duplex ultrasound (NICE CG147).

Various CI-AKI prevention strategies are suggested in the NICE Guideline on AKI. Oral hydration should be encouraged before and after procedures that use intravenous iodine-based CM in adults at increased risk of CI-AKI. Inpatients may be considered for intravenous volume expansion with either

isotonic sodium bicarbonate or 0.9% sodium chloride if they are at particularly high-risk. This may be defined as eGFR<30ml/min/1.73m^2, if they have had a renal transplant, or where a high volume of CM is required, for example. The NICE guideline also recommends that research should investigate the possibility of stratifying the risk of CI-AKI by eGFR threshold.

The Renal Association's Guidelines on Prevention of Contrast Induced Acute Kidney Injury (CI-AKI) In Adult Patients states that use of intravascular iodine-based CM is increasing and advises that clinicians adopt a trend of lowering doses. This guideline also recommends that CI-AKI risk should be identified prior to imaging using iodine-based CM, except where early-imaging benefits outweigh the risk. Measurements of eGFR should only be considered in stable outpatients. Where patients are identified as high-risk, a renal physician should be consulted to determine if the potential benefit from using iodinated-CM outweighs the risk of CK-AKI. Recommended prevention measures include using other imaging modalities, intravenous volume expansion and using the lowest possible volume of CM.

The Renal Association also suggest using the KDIGO definition of CI-AKI. Experts suggested that the KDIGO guideline is widely followed in practice worldwide. The KDIGO guidelines recommend using either iso-osmolar or low-osmolar iodinated CM (rather than high-osmolar) in patients at increased risk of CI-AKI.

The European Society of Cardiology 2019 guideline for the diagnosis and management of chronic coronary syndromes state that patients with CKD are less likely to receive invasive management for treatment of Coronary Artery Disease (CAD) even though benefits of invasive management have been reported in the literature (section 8.2.3.).

Experts considered that "Contrast-Associated AKI" may be a more accurate term than CI-AKI, as the evidence in the literature does not conclusively show iodine-based CM to be a causal factor in developing AKI.

Special considerations, including issues related to equality

People with chronic kidney disease, heart failure, diabetes, and renal transplant would be more at risk of CI-AKI.

Kidney disease occurs more frequently in males, people over the age of 60, and those of African-Caribbean, African or South-Asian family origin.

People who have an ileostomy or older people are at an increased risk of becoming dehydrated and may need special consideration. Conditions including alcoholism and hypoalbuminemia may also affect the ability to have pre- and post-scan hydration.

The company does not consider DyeVert a suitable substitute for hydration in general but suggests that it can be used as a replacement in patients at risk of CI-AKI in whom hydration is not suitable.

4 Clinical evidence selection

4.1 *Evidence search strategy and study selection*

The EAC considered the company's search strategy to be appropriate for the topic. The company submitted a separate clinical and economic search strategy; the EAC ran a single search to both cover the economic studies and clinical studies. The EAC's revised search strategies are in Appendix A. The EAC included all of the studies submitted by the company and did not identify any further studies.

The search results were exported into EndNote X9 library and sifted by two reviewers. The included full texts were shared among three members of the team to screen and identify the final included studies in this report. The PRISMA diagram is in Appendix A.

4.2 *Included and excluded studies*

Table 2: Studies selected by the EAC as the evidence base

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Desch et al. 2018 Impact of a novel contrast reduction system on contrast savings in coronary angiography – The DyeVert randomised controlled trial. Germany Funded by Osprey Medical Inc. ●	Prospective, single-centre, open label RCT. Coronary angiography with and without the DyeVert System. Angiography was performed according to best practice (defined as a minimum of 6 CM injections for the left CA and 2 for the right CA). ●	96 adults (18 years or over) scheduled for a diagnostic coronary angiogram due to suspected coronary artery disease or progression of known coronary artery disease using a 5 French catheter. 2 participants in the DyeVert group dropped out leaving 46. 48 participants in the control group. Mean age (years); Male (%): DyeVert: 68.6; 58.3 Control: 66.2; 58.3 ●	Mean CMV was significantly lower in the DyeVert group (36.9 ± 10.9 mL versus 62.5 ± 12.7 mL, $p < 0.001$); a 41% reduction (EAC calculated). No significant difference in adequate quality images between the DyeVert and Control groups (95.5% vs 95%, $p = 0.74$), based on clinician feedback and confirmed by an independent reviewer (90.7% vs 97.3%; 95% lower confidence bound−9.6, p=0.03 for non-inferiority). Total Fluoroscopy time did not differ significantly between the groups (3.9±3.9 minutes versus 3.7 ± 3.5 minutes, $p = 0.76$). ●	Blinding of the clinician performing the angiography or the Cath lab staff was not possible due to the nature of the procedure. Patients were not informed about treatment allocation. An independent reviewer, blinded to treatment allocation, assessed the image quality. 1:1 randomisation ratio to the by permuted block randomisation stratified by access site (radial/femoral). Sample size was calculated to be 96 patients, based on pilot results and a power of 80%. Half of the study cohort underwent angiography using a radial approach.

Gurm et al. 2019a Minimizing radiographic contrast administration during coronary angiography using a novel contrast reduction system: A multicenter observational study of the DyeVert™ plus contrast reduction system. The US. Funded by Osprey Medical Inc. 🟡	Prospective, multicentre, single-arm, observational study. DyeVert Plus System. 🟡	114 adult participants from 8 centres undergoing diagnostic coronary angiography (CAG) or other percutaneous coronary interventional procedures. A baseline eGFR rate of ≥20 and ≤60 mL/min/1.73m^2 was required for eligibility. Mean age 72 ± 9 years, 82% male. Mean baseline eGFR was 43 ± 11 mL/min/1.73m^2 Mean baseline Serum Creatinine was 1.6 ± 0.5mg/dL 🟢	Mean CMV delivered: 67 ± 51ml Overall difference in CMV per procedure : 40.1% ± 8.8% (95% CI: 38.4, 41.8; P < 0.0001). Mean baseline eGFR was 43 ± 11 mL/min/1.73 m^2 with 18 (16%) subjects having a baseline eGFR of 20–30 mL/min/1.73 m^2. Baseline serum creatinine was 1.6 ± 0.5 mg/dL. AKI (≥0.3 mg/dL increase in serum creatinine) at discharge was reported in 11 participants (9.6%), 7 of which occurred in those with a baseline eGFR <30. Three (2.6%) incidences were considered to be contrast-related by investigators. Rates of AKI increased with increasing values of CMV/eGFR ratios. 🟢	63% of procedures used a femoral access point and 65% were CAG only. Per protocol analysis, 9 participants were excluded.

Briguori et al. 2020 Impact of a contrast media volume control device on acute kidney injury rate in patients with acute coronary syndrome. Italy Funding not specified. ●	Retrospective, observational, single-centre, propensity-matched controlled, investigator-driven study Angiography and angioplasty with and without the DyeVert Plus EZ System ●	Adults with acute coronary syndrome who had urgent or immediate coronary angiography or angioplasty. Enrolled: DyeVert Group n=112; Control Group n=339 Completed study: DyeVert cases were propensity matched to Controls, n=180 Mean age (years); Male (%): DyeVert: 62.5; 71.0 Control: 63.5; 76.5 Mean baseline eGFR (mL/min/1.73 m^2): DyeVert: 74 ± 26; Control: 79 ± 28; p = 1.00 Median Serum Creatinine: Control: 0.97mg/dl; DyeVert 0.99mg/dl ●	CMV was significantly lower in the DyeVert group than in the Control group (99 [69–136] ml vs. 130 [120–188] ml; p <.001); a reduction of 24% (EAC calculated). In the DyeVert group the mean percent CMV saved was 38 ± 13%. AKI occurred in 7/90 patients (8%) in the DyeVert group and in 17/90 (19%) patients in the Control group (odds ratio = 0.37; p =0.047). A significant direct correlation between CMV and maximal absolute difference in serum creatinine was observed in the Control group but not in the DyeVert group. A ROC curve analysis showed that CMV significantly discriminated between patients with and without AKI only in the Control group (area under the curve [AUC] of 0.70 [95% confidence interval 0.59–0.81]; p =.010) but not in the DyeVert group ([AUC = 0.51 [95%	The authors note that the small sample size and the single-centre, observational, non-randomised design are limitations. However, the Control group was selected from patients treated in the same centre and matched to the DyeVert group using propensity score matching. No blinding discussed.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
			confidence interval 0.26–0.761]; p =.93) Length of in-hospital stay was longer in the Control group than in the DyeVert group (8 ± 4 vs. 6 ± 2 days; p =.003). ●	

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Bruno et al. 2019 Early clinical experiences with a novel contrast volume reduction system during invasive coronary angiography. Germany Funding provided by Osprey Medical, Inc. ●	Retrospective, observational, single-arm, single-centre pilot study DyeVert Power XT System (version 1). No comparator ●	9 adults who had diagnostic or interventional ICA over 2 consecutive days (all completed the study) Mean age (years) 71 ± 10; Male n=5 (56%) eGFR (MDRD; mL/min/1.73 m2), Mean ± SD: 71.5 ± 9.4 Mean baseline Serum Creatinine: 1.15 ± 0.36 mg/dL ●	Actual CMV injected: mean 80.6 ml (45.5 to 211.9) Mean percent CMV saved was 38.9% (range 31.0% to 47.0%) No device-related complications occurred. Clinicians noted no loss in image quality compared to their normal daily experiences (subjective assessment). ●	No comparator group. Small pilot study. No statistical analysis. The reduction in CM dose was an estimation based on contrast collection bag demarcations. Used the ACIST CVi Contrast Delivery System (power injector) rather than manual manifold injection.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Sapontis et al. 2017 A First in Human Evaluation of a Novel Contrast Media Saving Device Germany and Australia Funded by Osprey Medical Inc. ●	Prospective, multicentre, single-arm, pilot study. DyeVert System ●	44 adults (18 years or older) participants undergoing coronary diagnostic (n=34) or percutaneous coronary (n=10) interventions. Mean age 69.3 ± 10.6 years, 62.2% male. ●	Mean attempted volume of contrast was 173 ± 117ml and actual volume was 89 ± 57ml, a 47% saving ($p<0.0001$ for more than 15% saving). Based on physician evaluation, image quality was acceptable in 43/44 (98%) patients. ●	No information reported on access point. Image assessment was not blinded.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Corcione et al. 2017 Contrast minimization with the new generation DyeVert Plus System for contrast reduction and real-time monitoring during coronary and peripheral procedures: first experience. Italy Funding not reported. 🟡	Retrospective, observational, single-centre study. DyeVert Plus 🟡	10 consecutive patients having a coronary diagnostic procedure (n = 5), percutaneous coronary intervention (n = 3) or peripheral intervention (n = 2). Mean age 66.0 ± 12.04, 80% male. Baseline Serum Creatine: 0.98 mg/dL. 🟡	Mean total CMV: 79.9 ± 48.8ml (85%CI: 53.2 to 76.7) Mean absolute CMV saving: 55.8 ± 31.9ml (95% CI: 39.1 to 76.7) Mean relative CMV saving: 41.8 ± 7.3% (95% CI: 37.5 to 46.4; p<0.05). 🟢	7 patients had a radial access point.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Tajti et al. 2019 Use of the DyeVert System in Chronic Total Occlusion Percutaneous Coronary Intervention The US Funding not clear. 🟡	Retrospective, observational, single-centre study. Chronic Total Occlusion (CTO) Percutaneous Coronary Interventions (PCI) with and without DyeVert Plus. 🟡	130 participants undergoing 134 consecutive CTO-PCIs. DyeVert was used in 39 (30%) participants. Mean age: 66.6 ± 10.9 years, 79.2% men. Overall mean eGFR at baseline was 73.4 mL/min/1.73 m^2. 🟡	Median contrast volume: DyeVert: 200mL (IQR, 153 – 256) Non-DyeVert: 250mL (IQR, 170-303), p=0.04. Technical and procedural success rates were similar in the DyeVert and non-DyeVert groups (p = 0.37 and p = 0.61, respectively). Procedure time was significantly longer in the DyeVert group, 220 minutes (IQR, 128 - 294) vs 152 minutes in the non-DyeVert Group (IQR, 100 - 225, p=0.03). Fluoroscopy time and air kerma radiation dose were similar in both groups (p=0.2 and p=0.13, respectively). 🟢	Baseline patient characteristics were similar in most cases between those who had DyeVert and those who didn't, except for Prior myocardial infarction and Prior peripheral vascular disease, which were significantly more prevalent in the DyeVert group. The most common target vessel was the right coronary artery (54.5%), left anterior descending artery (26.1%), and circumflex artery (15.7%). Radial access was more commonly used in the DyeVert group (p<0.001). The most commonly used contrast media with the DyeVert system was iodixanol (Visipaque; GE Healthcare) in 79.5%, whereas iohexol (Omnipaque; GE Healthcare) was used in the remaining patients. The guide size was slightly smaller in the DyeVert group

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Zimin et al. 2020. A feasibility study of the DyeVert™ plus contrast reduction system to reduce contrast media volumes in percutaneous coronary procedures using optical coherence tomography (OCT). The US Partially funded by Osprey Medical Inc. ●	Prospective, clinical, multi-centre, feasibility study. Coronary Optical Coherence Tomography (OCT) for diagnostic or PCI procedures, with and without DyeVert Plus EZ. ●	29 adult participants (18 years or older) undergoing 30 procedures. 15 procedures were performed in 14 patients with DyeVert and 15 were performed in 15 patients without. Mean age 67 ± 11 years, 78.6% male. The mean eGFR at baseline was 71 ± 20 mL/min/1.73m^2. The mean serum creatinine at baseline was 1.04 ± 0.28 mg/dL. ●	Mean total procedure time: DyeVert, 63.0 ± 26.6 minutes Control, 47.98 ± 20.1 minutes (p=0.09). Mean CMV saved in DyeVert group: 125.81 ± 47.10 mL (97.5% CI: 95.29- 156.33), or 37.5 ± 5.3% per procedure. During OCT image acquisition, the mean CMV delivered per injection was 6.9 ± 1.1 mL Analysis of OCT images showed the clear region of interest (ROI) in the DyeVert group was non-inferior (p < 0.0001) to the control group. Clinicians described all images in the 15 DyeVert procedures as acceptable. ●	All procedural characteristics were similar between the groups. 8 procedures used femoral access in the DyeVert group, 9 used this access in the control group.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Abstracts				
Amoroso et al. 2020. First European experience using a novel contrast reduction system during coronary angiography with automated contrast injection. The Netherlands, Germany and the UK. No funding information. ●	Retrospective, observational, multicentre study. DyeVert Power XT System v1. ●	26 coronary angiography procedures performed at 3 hospitals. 54% were diagnostic only and 46% were interventional. ●	Mean CMV: 87.9±51.5 mL (range 30.6 – 211.9 mL). Mean CMV savings: 34.4 ± 6.2% (range 24.1– 47.0%) per procedure. Physicians characterised image quality as acceptable for 25 cases (96%). ●	The number of patients who had a procedure is not reported. 85% were performed using radial access.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Bath et al. 2019. Use of DyeVert Plus to reduce contrast exposure in high-risk patients undergoing coronary angiography. The US. 🟡	Prospective, single-centre, RCT. Diagnostic coronary angiography with and without DyeVert Plus. 🟢	108 participants with increased risk for CIN (eGFR 15-60ml/min/1.73m^2). 49 in DyeVert group, 59 in control group. 🟢	Mean Cumulative CMV: DyeVert: 62.7 ± 9.5ml Control: 87.6 ± 11.0ml, a saving of 28.4% (p=0.0004). CM in the DyeVert group 43.8% below the threshold volume (eGFRx3) compared to 31.4% in the control (p=0.05). 🟢	No power calculation reported. No information on randomisation processes or blinding.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Bunney et al. 2019 Contemporary use of contrast dye reduction technology in a tertiary academic hospital: patient characteristics and acute kidney injury outcomes following percutaneous coronary interventions. The US. 🟡	Retrospective, observational, single-centre, real world registry (NCDR) analysis. PCI with and without either the DyeVert or DyeVert Plus. 🟡	29 participants had PCI with DyeVert and 770 had PCI without DyeVert. Mean age: DyeVert: 63 Control: 61 Baseline eGFR<60: DyeVert; 55.2% Control: 23.5% 🟡	Mean CMV per procedure: DyeVert: 194ml Control: 192ml Those who had DyeVert underwent a higher proportion of complex PCIs with haemodynamic support (20% vs 3.7%). Non-risk-adjusted AKI rate was 3.45% in the DyeVert group and 9.35% in the non-DyeVert cohort. 🟢	

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Cameron et al. 2020 Reduction of contrast-induced acute kidney injury in a cardiac catheterization laboratory: A quality improvement initiative. The US	Retrospective, observational, single-centre, real world registry (NCDR) analysis. A quality improvement procotol was implemented including the use of DyeVert Plus & DyeVert Plus EZ.	1956 participants undergoing coronary angiographies (57% diagnostic and 43% PCI) were included; 1789 cases followed a CI-AKI reduction protocol. DyeVert was used in 423 cases	After implementation of CK-AKI reduction protocol, CK-AKI reduced to a risk-adjusted rate of 4.98%. In DyeVert Cases: Mean CMV savings: 53 ±28 mL (38.±8% per case). Mean CMV/eGFR ratio: 2.1 actual (84% of cases within CMV target); 3.4 attempted (58% of cases within CMV target).	This study has been reported through an abstract and a poster. The rate of CK-AKI is calculated for all cases, not just those in which DyeVert was used.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Kutschman et al. 2019a. Clinical and economic outcomes of a comprehensive clinical quality initiative for reducing acute kidney injury in chronic kidney disease patients undergoing coronary angiography. The US 🟡	Retrospective, Observational, single centre, real-world data analysis. DyeVert Plus & DyeVert Plus EZ. 🟡	206 participants with CKD undergoing Diagnostic Coronary Angiogram and/or Percutaneous Coronary Interventions. DyeVert was used in 128 cases. Mean age 69 ± 11 years, 57% men. Baseline eGFR: 43 ± 13 ml. 🟡	In DyeVert cases, overall CMV savings were 40.5 ± 8.2% per case. Mean CM Volume per case. was 103 ± 61ml. Relative reduction in AKI rates were 57% when DyeVert was used. Incremental cost offset was estimated to be at least $2,000 lower when DyeVert was used. 🟢	Results may not be representative of real-world practice as DyeVert was implemented alongside a wider risk-reduction programme.

Kutschman et al. 2019b. Comprehensive clinical quality initiative for reducing acute kidney injury in at-risk patients undergoing diagnostic coronary angiogram and/or percutaneous coronary interventions. The US ●	Retrospective, Observational, single centre, real-world data analysis. DyeVert Plus & DyeVert Plus EZ as part of a CMV reduction programme. Manual manifold injection. ●	551 participants undergoing diagnostic coronary angiography and/or percutaneous coronary interventions. Mean age: 66 ± 12 years Male: 63% Mean eGFR: 64 ± 32mL/min/1.73m^2 ●	In the cohort in which the DyeVert System was used (n=258), mean CMV savings were 58 ml or 40% of the attempted CMV per case and there was an overall 33% relative reduction in AKI compared to the cohort in which DyeVert was not used (6.9% vs 10.3%, respectively). In the Protocol Followed cohort, the overall relative reduction in AKI was 61% compared to the Protocol Not Followed cohort (p<0.02). For PCI cases, the mean contrast given was 138 mL and contrast given (mL)/baseline eGFR ratio was 3.8ml/min/1.73m^2. For diagnostic cases, the mean contrast given was 66 mL and contrast given (mL)/baseline eGFR ratio was 1.7 ml/min/1.73m^2. ●	Results presented in a poster. Results may not be representative of real-world practice as DyeVert was implemented alongside a wider risk-reduction programme.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Rao 2019 DyeVert Plus contrast reduction system use in patients undergoing highly complex peripheral vascular interventions. The US ●	Retrospective case series DyeVert Plus ●	7 participants undergoing highly complex peripheral vascular interventions Mean age: 66 years, male: 43% Mean eGFR: 45.7ml/min Mean CMV/eGFR ratio: 1.34 86% had CKD. ●	Image quality was maintained in all cases. Mean CMV: 50 ± 23 ml Actual CMV/eGFR ratios were <2 in 86% of cases. ●	Limited methodological information. No information on how image quality was measured.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Sattar et al. 2018. (poster presentation) Impact of using DyeVert PLUS on the incidence of acute kidney injury after cardiac catheterization with coronary interventions in high-risk patients. The US ●	Retrospective, observational, single-centre, real-world data analysis. DyeVert Plus. Standard angiography. ●	109 adults undergoing PCI. 41 patients (38%) had PCI using DyeVert and 68 (62%) underwent standard PCI Mean age (years); Male (%): DyeVert: 68.5; 41.0 Control: 71.3; 65.0 eGFR (mL/min/1.73 m^2), Mean: DyeVert: 43.6 Control: 47.7 ●	Mean pre and post procedure serum Creatinine (SCr): DyeVert: 1.56mg/dl and 1.56mg/dl with mean decrease of 0.002 (p=0.97). Without DyeVert: 1.51mg/dl and 1.54mg/dl respectively with mean increase of 0.35 (p=0.44) Change in SCr was not significant between the two groups. Incidence of CI-AKI in the DyeVert vs non-DyeVert group was 12.2% vs 16.2% (p=0.56 pearson Chi Sq, OR 0.71, 95% CI [0.23, 2.24]). Average contrast usage in DyeVert vs non-DyeVert group was 128 ml vs.155 ml; a reduction of 17% (EAC calculated). ●	Low overall incidence of AKI during the study - sample size too was too small to detect a significant difference between groups. Study was unblinded.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Turner & Tucker 2020. Real-world impact of a quality improvement program for acute kidney injury prevention in the cardiac cath lab. The US. ●	Retrospective, observational real-world data analysis from the National Cardiovascular Data Registry (NCDR) Cath PCI Registry. DyeVert Plus & DyeVert Plus EZ. Manual manifold injection. ●	703 patients undergoing PCI DyeVert use in n=536 patients with CKD or STEMI Approximately 30% of the cath lab population is at risk for CI-AKI eGFR <60 or Cr >1.5 or STEMI Q1 2018 to Q3 2019 ●	From Q1 2018 to Q3 2019 - absolute reduction in CI-AKI of 10.46% (83.7% relative reduction). Number-Need-to-Treat to Avoid 1 CI-AKI event = 10 Hospital budget impact estimated to be $650 cost saving per case ●	One author has financial interests in the company.
Unpublished				

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Acronyms: AKI: Acute Kidney Injury; AUC: Area-Under-the-Curve; CA: Coronary Artery; CAG**:** Coronary Angiography; CI-AKI: Contrast-Induced Acute Kidney Injury; CIN: Contrast Induced Nephropathy; CKD: Chronic Kidney Disease; CM: Contrast Media; CMV: Contrast Media Volume; CTO: Chronic Total Occlusion; eGFR: Estimated Glomerular Filtration Rate; ICA: Interventional Coronary Angiography; IQR: Inter-Quartile Range; MDRD: Modification of Diet in Renal Disease; NCDR: National Cardiovascular Data Registry; OCT: Optical Coherence Tomography; OR: Odds Ratio; PCI: Percutaneous Coronary Intervention; RCT: Randomised Controlled Trial; ROC: Receiver Operating Characteristic; SCr: Serum Creatinine; STEMI: ST-Elevation Myocardial Infarction

5 Clinical evidence review

5.1 *Overview of methodologies of all included studies*

The EAC included 19 studies; 8 studies were reported as full text published papers, 9 were reported as abstracts or posters and 2 are unpublished manuscripts. The full text studies included approximately 883 participants (some papers reported the number of cases but not participants or vice-versa). The abstracts included around 3695 participants and the [redacted], totaling just over 5500 participants.

Of the 8 full text papers, 1 is a prospective, single-centre, open label RCT (Desch et al. 2018). Three of the other full text studies are also prospective (Gurm et al. 2019a, Sapontis et al. 2017 and Zimin et al. 2020). All 3 were multi-centre studies, although 2 were pilot or feasibility studies (Sapontis 2017 and Zimin 2020). The 4 remaining full text studies were retrospective, single centre studies, of which 2 were comparative (Briguori et al. 2020 and Tajti et al. 2019) and 2 were non-comparative (Bruno et al. 2019 and Corcione et al. 2017). None of these studies were undertaken in the UK, with 3 studies recruiting in Germany, 3 recruiting in the US, 2 recruiting in Italy and 1 in Australia.

One of the 9 studies available only as an abstract or poster recruited some patients from the UK (Amoroso et al. 2020), although it is unclear how many of the 26 total participants were recruited here or in the Netherlands/Germany. The remainder of the 9 abstracts reported studies from the US. Bath et al. 2019 is a prospective, single-centre RCT including 108 participants. The remaining abstracts report retrospective studies, including 4 comparative (Bunney et al. 2019, Kutschman et al. 2019b, Sattar et al. 2018 and Turner & Tucker et al. 2020) and 4 non-comparative studies (Amoroso et al. 2020, Cameron et al. 2020, Kutschman et al. 2019a and Rao et al. 2019).

Two unpublished papers (Authors not provided) were provided by the company.

[redacted]

[redacted]

The percentage of male participants varied from 43% (Rao 2019) to 82% (Gurm 2019a), although men were more common in almost every study. Experts confirmed that men may be more likely to require angiography procedures due to most related morbidities being more common in men. The mean age ranged from 61 years (Bunney 2019) to 72 years (Gurm 2019a). Mean baseline eGFR ranged from 43ml/min/1.73m^2 (Gurm 2019a) to 74ml/min/1.73m^2 (Briguori 2020), although this wasn't always reported. Mean baseline serum creatinine ranged from 0.98 mg/dL (Corcione et al 2019) to 1.6 mg/dL (Gurm 2019a), although, again, this wasn't always reported. Notably, Gurm had the oldest, most male population, along with the lowest mean eGFR and highest level of serum creatinine, meaning that it included a population that may be at a higher-risk than the other studies. There is a lack of follow-up in all of the studies.

The evidence base is highly focused on coronary angiography, with only Corcione et al. 2017 and Rao 2019 including (a total of) 9 patients undergoing peripheral angiography. This is not unexpected; experts suggested that the DyeVert system would be much less likely to be used in peripheral angiography, possibly due to the lower volumes used in general and competing volume-reduction technologies.

The DyeVert System was used in 3 studies, while the DyeVert Plus and Plus EZ were used in 12 and 6 studies, respectively. The DyeVert Power XT (1st version) was used in 2 studies; no studies investigated the current version of the Power XT System. The RCTs used the DyeVert (Desch 2018) and the DyeVert Plus (Bath 2019).

5.2 *Critical appraisal of studies and review of company's critical appraisal*

The company's submission did not contain a formal critical appraisal of the evidence. The submission does outline the overall strengths and limitations of the evidence base and of the individual studies. The EAC carried out a quality appraisal of the 17 available published papers. Broadly, the EAC also agree with the company's overall assessment of the strengths and weaknesses of the included studies.

Only 2 RCTs are reported in the literature (Desch et al. 2018 and Bath et al. 2019). Only Desch et al. (2018) is reported as full text and as such is considered to be the highest quality study. This study compared angiography procedures with and without the DyeVert System. The Cochrane Risk of Bias 2 was used to assess Desch et al. (2018). The EAC believe the study to have a low risk of bias (see appendix B). The allocation sequence was random and stratified by access site (femoral or radial). Blinding of physicians as not possible as the DyeVert system is visibly different from a standard manifold. Baseline characteristics were not significantly different in the 2 groups. Image quality was assessed by a blinded independent reviewer. The study included 96 adults and appears to be powered based on pilot study results and an 80% power, although 2 patients dropped out. The EAC believes that this study is still adequately powered. Desch et al. (2018) reported a significantly lower CMV in the DyeVert group ($p<0.001$) and did not find a significant difference in image quality or total fluoroscopy time (between the groups). Bath et al. (2019), is also an RCT but is only reported as an abstract, making it difficult to assess its methodological quality.

There are 8 other comparative studies included in the evidence base, of which 4 are retrospective. Although the populations are large, retrospective data-collection may limit the validity of their results. This, in turn, may limit the validity of the company meta-analyses (see section 7), which gives significant weight to retrospective studies, such as Kutschman et al. 2019. The prospective studies often have small populations and several are single-centre. Many of the studies are at least in part funded by the company which could be a source of bias.

5.3 *Results from the evidence base*

Table 3: Results from Included Studies

Full texts

Study	Contrast volume	Image quality	AKI incidence	Length of hospital stay
Desch et al. 2018	CM volume was significantly lower in the DyeVert group (36.9 ± 10.9 mL versus 62.5 ± 12.7 mL, p < 0.001).	No significant difference in adequate quality images between the DyeVert and Control groups (95.5% vs 95%, p = 0.74),	Not reported	Not reported
Gurm et al. 2019a	Mean CMV delivered: 67 ± 51ml. Overall difference in CMV per procedure : 40.1% ± 8.8% (95% CI: 38.4, 41.8; P < 0.0001). Rates of AKI increased with increasing values of CMV/eGFR ratios.	Image quality maintained in 113/114 cases.	AKI (≥0.3 mg/dL increase in serum creatinine) at discharge was reported in 11 participants (9.6%),	Not reported

Study	Contrast volume	Image quality	AKI incidence	Length of hospital stay
Briguori et al. 2020	CM volume was significantly lower in the DyeVert group than in the Control group (99 [69–136] ml vs. 130 [120–188] ml; p <.001)	Clinicians noted no loss in image quality.	AKI occurred in 7/90 patients (8%) in the DyeVert group and in 17/90 (19%) patients in the Control group (odds ratio = 0.37; p =0.047).	Length of in-hospital stay was longer in the Control group than in the DyeVert group (8 ± 4 vs. 6 ± 2 days; p =.003).
Bruno et al. 2019	Actual CM volume injected: mean 80.6 ml (45.5 to 211.9)	Clinicians noted no loss in image quality.	No device-related complications occurred.	Not reported
Sapontis et al. 2017	Mean attempted volume of contrast was 173 ± 117ml and actual volume was 89 ± 57ml,	Image quality was acceptable in 43/44 (98%) patients.	Not reported	Not reported
Corcione et al. 2017	Mean total CV: 79.9 ± 48.8ml (85%CI: 53.2 to 76.7)	Clinician reported no loss in image quality.	Not reported	Not reported

Study	Contrast volume	Image quality	AKI incidence	Length of hospital stay
Tajti et al. 2019	Median contrast volume: DyeVert, 200mL (IQR, 153 – 256) Non-DyeVert:250mL (IQR, 170-303), p=0.04.	Not reported	Not reported	Not reported
Zimin et al. 2020.	Mean CV saved in DyeVert group: 125.81 ± 47.10 mL (97.5% CI: 158.62 – 273.79), or 37.5 ± 5.3% per procedure.	The clear region of interest (ROI) in the DyeVert group was non-inferior ($p < 0.0001$) to the control group. Clinicians described all images in the 15 DyeVert procedures as acceptable.	Not reported	Not reported

Abstracts

Study	Contrast volume	Image quality	AKI incidence
Amoroso et al. 2020.	Mean CMV: 87.9±51.5 mL (range 30.6 – 211.9 mL).	Image quality was acceptable for 25 cases (96%).	Not reported
Bath et al. 2019.	Mean Cumulative CMV: DyeVert: 62.7 ± 9.5ml Control: 87.6 ± 11.0ml, a saving of 28.4% (p=0.0004)	Not reported	Not reported
Bunney et al. 2019	Mean CMV per procedure: DyeVert: 194ml Control: 192ml	Not reported	Non-risk-adjusted AKI rate was 3.45% in the DyeVert group and 9.35% in the non-DyeVert cohort.
Cameron et al. 2020	Mean contrast savings: 53± 28 mL (38±8% per case). Mean CMV/eGFR ratio: 2.1 actual (84% of cases within CMV target); 3.4 attempted (58% of cases within CMV target).	Not reported	After implementation of CK-AKI reduction protocol, CK-AKI reduced to a risk-adjusted rate of 4.98%.

Study	Contrast volume	Image quality	AKI incidence
Kutschman et al. 2019a.	In DyeVert cases, overall CMV savings were 40.5 ± 8.2% per person	Not reported	Relative reduction in AKI rates were 57% when DyeVert was used
Kutschman et al. 2019b.	Mean contrast savings of 58 ml or 40% per case	Not reported	Preliminary results show a 75% reduction in AKI rate when the AKI reduction protocol was followed.
Rao et al. 2019	Mean CMV: 50ml. Actual CMV/eGFR ratios were <2 in 86% of cases.	Image quality was maintained in all cases	No patients had worsening of renal function post-procedure.
Sattar et al. 2018.	Average contrast usage in DyeVert vs non-DyeVert group was 128 ml vs.155 ml.	Not reported	Incidence of CI-AKI in the DyeVert vs non-DyeVert group was 12.2% vs 16.2% (p=0.56 pearson Chi Sq, OR 0.71, 95% CI [0.23, 2.24]).
Turner & Tucker 2020.	Mean contrast savings of 42 ± 28 ml per case	Not reported	From Q1 2018 to Q3 2019 - absolute reduction in CI-AKI of 10.46% (83.7% relative reduction).

6 Adverse events

The EAC searched the MHRA and FDA databases on the 25th of February using the terms “DyeVert” and “Osprey”. No results were found on the MHRA database. Four results were found on the FDA database. The first AE report

(18 February 2016) details a user error while using the “DyeVert Contrast Modulation System” that led to an air bubble in the reservoir. There was no impact to the patient. Similarly, the second AE (15 March 2017) is also a user error that led to no adverse consequence for the patient. The third AE (5 November 2020) details an issue with the DyeVert Plus EZ, in which air was reported to be in the tubing, leading to the module being replaced. There was no impact to the patient and the module was not returned to the manufacturer for further investigation. The fourth entry (6 November 2020) appears to be the same AE, following investigation from the manufacturer who identified this as an isolated manufacturing issue. Briguori et al. 2020 reported 4 major adverse events in the DyeVert group vs 8 in the control group. No device-related AEs were reported in the literature, [redacted]

7 Evidence synthesis and meta-analysis

The company performed 6 separate fixed and random effects meta-analyses looking at different outcomes. The number of studies in each meta-analysis (MA) varied depending on the outcomes reported, from 4 to 8. The results of the MAs are as follows:

1) Pooled estimate of the relative risk of CI-AKI in the intervention (DyeVert) versus control group among 4 double-arm studies, calculated as **0.59 (95%CI: 0.38-0.89)**

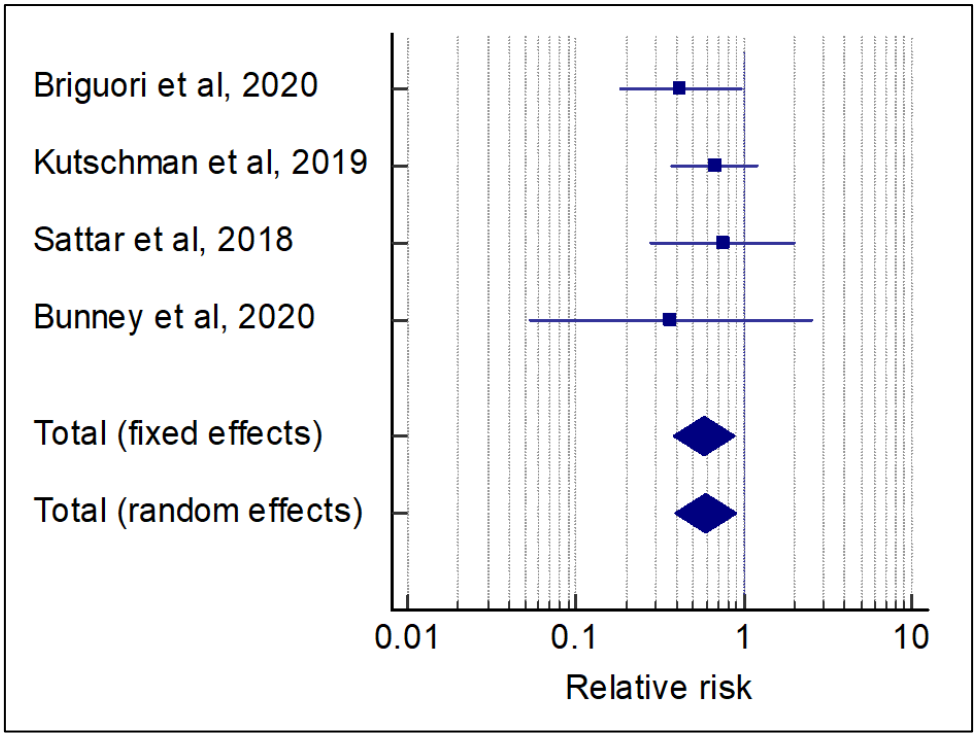

Figure 1- Forest Plot of Relative Risk of CI-AKI (copyright of the company)

2) Pooled estimate of the rate of CI-AKI in the intervention group (DyeVert) among 4 double-arm studies, calculated as **7.71% (95%CI: 5.36%-10.44%)**
3) Pooled estimate of the rate of CI-AKI in the control group among 4 double-arm studies, calculated as **12.55% (95%CI: 8.74%-16.93%)**
4) [redacted]
5) Pooled estimate of the standardized mean difference in absolute contrast volume (mL) in the intervention and control group calculated as **-1.463 (95%CI: -2.339: -0.588)** among 4 **published** double-arm studies. Two double-arm studies (Bunney et al, 2020 and Sattar et al, 2018 excluded from the meta-analysis because they did not report the standard deviation of mean in the abstract)
6) [redacted]
7) Pooled estimate of the contrast volume saving (%) in the intervention group among 8 **published** single-arm studies calculated as **39.43% (95%CI: 36.09%-42.82%)**
8) [redacted]

9) Pooled estimate of the image quality (%) among 7 published clinical studies calculated as 98.20% (95%CI: 96.54%-99.33%).

10) Pooled estimate of actual versus attempted CV/eGFR ratio; Hedges' g: -0.56 (95%CI: -0.70 to -0.42).

11) Pooled estimate of actual versus attempted CV/eGFR ratios by CV/eGFR group (CV/eGFR ratio <3 group RD -0.26 (CI%95: -0.36, -0.16); CV/eGFR ratio <2 group RD -0.20 (95%CI: -0.31, -0.08); CV/eGFR ratio <1 group RD -0.14 (CI%95: -0.23, -0.05)).

12) Pooled estimate of contrast threshold management (Risk Difference -0.31 (95%CI: -0.48, -0.13)).

Please see appendix D for full results of the company meta-analyses.

The EAC reviewed the company MAs and considered them in general to be fairly robust. Therefore, the EAC did not conduct its own MA. It should be noted that some of the analyses included a small number of studies. In the case of meta-analysis (1), which is used in the company economic model (see section 9), only 4 studies are included. These studies were judged by the EAC to be of moderate quality, so conclusions should be made with some caution. Further, the sample size in some of the included studies is much greater than others, such that they dominate the results (Kutschman et al. 2019 in MA(1) and MA(2) and Bunney et al. 2020 in MA(3), for example). Nevertheless, the EAC believes that appropriate methods were used, and effects were properly programmed. Heterogeneity is very low in almost all of the analyses, apart from MA(3) and MA(4), where it is very high.

8 Interpretation of the clinical evidence

The evidence base is almost completely comprised of data from outside of the UK (largely the US and Germany), meaning that it may not be generalisable to the NHS. However, experts suggested that angiography practice is very homogeneous across developed nations and most follow the KDIGO guidelines (see section 3). One expert confirmed that practice in the UK and New Zealand (where they had previous experience) was very similar.

The literature consistently shows that using DyeVert reduced CMV injected compared to standard angiography using a manual manifold. While there are

only 2 RCTs and a large number of retrospective studies, it is clear that under all study designs, DyeVert successfully reduced injected volume, either in comparison to a control group or compared to the attempted CMV. Mean CMV injected ranged from around 17% to 41% less in the DyeVert group in the comparative studies (EAC calculated). Image quality is also consistently maintained (or deemed acceptable) in all studies where it is measured. However, in several studies (Rao et al. 2019, Amoroso et al. 2020, Sapontis et al. 2017 and Bruno et al. 2019) image quality is measured subjectively and is not blinded or independent (or this detail is not available).

There is a lack of follow-up in the studies, which may limit the utility of AKI incidence results. Incidence of CI-AKI peaks after 4-5 days post-procedure according to one expert, with symptoms manifesting as late as 7-10 days. Another expert suggested that there are longer-term side effects that are still being actively researched. Gurm et al. 2019a reported AKI at discharge (9.6% of participants) but did not report the length of stay. Briguori et al. 2020 did report a significantly reduced rate of AKI in the DyeVert group (8% in the DyeVert group and 19% in the Control group (odds ratio = 0.37; p=0.047) alongside a significantly reduced hospital stay (8 ± 4 vs. 6 ± 2 days; p = 0.003), however. Several abstracts report AKI rates, however, there is very little methodological information available to report how long incidence of AKI was measured for post-procedure.

Experts suggested that there is no consensus on the relationship between CMV and AKI, so it is difficult to determine the clinical utility of the DyeVert System from the current evidence base. While the evidence is consistent in showing that CMV is reduced, changes to the risk of AKI is less clear. The pooled estimate of the relative risk of CI-AKI in the DyeVert vs control group (as calculated by the company) shows a 41% reduction; this informs the economic model. However, this figure is derived from only 4 studies which are of moderate quality, while 51.45% of the weight is given to Kutschman et al. 2019. This is a retrospective study and is not reported as full text, so caution should be taken when interpreting this result.

Baseline patient characteristics may have an effect on the efficacy of the DyeVert system, due to the baseline risk of developing AKI. The mean age ranged from 61 to 72 years. Older patients are more likely to be at risk of AKI. Mean eGFR at baseline ranged from 43 to 74 ml/min/1.73m^2. It is notable that experts felt that only patients with an eGFR of <30 (i.e. a CKD stage of 4 or 5) should be considered at high-risk for AKI (and therefore be considered for DyeVert). This may suggest that the populations included in the evidence base are at less risk of CI-AKI than the population who would be considered for DyeVert in the UK. Further, the company's economic model includes patients with CKD stage 3 or over (GFR <60), which may not be representative of UK practice.

Although the DyeVert system is indicated for use in both coronary and peripheral angiography, there is very little evidence of it being used in the latter. Only Rao 2019 (n=7) and Corcione et al. 2017 (n=2) included participants undergoing peripheral angiography. Both were non-comparative studies. Rao 2019 reported a 50ml mean CMV per case, from 7 highly complex peripheral interventions. All images were considered to be of adequate quality. Corcione et al. 2017 reported the contrast saved for 2 peripheral angiography patients as 28% and 41%, broadly in the same range as the 8 remaining coronary angiography patients (36.2% – 54.1%). It is difficult to make any conclusions on the efficacy of DyeVert in peripheral angiography from the available evidence.

There are several versions of the DyeVert system (see section 2) and the available evidence evaluates all available versions to different degrees. The evidence available for the DyeVert, DyeVert Plus and Plus EZ systems is likely to be generalisable. The improvements to the systems are cosmetic or for improvements in ease of use and the principle mechanism remains the same. Clinical experts felt that the evidence for these systems would be broadly comparable. Results are consistent across the various systems, for example the mean CMV was significantly lower in Desch et al. 2018, Gurm et al 2019a and Briguori et al. 2020, which evaluate the DyeVert, Plus and Plus EZ systems, respectively.

However, there is a lack of evidence on the DyeVert Power XT System, with only Bruno et al. 2019 and Amoroso et al. 2020 evaluating the first version of this system and no evidence on the newest version. It may be difficult to generalise between this system and the Plus EZ system. The clinical experts supporting this report had no experience of using the Power XT system. The diversion mechanism is almost identical to that used in the manual injection system; however, it is not clear if the difference in injector would affect clinical results. It should be noted that percentage saving in CMV is similar between the Power XT in Amoroso et al. 2020 (34.4%) and Bruno et al. 2019 (38.9%) compared to Briguori et al. 2020 (38%), which used the Plus EZ system.

Many of the studies are in part or fully sponsored by Osprey Medical, which could impart some bias to the results.

8.1 *Integration into the NHS*

One study (Amoroso et al. 2020) recruited a small number of patients from the UK. Twenty-six patients were recruited in total and is not clear how many of these were recruited in the UK. As mentioned previously, however, angiography practice is reasonably homogeneous amongst developed countries.

The EAC believes that the DyeVert system is unlikely to require any significant changes to the current care pathway. The company claims that the system can be set up in cath lab in the same way as standard manifolds. [redacted] Two studies (Tajti 2019 and Zimin 2020) reported that procedure time with the DyeVert System was increased (220 vs 152 minutes, p=0.03; 63 vs 48 minutes, p=0.09, respectively). Tajti et al. 2019 investigated DyeVert during CTO PCO, while Zimin et al. 2020 reported cases of OCT for diagnostic PCI. It should be noted, however, that fluoroscopy time was shown to be equivalent in both groups in Desch et al. 2018.

Clinics will generally use either a manual or power injector, so will only use either the Plus EZ or Power XT system. The company believes that power

injector use in the UK makes up around 10% of the market. The experts consulted for this report only had experience with the manual injection system; none had used the Power XT. In one expert's experience in peripheral angiography, the choice of manual or power injection is made on a case-by-case basis.

The company suggest that no training is required for either the Cath lab staff who prepare the system or for the angiographer performing the procedure. Informal training/instruction is given at the product evaluation stage, prior to purchase. The company will provide training for free if requested, however. Company staff are available to provide walkthroughs of the system during a product evaluation phase, prior to purchase. Youtube videos are also available explaining how to set-up and use the system. The monitor also has a built-in walkthrough of the priming process. Experts did not suggest that using the DyeVert had any significant effects on how they carried out angiography, in terms of the required time or technique. However, one expert believed that there was a learning curve of around 25 to 30 cases before a practitioner would be fully proficient in using DyeVert.

The experts agreed that their local protocols suggest only using DyeVert in patients with an eGFR<30, which differs from the company suggestion that DyeVert be used in patients with CKD stage 3+ (i.e. eGFR<60). It should be noted that in some emergency cases, AKI risk cannot be defined prior to angiography.

8.2 *Ongoing studies*

The company submission identified 2 ongoing studies (NCT04279457 and NCT03825094). The EAC identified 1 further ongoing study (NCT04714736).

Table 4: Details of Ongoing Studies

Study Code, Title & Location	Study Start Date	Estimated Completion Date	Target Sample Size	Inclusion Criteria	Comparator	Study Design	Primary Outcome
NCT04279457 Single-Center Prospective Study to Investigate the Difference in the Incidence of Contrast-Induced Nephropathy in High-Risk Patients With the Use of the Dye-Vert Plus System (Dye-Vert Plus). The US	03/02/2020	03/02/2022	1802	- 18 years of age or older - Scheduled to undergo CAG and/or PCI - Baseline estimated glomerular filtration rate (eGFR) of ≥20 and ≤60 mL/ min/1.73 m2 - Serum creatinine > 1.5mg/dl - Obtaining a Cardiac catheterization. - HTN/Diabetes - Inpatient and outpatient	Standardized Hydration	RCT	Monitoring of AKI [Time Frame: 3 days] Determined by GFR level
NCT03825094	07/05/2019	Dec 2023	10000	- DyeVert Group Patients: Patient underwent a	Non-comparative	Retrospective, observational, cohort study	Evaluate contrast media volume (CMV) threshold setting

DyeVert™ System for Contrast Monitoring in At-Risk Patients Undergoing Angiography: A Real-World Registry (DyeMINISH) The US.				diagnostic and/or interventional angiography procedure in which the DyeVert System was used in a majority of the case - Patient is willing and able to provide appropriate informed consent (if required)			practices and contrast media (CM) usage during index cath lab procedures in which the DyeVert System was used
NCT04714736 DyeVert System and Contrast-induced Acute Kidney Injury (REMEDIALIV) The US	10/02/2020	31/12/2023	348	Urgent or immediate (within 2 hours) coronary procedure with iodinated contrast media administration in the setting of an acute coronary syndrome	Coronary angiography using conventional manual injection syringe	RCT	Rate of contrast-induced Acute Kidney Injury (CI-AKI). [Time Frame: 30 days]

9 Economic evidence

9.1 *Published economic evidence*

Search strategy and selection

A search for economic evidence was carried out by the company on MEDLINE(R) and Medline in press, Embase, NHS EED, DARE, HTA via CRD Database, CEA registry via Centre for the Evaluation of Value and Risk in Health. The EAC reviewed the search strategy used by the company (Appendix A of company submission) and found it to be appropriate. The search resulted in the inclusion of 4 papers. The EAC conducted its own search (see section 4.1 and Appendix A) to confirm no relevant papers had been missed. The EAC included the following databases in its search; Embase, MEDLINE, PubMed, ClinicalTrials, WHO ICTR, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, INAHTA Database, and EconLit. Following the application of cost and economic filters, the EAC confirmed that no economic evidence in addition to the studies submitted by the company was available.

Specific inclusion and exclusion criteria were applied for study selection. The inclusion criteria were adult patients undergoing CAG and/or PCI procedures which require injection of contrast media; interventions included DyeVert™, DyeVert™ Plus, DyeVert™ Plus EZ, DyeVert Power XT; outcomes included life-years gained, Quality Adjusted Life Years gained (QALYs),Incremental Cost-Effectiveness Ratios (ICERs), clinical effectiveness (e.g. survival rates, healing rates, etc.), and details of the results of sensitivity analyses; study design included Cost-effectiveness analyses (CEA),Cost-utility analyses (CUA),Cost-benefit analyses (CBA),Cost-minimization analyses (CMA),Cost-consequence studies, Budget impact models, and Cost studies. Language restrictions included English language only. There was no restriction on search dates and country. Exclusion criteria included data unrelated to safety or efficacy and study designs which were editorials, reviews, letters, or book chapters. The EAC accepted the inclusion and exclusion criteria used by the company, except that conference abstracts were included in the EAC review.

The search identified 9 relevant economic studies; 5 were excluded as they contained no cost analysis, resulting in the inclusion of 4 studies. The articles identified as relevant to the company's decision problem were 2 studies (Javanbakht et al. 2020 and an unpublished data analysis from the US published in 2020), 1 short article (Kutschman, 2019) and 1 abstract (Turner and Tucker, 2020). Javanbakht et al. 2020 was a UK-based Cost-Utility analysis for a hypothetical cohort of patients. Kutschman, 2019 did not provide economic evidence, costs, resource use or healthcare utilisation for DyeVert.

[redacted]. Turner & Tucker, 2020 provided brief evidence on economic outcomes. The EAC thus included the 2 studies (Javanbhakt et al 2020 and unpublished study) and the 2 abstracts (Kutschman,2019 and Turner & Tucker, 2020), as included by the company.

Published economic evidence review

Javanbakht et al. (2020) presented a decision tree followed by a Markov model with 6 health states for a hypothetical cohort of patients with (CKD) stage 3–4 undergoing diagnostic (CAG) and/or PCI comparing DyeVert PLUS EZ with the Standard of Care. This model has a lifetime time horizon with costs and benefits estimated in the decision tree for the first 3 months and in the Markov model for the remainder of the patient's lifetime. Patients in each model state incur associated costs and quality-adjusted life-years (QALYs). Simulated patients are at risk of death from all causes during any given cycle period. Risk of death is conditional on CKD stage, history of AKI and/or MI, gender, and age.

Clinical data used to populate the model were derived from the literature or were based on assumptions informed by expert clinical input. Costs included in the model were from the NHS and personal social services perspective and obtained from the literature and UK-based routine sources. Probabilistic

distributions were assigned to the majority of model parameters so that a probabilistic analysis could be undertaken, while deterministic sensitivity analyses were also carried out to explore the impact of key parameter variation on the model results.

The EAC considers the structure of the model to be well constructed. The input parameters and results reflect real world circumstances and are consistent with the wider literature. The sensitivity analyses are rigorous and support internal validity. Extreme values were assigned to the input parameters and the outputs remained robust. While the model inputs are well described, some assumptions were not clear. For instance, a key assumption in the model is the reduction in risk of CI-AKI, which was estimated at 21.4% based on 1 data source. However, alternative approaches were included (contrast volume reduction per procedure of 40.1% and reduction in risk associated with 40.1% reduction in contrast media of 15.1%) and different levels of risk (up to +/-75%) were explored in the sensitivity analyses. Given the limited evidence on the clinical efficacy, it is possible that the reduction in risk lies outside these ranges. Furthermore, it is unclear how estimated glomerular filtration rate (eGFR) contrast volume (Contrast given (ml)/Baseline EGFR Ratio) was derived by the authors. This ratio influences the risk of developing AKI (Kutschman 2019).

A shortcoming of the model, which the authors acknowledge, is the assumption that the risk of developing CI-AKI does not change whether the patient initially received DAG, PCI or both. Further assumptions that may not reflect the standard of care in the UK were made regarding the administered epoetin dosage, frequency of check-up appointments, number of hospital admissions, number of specialist nurse home visits and renal replacement therapies. Utilities were obtained from a Japanese study and adjusted to the UK population for the ages 65-75 years. However, it is unclear how utilities were calibrated to account for a wider age span (18-64 and 75+ years) modelled by the authors. While the authors do acknowledge that they lacked utility data for patients who experienced MI, it is possible they overestimated

utility values for this cohort by assigning the same values as those in CKD stage 3-4/cycle.

Kutschman (2019) reports results of a clinical quality initiative aimed at reducing AKI in at-risk patients undergoing DCA and/or PCI at a US hospital. The results were based on a cohort of 206 patients treated with DyeVert in the period of 6 months from October 2018. No details on economic analysis were included in the methods.

[redacted]

Turner & Tucker (2020) reported an outcome analysis on a longitudinal, CI-AKI quality improvement programme over the period of 2018 to 2019. The DyeVert System was introduced for patients with an estimated glomerular filtration rate (eGFR) < 60ml/min1.73m^2 or SCr > 1.5 mg/dl. The CI-AKI rate reduced from 12.5% in the first quarter of 2018 to 2.04% by the third quarter of 2019 (10.46% in absolute value). This translates to number-needed-to-treat to avoid one CI-AKI event of 10. The cost of DyeVert was assumed to be $350 per procedure and the estimated incremental cost of CI-AKI was

assumed to be $10,000 per event. The result showed the use of DyeVert to be cost-saving at $696 per procedure. [redacted]

Results from the economic evidence

Javanbakht et al. (2020) reports that using DyeVert leads to cost savings (−£435) and improved effectiveness (+ 0.028 QALYs) over the patient's lifetime compared with current practice. Output from the probabilistic analysis points to a high likelihood of the intervention being cost-effective across a range of cost-effectiveness thresholds. The overall long-term cost savings are mainly driven by a lower risk of subsequent diseases and their associated costs. These include lower risk of recurrent AKI and MI in subsequent years and lower probability of progression to Stage 5 CKD. Cost estimates included the following assumptions, which have not been referenced: nephrologist's appointments for stage 5, weekly eGFR, and monthly visits by specialist nurse. However, the costs were varied by up to 50% and the Net Monetary Benefit (NMB) of the interventions remained positive.

[redacted]

[redacted]

[redacted]

Turner & Tucker (2020) applied a lower assumption of incremental cost of CI-AKI per event at $10,000 USD, [redacted] However, there was no information on the economic model used to estimate these results. Additionally, both studies apply a hospital setting in the US where costs of care are typically much higher than the UK, thus limiting transferability to the UK setting.

From the published economic studies, DyeVert technology provides cost savings in various settings.

9.2 *Company de novo cost analysis*

Economic model structure

The company's economic model is based on the model used for the Javanbakht publication (Javanbakht 2020), and this in turn closely aligns with the modelling undertaken for NICE CG169 in 2013. All of these analyses consider patients with stage 3 or stage 4 kidney disease, a population deemed representative of people at risk of contrast-induced acute kidney injury (CI-AKI) undergoing coronary or peripheral angiography with contrast media. Application of the DyeVert Systems during coronary or peripheral angiography and/or percutaneous coronary intervention are compared to current standard care (i.e., conventional hand or automated injection of contrast media in the absence of the DyeVert Systems). The EAC thinks the population included and the comparators are valid.

The company's submission does not detail any assumption regarding prophylactic measures to prevent CI-AKI, such as oral hydration, prior to angiography. Evidence on the effectiveness of different prophylactic regimes was assessed as part of the evidence review to the update of CG169 in 2019. That analysis concluded that oral hydration and oral Sodium Bicarbonate was

the most effective intervention to prevent CI-AKI, and that the risk of CI-AKI, under this regimen, is reduced to 2.74% in patients with stage 3/4 CKD.

The EAC notes that the population modelled in NICE guidelines (NG148) were patients with CKD stages 3 to 5.

The company's model structure includes a decision tree for the first 3 months followed by a Markov model (Figure 2) for the remainder of the patient's lifetime. The EAC notes some simplifications in the Markov model structure provided by the company. The model includes additional tunnel states for MI and for CKD stage 5. In addition to the transitions shown in the figure, the Markov model allows for an MI event for patients in the CKD stage 3-4 and CKD stage 3-4 (CI-AKI history) states. Patients in the Markov model transition between health states in 3-month time cycles. Following initial angiography, patients may or may not experience a CI-AKI. Patients then enter the Markov model. The model simulates the risk of further AKI episodes, MI, progression to CKD stage 5 and death. The risks of adverse events are dependent on the previous history of CI-AKI. Patients surviving an MI event are at risk of further AKI episodes or progression to CKD stage 5, as well as an elevated risk of death. Patients progressing to CKD stage 5 do not experience AKI or MI but are at elevated risk of death. Simulated patients are at risk of death from all causes during any model cycle. Risk of death is conditional on CKD stage, history of AKI and/or MI, and age. Considering the structure and health states, the EAC thinks the model structure, cycle lengths and time horizon are appropriate to capture the cost savings of the technology.

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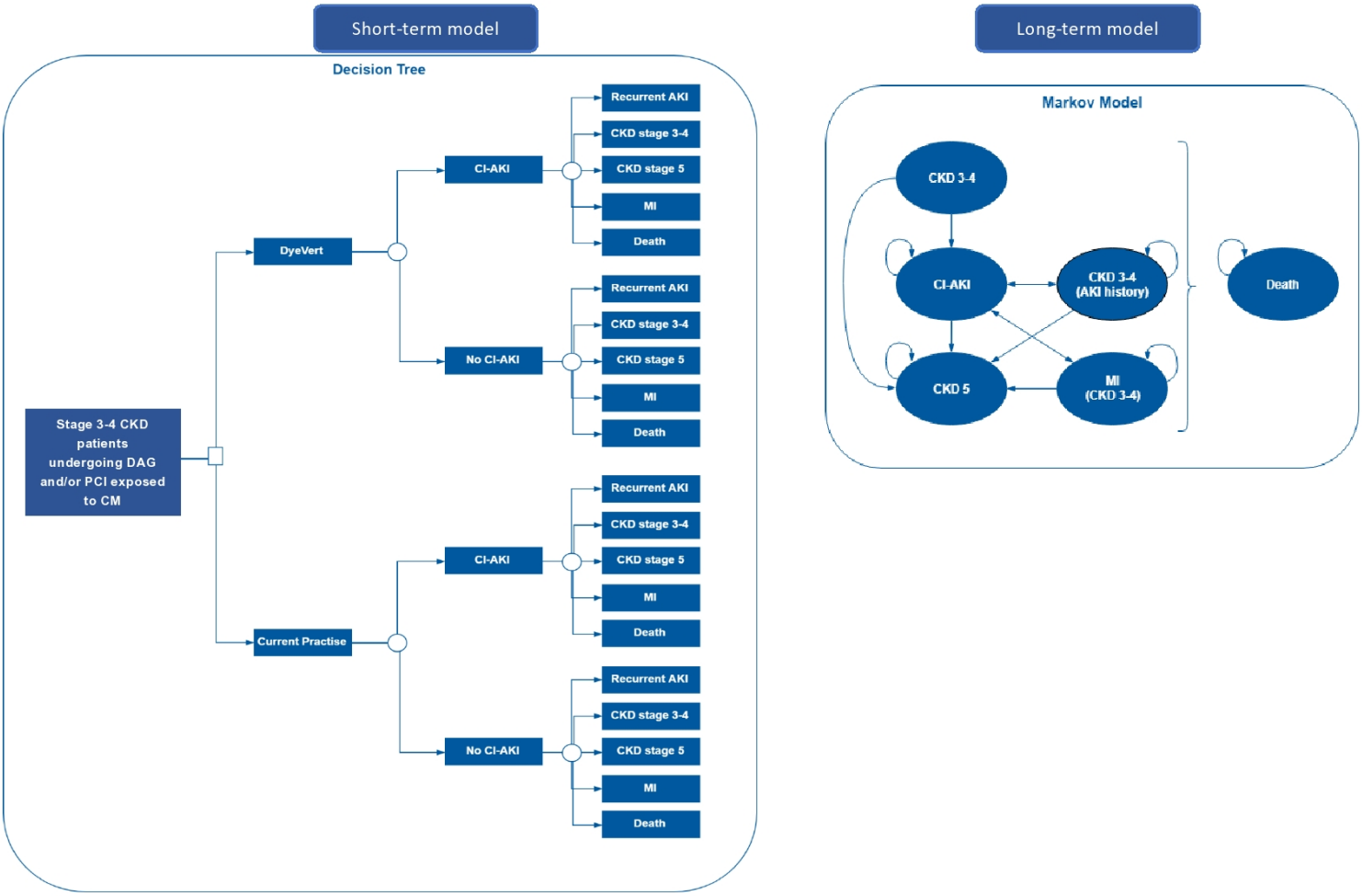
Figure 2: Company model structure



The model makes the following assumptions, which the EAC thinks are reasonable:

- People who have had CI-AKI are at a higher risk of recurrent AKI (Valle et al. 2017). This assumption is also present in the model informing NICE guidance NG148. & Valle et al. 2017).
- The risk of developing CI-AKI in CAG, in PCI, and in CAG with PCI is the same since there was no evidence to support differences.
- 26% of patients in the 'CKD 3-4 stage' are in stage 4 (NICE Guideline CG169, 2013), of whom 60% will require Furosemide as a diuretic.

- As per NICE guideline CG169 (2013), for CKD stage 5, it is also assumed that 90% of patients will be receiving renal replacement therapy (RRT). Finally, patients in this stage are assumed to have more frequent eGFR measurements and home visits than patients in CKD stage 3-4, as well as 33% of them receiving Epoetin alfa.

- Patients are no longer at risk of AKI generating additional treatment costs or mortality once they progress to CKD stage 5.

- Patients experiencing MI are no longer at risk of progression to CKD stage 5. The EAC accepts this simplification to preserve a parsimonious Markov model, although it notes that the subsequent costs of MI are sharply lower than the costs of CKD stage 5 disease.

The company's model is similar to the model used in the original CG169 (2013). However, the company's model allows for recurrence of AKI and explicitly models MI. The EAC regards these amendments as reasonable. The company's model does not consider the possibility of further angiography, unlike the model used in CG169. The EAC considers this an acceptable simplification, but one that is likely to underestimate the cost of DyeVert. The longer term cost savings through the multiple use of DyeVert are unlikely to scale linearly with the number of procedures, unlike the cost of DyeVert.

The updated CG169 made some changes to the original model. Patients with stage 5 disease, not yet on RRT were included with patients at CKD stage 3-4, and all patients in stage 5 were assumed to require RRT. Changes were made to the source of data for the risk of progression to CKD stage 5. The company's model retains the data source from the 2013 guidelines for the risk of progression. Finally, the updated model included the cost of kidney replacement. This adds a very significant cost to patients in stage 5. The company's model does not include costs of kidney replacement.

The EAC found a number of errors in the company's model which included cell referencing errors, errors in the transcribing of patients from the decision

tree to the Markov model and erroneous implementation of a half cycle correction. These errors were corrected in subsequent analysis undertaken by the EAC. The impact of these errors on the company's results were modest.

Economic model parameters

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Clinical parameters and variables

- The age of the cohort is 65 years old. The related publication, Javanbhakt et 2020, modelled patients aged 72 years, based on Gurm et al 2018. The company reports that they revised the age to 65 years based on analysis of data from Hospital Episode Statistics (HES).

- The model assumes a baseline risk of 30% for CI-AKI for CKD 3-4 (Mehran et al. 2004). The EAC considers it unlikely that the baseline risk is this high for patients appropriately hydrated. The updated NICE guidance (NG148) assumed a baseline risk of 11.5% taken from Maioli (2008), in which patients were given 0.9% Sodium Chloride and N-acetylcysteine as prophylaxis.

- RR reduction of CI-AKI due to DyeVert is 0.41 and is based on the company's meta-analysis. The EAC accepts the statistical validity of the meta-analysis but notes that the strength of the included studies is low-to-moderate.

- The Hazard Ratio of CI-AKI to death is 2.13 based on literature (Valle et al. 2017) and is acceptable to the EAC.

- The probability of progression to CKD stage 5 as a direct result of CI-AKI is 3.28%, based on James et al. (2010). The EAC finds it acceptable but notes that the correct reference has not been provided in the submission.

- Subsequent risk of progression from CKD stages 3/4 to CKD stage 5 is a function of age and CI-AKI history. For patients without a history of CI-AKI the rates are 0.02% for patients aged under 70, 0.10% for patients aged 70-79, and 0.88% for patients aged 80 or over. These values have been sourced from literature (Eriksen and Ingebretsen, 2006). The EAC considers this appropriate and notes that the modelling which informed NICE guidance CG169 used the same source.

- For patients with a history of CI-AKI, a relative risk of 4.81 has been applied to age based risk of progression to CKD stage 5 based on See et al. (2019) and is acceptable to the EAC.

- The risk of recurrent AKI with the first 3 month and subsequently for patients with and without AKI, has been sourced from a reliable source (Valle et al. 2017) and is acceptable to the EAC. The estimates are provided in Table 5.

- The risk of MI is taken from Valle et al. 2017 and the model differentiates four different risks: long term risks according to history of CI-AKI and the acute risk following angiography (as a function of CI-AKI occurrence). These estimates are acceptable to the EAC. The estimates are provided in Table 5.

- Risks of death were conditional on CKD stage, history of AKI or MI, and age. The all-cause mortality rates were derived from national life tables and were adjusted to reflect the extra mortality associated with CI-AKI and renal insufficiency. Standardised mortality ratios for each health state included in the model were applied to the relevant age-dependent mortality rates. This approach is acceptable to the EAC.

- Utilities were obtained from a Japanese study as a function of kidney disease state (Tajima et al. 2010) and adjusted to the UK population for the age range 65-75. However, it is unclear how utilities were

calibrated to account for a wider age span (18-64 and 75+) modelled by the authors. No adjustment was made to quality of life following MI.

Table 5: Clinical parameters used in the company's model and any changes made by the EAC

Variable	Company value	Source	EAC value	EAC comment
CKD 3-4 to CI-AKI	30%	Mehran et al., 2004	8.74%	Parameter taken from CG169 review (2019) assuming hydration with oral fluids
RR reduction of CI-AKI due to DyeVert	0.41	Company Meta-analysis	Unchanged	
HR of CI-AKI to Death	2.13	Valle et al., 2017	Unchanged	
CI-AKI to CKD 5	3.28%	James et al 2010	Unchanged	
CKD 3-4 to CKD 5				
<69 years	0.02%	Eriksen and Ingebretsen, 2006 & CG169, 2013	Unchanged	
70–79 years	0.10%	Eriksen and Ingebretsen, 2006 & CG169, 2013	Unchanged	
>79 years	0.08%	Eriksen and Ingebretsen, 2006 & CG169, 2013	Unchanged	
RR of CKD 5 after CI-AKI	4.81	See at al 2019	Unchanged	
Risk of recurrent AKI, first 3 months (without previous CI-AKI)	1.78%	Valle et al., 2017	Unchanged	

Risk of recurrent AKI, subsequent (without previous CI-AKI)	0.91%	Valle et al., 2017	Unchanged	
Risk of recurrent AKI, first 3 months (with previous CI-AKI)	6.61%	Valle et al., 2017	Unchanged	
Risk of recurrent AKI, subsequent (with previous CI-AKI)	2.26%	Valle et al., 2017	Unchanged	
Risk of MI, acute phase (with previous CI-AKI)	2.58%	Valle et al., 2017	Unchanged	
Risk of MI, subsequent (with previous CI-AKI)	1.23%	Valle et al., 2017	Unchanged	
Risk of MI, acute phase (without previous CI-AKI)	1.42%	Valle et al., 2017	Unchanged	
Risk of MI, subsequent (without previous CI-AKI)	0.67%	Valle et al., 2017	Unchanged	
Risk of AKI requiring dialysis, acute phase (with previous CI-AKI)	0.79%	Valle et al., 2017	Unchanged	
Risk of AKI requiring dialysis, subsequent (with previous CI-AKI)	0.16%	Valle et al., 2017	Unchanged	
Risk of AKI requiring dialysis, acute phase (without previous CIAKI)	0.11%	Valle et al., 2017	Unchanged	

Risk of AKI requiring dialysis, subsequent (without previous CIAKI)	0.04%	Valle et al., 2017	Unchanged	
Mortality				
CKD 3–4 to death RR			Unchanged	
Underlying mortality risk	Age specific	Lifetable data, ONS	Unchanged	
Male <69 years	3.60	Valle et al., 2017	Unchanged	
Female <69 years	2.70	Valle et al., 2017	Unchanged	
Male 70-79 years	2.40	Valle et al., 2017	Unchanged	
Female 70-79 years	1.80	Valle et al., 2017	Unchanged	
Male >79	2.30	Valle et al., 2017	Unchanged	
Female >79	2.10	Valle et al., 2017	Unchanged	
CKD 5 to death RR				
Male 18-64 years	10.00	Villar et al., 2007, See et al., 2018	Unchanged	
Female 18-64 years	16.40	Villar et al., 2007, See et al., 2018	Unchanged	
Male >64 years	4.80	Villar et al., 2007, See et al., 2018	Unchanged	
Female >64 years	7.10	Villar et al., 2007, See et al., 2018	Unchanged	
MI (acute) to death SMR	5.84	TA236, 2011	Unchanged	

MI (subsequent) to death SMR	2.21	TA236, 2011	Unchanged	

Resource identification, measurement and valuation

The company calculated treatment costs in CKD stage 3-4 of £260 per cycle. This assumes that in each three month cycle, patients incur costs associated with one nephrologist consultation along with lab costs and measurement of eGFR requiring 5-minutes of a phlebotomist time. Additionally, 9% of patients require Epoetin-alpha to treat anaemia 26% of patients require diuretics. Finally, 60% of patients with CKD stage 4 are assumed to require 40mg daily dose of Furosemide. These assumptions mirror those in the review of CG169 in the updated NICE guidance NG148 (2019). CG169 applies much lower unit costs for Epoetin-alpha than that applied in the company's model. CG169 sourced the unit costs from NHS Business Services authority; the company's model used the British National Formulary. As a result, the company estimates higher costs for this state than assumed in CG169. The impact of this is unlikely to be large but would disfavour DyeVert, as reductions in CI-AKI will increase time spent in CKD stages 3-4.

Patients in stage 5 CKD incur costs associated with Renal Replacement Therapy (RRT) (90% of patients) or conservative management (10% of patients). For patients requiring RRT, it is assumed that 79% of the patients would receive haemodialysis and 21% Peritoneal dialysis. This assumption mirrors that in CG169, 2013. In the updated analysis (CG169, 2019) 87% of patients are assumed to receive haemodialysis. The weighted average cost of haemodialysis is £153.92 (NHS reference cost 2018-19 codes LDA 01-10) and peritoneal dialysis is £70.72 (NHS reference cost 2018-19 codes LDA 11-12). Assuming 3 days frequency per week for haemodialysis and 7 days frequency per week for peritoneal dialysis, the estimated 3 month cycle cost is £5,625.

Patients entering the CKD stage 5 require an access procedure to facilitate permanent access for RRT. The cost depends on the type of RRT (haemodialysis or peritoneal). The company sourced unit costs of £845 for

peritoneal access and £1643 for haemodialysis access from NHS reference costs 2018/19, which the EAC considers appropriate. The company erroneously reversed the percentages of patients receiving haemodialysis and peritoneal dialysis in their submission to generate a weighted cost of access of £1,013 (1,643 x 0.21 + 845 x 0.79). The cost was amended by the EAC to £1,475 (1,643 x 0.79 + 845 x 0.21). Drugs and check-ups are also required and are more frequent in CKD stage 5. It was assumed all patients in this stage would have an eGFR more frequently (on a weekly basis), and two nephrologist appointments per three months. Epoetin was assumed to be administered to 33% of the patients in the same dosage as for patients in CKD 3-4 stages. These assumptions align with the original CG169 (2013). Patients receiving conservative management are assumed to receive monthly home visits by a specialist nurse as well as telephone calls on a weekly basis. It was assumed that diuretics will be used by 90% of the patients with double the dosage for those in CKD stages 3-4 (80mg), in line with the assumptions in (CG169, 2013). The EAC notes that unit costs have been inflated to 2018/19 values from 2017 values. This inflation is erroneous as the existing sources provide data in 2019 prices.

The cost of MI of £6364 in the first cycle and £512 in subsequent cycles is calculated from data in Walker et al. 2016 after inflation to 2019 prices. The EAC considers these estimates to be acceptable. The EAC was unable to reconcile the inflation of the data in Walker to match the figures used in the company model, but the discrepancies were small. The EAC notes that data taken from Walker refer to patients surviving an MI; the cost for a fatal MI is considerably less. The company's model applied the cost for a non-fatal MI to all MI events.

The cost of CI AKI index admission is estimated as £2834, which is a weighted average of NHS reference cost LA07H-P for a non-elective long stay. The EAC notes that CG169 pooled reference costs LA07H-P for all admissions and not just non-elective long stays, generating a pooled estimate of £1865. The cost of CI-AKI in CG169 included further costs of both temporary and permanent RRT generating an overall cost of £3,617. The

EAC was not convinced of the justification for the inclusion of permanent RRT costs in the cost estimate for CI-AKI used in CG169, considering this element to be included in the risk of progression to stage 5 CKD. Hence the EAC does not consider CG169 to provide a better estimate of the cost of CI-AKI and accepts the company's estimate.

The CI-AKI cost (£1421) of extended hospital admission is derived from the elective inpatient excess bed days cost for AKI(LA07H-P); of £358 inflated to 2018/19 values and combined with an estimate of 3.75 additional days taken from Subramaniam et al 2007. The EAC agrees with this estimate but notes that the cost of a bed day has been incorrectly inflated. The EAC amended the cost to £1375.

The technology cost is £350 and is the list price provided by the company.

The cost of CAG (£1,786) and PCI (£2,836) is appropriately sourced from NHS reference costs. The EAC notes that these costs are incurred by both treatment and comparator, and hence their impact on incremental cost is zero.

Table 6: Cost parameters used in the company's model and changes made by the EAC

Parameter	Company value	Source	EAC value	EAC comment
CKD stage 3-4/cycle	£260	Company estimation	£260	Unchanged
CKD stage 5 first cycle/cycle	£7,135	NHS reference costs, 2017/18, British National Formulary	£7,111	Error in cost inflation and in estimation of access costs amended
CKD stage 5 subsequent cycles/cycle	£6,113	NHS reference costs, 2017/18, British National Formulary	£5,783	EAC amended cost inflation
Cost of non-fatal MI (initial)/cycle	£6,364	Walker et al., 2016	£6,727	EAC amended cost inflation
Cost of fatal MI (initial)/cycle	£6,364	Walker et al., 2016,	£2,209	EAC differentiated

				fatal and non-fatal MI
Cost of MI (subsequent)/cycle	£512	Walker et al., 2016	£573	EAC amended cost inflation
CI-AKI cost of index admission	£2,834	NHS reference cost 2018/19 LA07H-P	£2,834	Unchanged
CI-AKI cost of extended hospital admission	£1,421	Excess bed day cost NHS reference cost 2017/18 inflated to current prices and Subramanian et al. 2007	£1,375	EAC amended cost inflation
DyeVert Cost	£350	Company list price	£350	Unchanged
Cost of CAG	£1,786	NHS reference costs 2018/19 (HRG codes: EY40A, EY40B,EY40C, EY40D, EY41A,EY41B, EY41C, EY41D)	£1,786	Unchanged
Cost of PCI	£2,836	NHS reference costs 2018/19 (HRGcodes: EY42A, EY42B,EY42C, EY42D, EY43A,EY43B, EY43C, EY43D,EY43E, EY43F)	£2,836	Unchanged

Sensitivity analysis

The company reported a deterministic and a probabilistic sensitivity analysis. In the deterministic analysis, all model parameters were varied by +/- 25% to explore the impact that this had on the incremental cost of the intervention. Probabilistic analysis was run by specifying distributions for each parameter. The parameters varied in one-way sensitivity analysis include discount rate, proportion of extended hospital admissions compared to new admissions for AKI post (PCI/CAG), Baseline risk of CI-AKI, relative risk reduction of CI-AKI due to DyeVert Systems, hazard ratio of death post CI-AKI, probability of transition to stage 5 CKD post CI-AKI, relative risk of transition to stage 5 CKD post CI-AKI, risk of recurrent AKI in subsequent years (without previous history of CI-AKI), risk of recurrent AKI in subsequent years (with previous

history of CI-AKI), risk of MI in subsequent years (with previous history of CI-AKI), risk of AKI requiring dialysis in subsequent years (with previous history of CI-AKI), health-state costs (CKD stage 3-4), health-state costs (CKD stage 5 first cycle), health-state costs (CKD stage 5 subsequent cycles), health-state costs (MI first cycle), health-state costs (MI subsequent cycle), cost of admission due to CI-AKI, cost of extended hospital admission due to CI-AKI, cost of DyeVert Systems, health utility of CKD stage 3-4 (3 months), health utility of CKD stage 5 (3 months), and health utility of CI-AKI.

In addition, two-way sensitivity analysis of the baseline risk of CI-AKI and absolute risk reduction associated with using DyeVert Systems was performed. It examined the combined impact of lower absolute and lower relative risks of CI-AKI with DyeVert.

The EAC thinks both the deterministic and probabilistic sensitivity and scenario analysis have been appropriately implemented.

9.3 *Results from the economic modelling*

Base case results

Table 7: Summary of base case results

	Company's results			**EAC's results**		
	Technology	**Comparator**	**Cost saving per patient**	**Technology**	**Comparator**	**Cost saving per patient**
Device cost per procedure	£350	0	£350	£350	0	£350
Adverse events (first 3 months of model)	£668	£947	-£279	£275	£360	-£85
Subsequent disease management	£24,164	£25,586	-£1,421	£19,942	£20,230	-£288

Total	**£28,701**	**£30,051**	**-£1,350**	**£20,567**	**£20,590**	**-£23**
QALYS	**6.05**	**6.00**	**0.057**	**6.05**	**6.04**	**0.013**

The company's submission reports cost savings of £1350 per patient when DyeVert is used. In addition, the company has also presented the impact of DyeVert on QALYs, and DyeVert leads to a gain of 0.057 QALYs. Since DyeVert technology results in lower costs and higher QALYs, it is a dominant strategy in terms of cost-effectiveness.

Alongside the correction of errors, the EAC made the following changes to the company's model. The EAC applied a cost of £2,209 to fatal MI events derived from Walker et al. 2016 and inflated to 2018/19 prices. The EAC amended the base case rate of CI-AKI to 8.74%, reflecting the rate reported for patients with CKD stages 3-4 given oral hydration in CG169 (2019). The EAC undertook sensitivity analysis assuming a higher rate of CI-AKI of 13.89% (the value estimated following prophylaxis with intravenous 0.9% saline in CG169) and a lower rate of 2.74% (the value estimated following prophylaxis with oral sodium bicarbonate and oral fluids in CG169). The EAC notes that the economic analysis published as part of the updated CG169 recommended the use of oral sodium bicarbonate and oral fluids. However, the clinical experts cast doubt on the evidence supporting the suppression of CI-AKI with this regimen. The EAC also undertook analysis for a cohort of patients aged 70, 75 and 80.

In the EAC's base case analysis, DyeVert leads to a cost saving of £23 and a modest gain in QALYs of 0.013. DyeVert remains a dominant intervention.

Sensitivity analysis results

The company's sensitivity analysis results (Figure 3) show that the parameters which have the largest impact on cost results are the baseline probability of CI-AKI following the initial procedure and the risk reduction in experiencing CI-AKI following use of the DyeVert Systems. When these

parameter values are reduced, cost savings associated with implementing the intervention are reduced also. The company's two-way scenario analysis predicts DyeVert System to be a cost saving intervention at levels of baseline CI-AKI rates and relative reductions in CI-AKI much lower than those used in the base case. DyeVert only becomes cost incurring when the relative risk reduction with CI-AKI is 21.4% (as reported in Javanbakht 2020), and the absolute risk of CI-AKI without DyeVert falls to 11.5%.

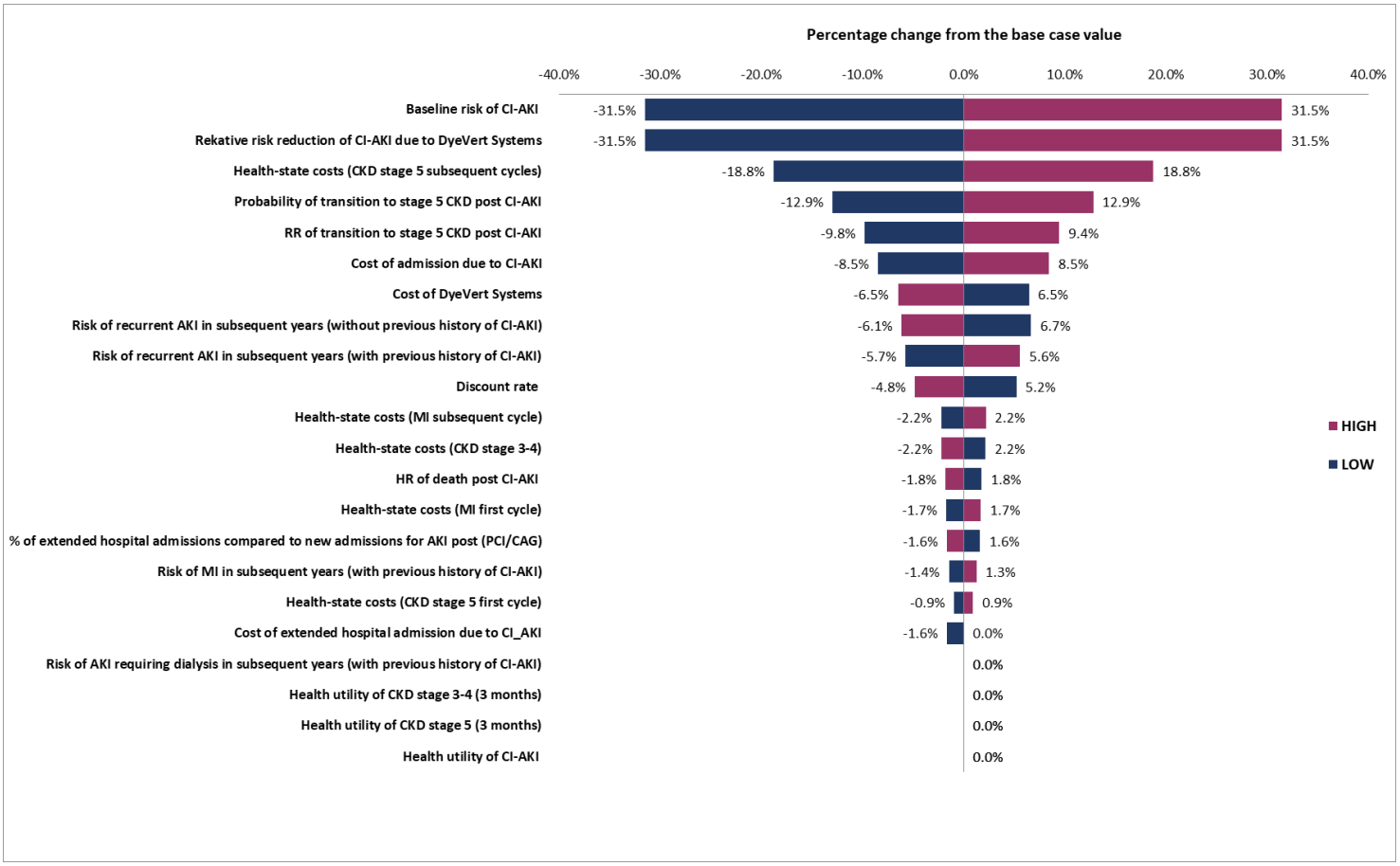


Figure 3: Sensitivity Analysis

Table 8 : Two way scenario analysis

		Risk reduction

Scenario(Source)	Baseline CI-AKI risk	Javanbakht al 2020 (21.4%)	Assumption (25%)	Assumption (30%)	Assumption (35%)
Mehran et al.2004	30%	-£537.4	-£686.7	-£894.0	-£1,101.4
Maioli et al.2008	11.50%	**£9.8**	-£47.4	-£126.9	-£206.4
Rashid et al.2004	14.30%	-£73.0	-£144.2	-£243.0	-£341.8
Pooled RCT data, all trials	13.10%	-£37.5	-£102.7	-£193.2	-£283.8
Pooled RCT data, elective trials	10.80%	**£30.5**	-£23.2	-£97.9	-£172.5
Pooled RCT data, emergency trials	19.60%	-£229.8	-£327.3	-£462.8	-£598.2
Dangas et al.2005	19.20%	-£217.9	-£313.5	-£446.2	-£578.9

The EAC undertook two-way sensitivity analysis varying the starting age of the cohort and the baseline risk of CI-AKI. The results are reported in Table 9 below.

		Risk of CI-AKI		
		2.74%	8.74%	13.89%
Starting age	65	£233	£-23	-£243
	70	£221	£-61	-£302
	75	£258	£58	-£114
	80	£288	£154	£38

Table 9: EAC two sensitivity analysis

At the baseline risk of CI-AKI of 8.74% DyeVert is cost saving for 65 and 70 year olds, but becomes cost incurring for 75 and 80 year olds. When the risk of CI-AKI is reduced to 2.74%, DyeVert is cost incurring for all age groups. When the risk of CI-AKI is increased to 13.89%, DyeVert is cost saving for patients aged 65, 70 and 75, and cost incurring for patients aged 80. For patients aged 65, the breakeven risk of CI-AKI is 8.2%. For patients aged 65,

and assuming their baseline risk of CI-AKI is 8.74%, the breakeven cost of DyeVert is £373. The break even relative risk reduction of C-AKI due to Dyevert system is 38.5%.

The EAC undertook deterministic one-way sensitivity analysis on each of the model parameters using the amended model (Fig 4). The ordering of parameters with respect to the impact of incremental cost were similar to the original analysis undertaken by the company. The two parameters with the biggest impact were the baseline risk of CI-AKI and relative risk reduction of CI-AKI due to Dyevert systems. In the EAC's model the cost of DyeVert systems was the parameter with the third biggest impact, with the cost of CKD stage 5 in subsequent cycles displaced to fourth highest impact.

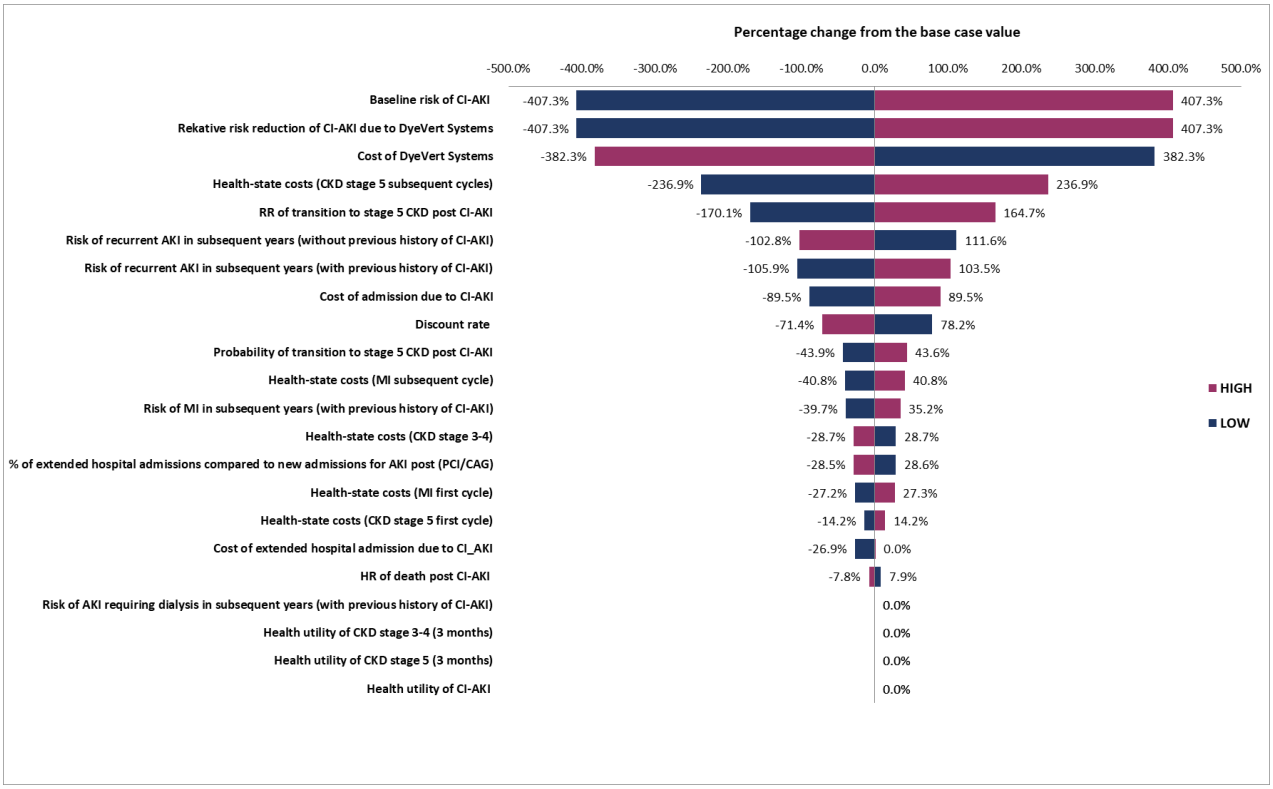


Fig 4. EAC sensitivity analysis

Additional results

In a further sensitivity analysis, the EAC applied costs for the first and subsequent cycles of the CKD-5 state for the 90% of patients receiving RRT of £40,588 and £4,684, respectively, as reported in the updated CG169 (2019). The first cycle cost includes all the costs of kidney transplant and RRT

prior to that transplant (after 2.14 years), in addition to RRT initial costs for all patients. The cost in subsequent cycles then assumes 46% of patients are receiving RRT and 54% have undergone kidney transplantation. The EAC notes that these costs are in 2017/18 prices. The EAC was unable to replicate the costing used in CG169 to confidently inflate these costs 2018/19 prices.

After amending the costs of stage 5 CKD to include the cost of kidney transplantation, DyeVert results in cost savings of £21. The impact of the additional stage 5 CKD costs are small when the baseline risk of CI-AKI is 8.74%. When the baseline risk of CI-AKI is raised to 13.89%, DyeVert generates cost savings of £240. When the baseline risk of CI-AKI is lowered to 2.74%, DyeVert generates additional costs of £234. The overall impact of including costs for kidney transplantation is modest with respect to the incremental cost of DyeVert.

9.4 *The EAC's interpretation of the economic evidence*

The EAC corrected error's it discovered in the company's model. These had only a modest impact on the incremental cost of DyeVert. The EAC made two further changes to the base case analysis. It differentiated the cost of fatal and non-fatal MI. The company's model applied the cost for a non-fatal MI to all MI events. Whilst a fatal MI is considerably less costly, the overall impact of this change was small. The EAC also changed the risk of CI-AKI. This was reduced substantially in the base case of the analysis undertaken by the EAC.

The EAC reviewed the updated CG169 guidelines to select an appropriate rate of CI-AKI. It also sought the views of clinical experts. The guidelines indicate that the risk of CI-AKI can be reduced to below 3% in patients with CKD stages 3-4 with the use of oral fluids and oral sodium bicarbonate, and recommend this intervention. However, the clinical experts cast doubt on the effectiveness of oral sodium bicarbonate solution and did not use it in their practice. They advised that oral fluids were given where possible, but interventional procedures often necessitated fasting, in which case

intravenous saline was used. In the light of this the EAC selected a rate of CI-AKI of 8.74% in their base case, which is the rate reported following prophylaxis with oral fluids in CG169. The rates reported in CG169 following prophylaxis with oral fluids and oral sodium bicarbonate solution (2.74%), and 0.9% intravenous saline (13.89%) were selected as low and high rates in sensitivity analysis.

The EAC's revised analysis indicates that DyeVert remains cost saving. For patients aged 65, the breakeven risk of CI-AKI is 8.2%. The clinical experts indicated that the probability of CI-AKI in patients considered at risk is above 10%. Hence the EAC thinks the evidence supports the case for adoption of the technology. In sensitivity analysis in which the baseline risk of CI-AKI was 2.74%, DyeVert was neither cost saving or cost-effective. Unsurprisingly, large changes in the risk of CI-AKI have a large impact on the incremental cost of DyeVert.

The clinical experts expressed considerable uncertainty regarding the risk of CI-AKI and the relative impact of factors which influence this risk, including the volume of contrast media, the type of procedure and CKD stage. The sensitivity analysis indicates that DyeVert may not be either cost saving or cost-effective in patients with a very low risk of CI-AKI. Currently, there appears to be insufficient evidence to definitively identify this group of patients. Should further evidence emerge to support the use of oral sodium bicarbonate to mitigate the risk of CI-AKI below 8% the case for adoption of DyeVert would be undermined. However, given the current clinical evidence on the risk of CI-AKI, and on the basis of the amended cost analysis, the EAC considers DyeVert likely to be cost saving.

10 Conclusions

10.1 *Conclusions from the clinical evidence*

The company included 8 full text studies, 9 abstracts and 2 unpublished manuscripts in their submission; the EAC included all of these studies and did not identify any other relevant evidence. Overall, the EAC believes the clinical evidence base to be of moderate quality. Two RCTs were included in the evidence base, one of which was reported in full text (Desch et al. 2018) and one as an abstract (Bath et al. 2019). Desch et al. 2018 is judged to be at low risk of bias.

Contrast Media Volume was consistently shown to be reduced when using the DyeVert system compared with standard angiography. Comparative studies reported a mean reduction of between 17-41% when using DyeVert. Image quality was also consistently shown to be non-inferior or 'acceptable', however study methods were not consistent or particularly robust in some cases. One study (Brigurori et al. 2020) reported that in-hospital stay was longer in the Control group than in the DyeVert group (8 ± 4 vs. 6 ± 2 days; p =0.003).

Only 1 study included patients recruited in the UK (Amoroso et al. 2020). This retrospective study included 26 coronary angiography procedures from the Netherlands, Germany and the UK. Experts do not believe that practice differs significantly in other developed nations, such as Germany and the US, where most of the evidence has been gathered.

The company performed 6 separate fixed and random effects meta-analyses looking at different outcomes, including between 4 and 8 studies each. Heterogeneity was found to be very low in most analyses and the EAC judged the methods to be robust. The

pooled estimate of the relative risk of CI-AKI in the intervention (DyeVert) versus control group among 4 double-arm studies was calculated as 0.59 (95%CI: 0.38-0.89). The EAC has concerns that the included studies are of moderate quality and that a retrospective study (Kutschman et al. 2019) has more than 50% weight for this result.

10.2 *Conclusions from the economic evidence*

The economic analysis undertaken by the EAC indicates DyeVert is cost saving for patients with stage 3-4 CKD, representing a population at risk of CI-AKI. Considerable uncertainty exists on both the baseline risk of CI-AKI and the effectiveness of hydration measures to reduce this risk. The cost analysis indicates that DyeVert begins to save money as the risk of CI-AKI climbs above 8%. The clinicians cast doubt on the ability of prophylactic hydration regimes to reduce the risk below this value in patients with stage 3-4 CKD. Hence, the EAC considers the evidence supports the adoption of DyeVert, but it is cautious in this conclusion.

The EAC considers the company's submission to directly address the decision problem defined in the scope. The EAC notes the similarity of the company's model structure with the model informing the first iteration of CG169 (2013). Amendments were made to the model in the updated CG169 (2019). These amendments are not judged substantial by the EAC. Hence the company's analysis reflects analysis undertaken to inform CG169. The main source of uncertainty in the analysis is the risk of CI-AKI.

The EAC notes that the evidence on which the analysis rests does not distinguish the risk for stage 3 versus stage 4 CKD or the risk for peripheral versus coronary angiography. It seems probable that the risk of CI-AKI in some patients with well managed CKD disease undergoing peripheral angiography may be below 8%. In these patients DyeVert is unlikely to be cost saving and may not be cost-effective. Further evidence on the absolute risk of CI-AKI would be required to identify this subgroup with confidence.

11 Summary of the combined clinical and economic sections

The EAC believes that the evidence for DyeVert supports its adoption but with several significant provisos. The most major uncertainty that remains is the baseline risk of CI-AKI and the risk reduction that DyeVert provides. The baseline risk of developing CI-AKI may vary quite significantly and DyeVert does not become cost-saving until the risk rises to 8%. This rate may be unlikely, particularly in patients undergoing peripheral angiography. Further, the relative reduction of CI-AKI, calculated by the company meta-analysis, is derived from low-to-moderate quality studies.

There is a lack of evidence investigating the Power XT system, with only 2 studies evaluating the first version of this system and no evidence on the newest version. It should be noted that the percentage saving in contrast media volume is similar in studies investigating the Power XT and Plus EZ, however, meaning that evidence may be generalizable between the 2 systems. There is a further lack of evidence on the use of any DyeVert system in peripheral angiography, meaning that strong conclusions cannot be made for this usage.

12 Implications for research

Ideally, a well-powered, UK-based RCT in a high-risk population (i.e. CKD stage 4 and 5) should be performed to fill in the gaps in the evidence. Most importantly, such a study should have adequate follow up of at least 10 days and should collect data on several outcomes that have not been reported in the literature to this point. This includes rate of AKI after 10 days post-procedure, severity of AKI and related clinical utility outcomes, such as morbidity, mortality, transplantation, transfer to intensive care and heart failure

related to contrast agent injection. More data should also be collected on length of hospital stay and in peripheral angiography. Finally, more data should be collected on the Power XT system. A study comparing the Plus EZ system and Power XT system to each other and to standard care could be beneficial but may not be necessary. Subgroup analysis into different stages of CKD would also be beneficial to understand any differences in the utility of the DyeVert system for each stage.

The ongoing study, DyeVert System and Contrast-induced Acute Kidney Injury (REMEDIALIV), (NCT04714736) looks likely to fulfil at least some of the most important requirements for research, particularly the need for longer follow-up. This study aims to recruit 348 patients by the end of 2023 and will measure CI-AKI rate for 30 days post-procedure, however it is based in the US.

13 References

Amoroso G, Jung C, Abell C. (2020) First European experience using a novel contrast reduction system during coronary angiography with automated contrast injection. EuroIntervention. 16(Suppl):387.

Bath A, Bobba K, Gautam S, et al. (2019) USE OF DYEVERT PLUS TO REDUCE CONTRAST EXPOSURE IN HIGH-RISK PATIENTS UNDERGOING CORONARY ANGIOGRAPHY. Journal of the American College of Cardiology. 73(9 Supplement 1):1193.

Briguori C, Golino M, Porchetta N, et al. (2020) Impact of a contrast media volume control device on acute kidney injury rate in patients with acute coronary syndrome. Catheterization and cardiovascular interventions.

Bruno RR, Nia AM, Wolff G, Erkens et al. (2019) Early clinical experiences with a novel contrast volume reduction system during invasive coronary angiography. IJC Heart and Vasculature.;23:100377.

Bunney R, Saenger E, Shah C et al. (2019) Contemporary use of contrast dye reduction technology in a tertiary academic hospital: patient characteristics and acute kidney injury outcomes following percutaneous coronary interventions. American College of Cardiology (ACC) Quality Summit; March 2019; New Orleans, LA.

Cameron A, Espinosa T. (2020) Reducing Contrast-Induced Acute Kidney Injury in a Cardiac Catherization Laboratory: A Quality Improvement Initiative. Society for Cardiac Angiography & Interventions Scientific Sessions Virtual Conference Catheterization and Cardiovascular Interventions. 95(Suppl 2):S25-S6.

Corcione N, Biondi-Zoccai G, Ferraro P et al. (2017) Contrast Minimization With the New-Generation DyeVert Plus System for Contrast Reduction and Real-Time Monitoring During Coronary and Peripheral Procedures: First Experience. The Journal of invasive cardiology. 29(8):259-62.

Desch S, Fuernau G, Pöss J, et al. (2018) Impact of a novel contrast reduction system on contrast savings in coronary angiography – The DyeVert randomised controlled trial. International Journal of Cardiology. 257:50-53.

Gurm HS, Mavromatis K, Bertolet B et al. (2019) Minimizing radiographic contrast administration during coronary angiography using a novel contrast reduction system: A multicenter observational study of the DyeVertTM plus contrast reduction system. Catheterization and Cardiovascular Interventions. 93(7):1228-35.

Eriksen, B. O. & Ingebretsen, O. C. (2006). The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age. Kidney Int, 69, 375-82.

Javanbakht M, Hemami M, Mashayekhi A, et al. (2020) DyeVert™ PLUS EZ System for Preventing Contrast-Induced Acute Kidney Injury in Patients Undergoing Diagnostic Coronary Angiography and/or Percutaneous Coronary Intervention: A UK-Based Cost–Utility Analysis. PharmacoEconomics - Open. 4(3):459-472.

James MT, Samuel SM, Manning MA, et al. (2013) Contrast-induced acute kidney injury and risk of adverse clinical outcomes after coronary angiography: a systematic review and meta-analysis. Circulation: Cardiovascular Interventions Feb;6(1):37-43.

KDIGO. (2012) Kidney International Supplements(2012)2,2; doi:10.1038

Knuuti J, Wijns W, Saraste A et al. (2019) ESC Guidelines for the diagnosis and management of chronic coronary syndromes The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). Russian Journal of Cardiology. 25(2):119-180.

Kutschman R. (2019) Clinical and Economic Outcomes of a Comprehensive Clinical Quality Initiative for Reducing Acute Kidney Injury in Chronic Kidney Disease Patients Undergoing Coronary Angiography. Journal of the American College of Cardiology. 74(13 Supplement):B605.

Kutschman R, Davison L, Beyer J. (2019) Comprehensive clinical quality initiative for reducing acute kidney injury in at-risk patients undergoing diagnostic coronary angiogram and/or percutaneous coronary interventions. Catheterization and Cardiovascular Interventions. 93(Supplement 2):S150.

Lewington A, MacTier R, Hoefield R et al. (2013) Prevention of Contrast Induced Acute Kidney Injury (CI-AKI) In Adult Patients. KIDNEYS. 9(1):58-60.

Mehran, R., Aymong, e. D., Nikolsky, e., et al. (2004). A simple risk score for prediction of contrastinduced nephropathy after percutaneous coronary intervention: development and initial validation. J Am Coll Cardiol, 44, 1393-9.

NICE. (2015) Chronic kidney disease in adults: assessment and management (CG182). Available at: https://www.nice.org.uk/guidance/cg182

NICE. (2016) Recent-onset chest pain of suspected cardiac origin: assessment and diagnosiis (CG95). Available at: https://www.nice.org.uk/guidance/cg95

NICE. (2017) Stable angina (QS21). Available at: https://www.nice.org.uk/guidance/qs21

NICE. (2019) Acute kidney injury: prevention, detection and management (NG148). Available at https://www.nice.org.uk/guidance/ng148

NICE. (2020) Acute coronary syndromes in adults (QS68). Available at: https://www.nice.org.uk/guidance/qs68

NICE. (2020) Peripheral arterial disease: diagnosis and management (CG147). Available at: https://www.nice.org.uk/guidance/cg147

Rao S. (2019) DyeVert Plus Contrast Reduction System Use in Patients Undergoing Highly Complex Peripheral Vascular Interventions. Journal of Vascular and Interventional Radiology. 30:e16.

Sapontis J, Barron G, Seneviratne S et al. (2017) A first in human evaluation of a novel contrast media saving device. Catheterization and cardiovascular interventions: official journal of the Society for Cardiac Angiography & Interventions. 90(6):928-34.

Sattar A, Darby M, Schnatz R, et al. (2019). Impact of using DyeVert PLUS on incidence of acute kidney injury after cardiac catheterization with coronary interventions in high-risk patients. American College of Cardiology Annual Meeting; April 2018; Charleston, WV. 2018.

Tajti P, Xenogiannis I, Hall A et al. (2019) Use of the DyeVert System in Chronic Total Occlusion Percutaneous Coronary Intervention. The Journal of invasive cardiology. 31(9):253-9.

Tajima, R., Kondo, M., Kai, H., et al. (2010). Measurement of health-related quality of life in patients with chronic kidney disease in Japan with EuroQol (EQ-5D). Clin Exp Nephrol, 14(4), 340-348.

Turner C, Tucker PA. (2020) Real-world impact of a quality improvement program for AKI prevention in the cardiac cath LAB. Catheterization and Cardiovascular Interventions. 95(Supplement 2): S112-S3.

Valle JA, McCoy LA, Maddox TM, et al. (2017) Longitudinal risk of adverse events in patients with acute kidney injury after percutaneous coronary intervention: insights from the national cardiovascular data registry. Catheterization and Cardiovascular Interventions 10(4): e004439. doi:10.1161/CIRCINTERVENTIONS.116.004439.

Walker, S., Asaria, M., Manca, A et al. (2016). Long-term healthcare use and costs in patients with stable coronary artery disease: a population-based cohort using linked health records (CALIBER). Eur Heart J Qual Care Clin Outcomes, 2, 125-40.

Zimin VN, Jones MR, Richmond Iv et al. (2020) A feasibility study of the DyeVert TM plus contrast reduction system to reduce contrast media volumes in percutaneous coronary procedures using optical coherence tomography. Cardiovascular revascularization medicine: including molecular interventions.

14 Appendices

Appendix A

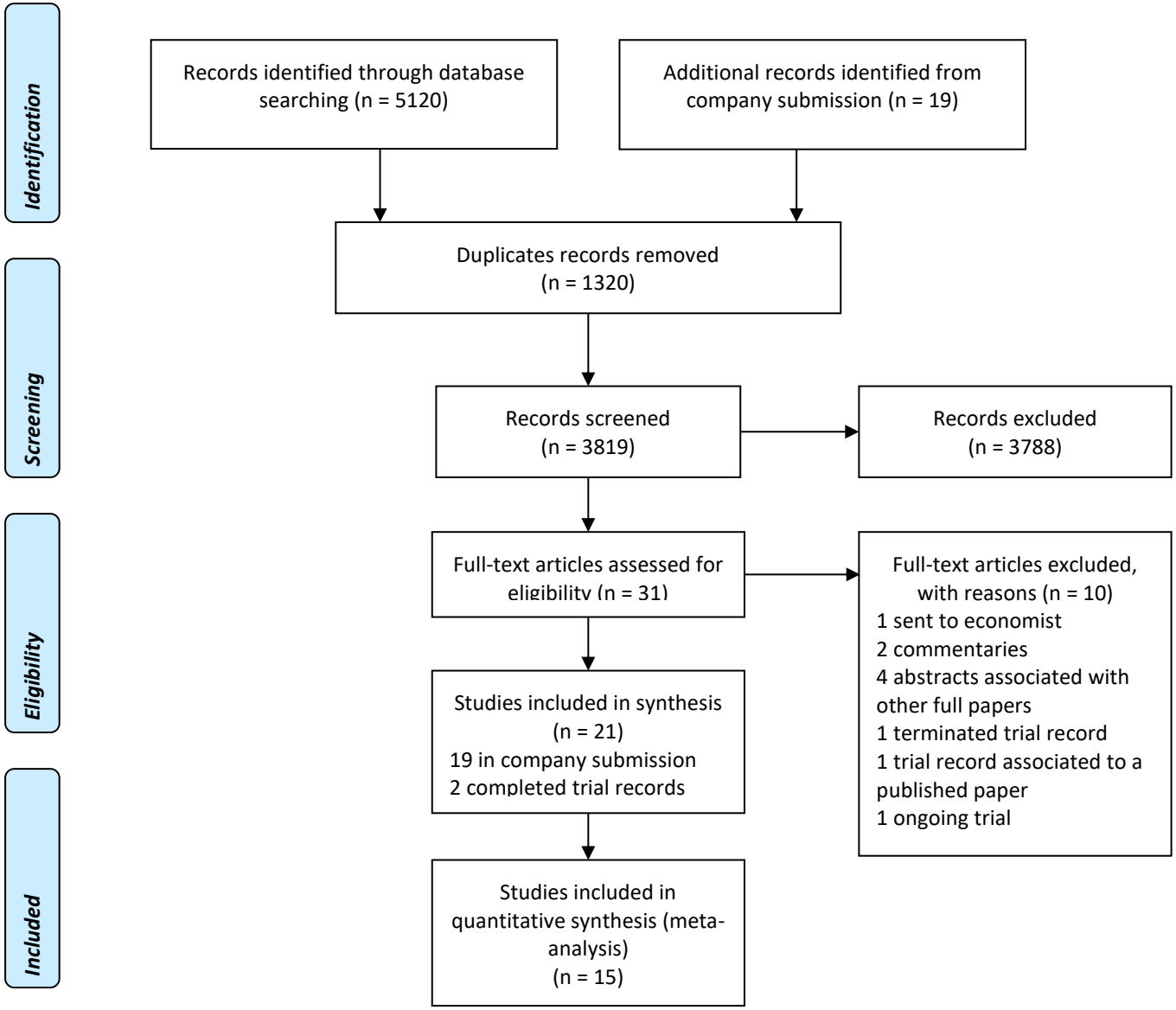
Searches sources on 5th February 2021

Source	Results
Cochrane Library Databases: Cochrane Database of Systematic Reviews (CDSR) Cochrane Central Register of Controlled Trials (CENTRAL)	1105

Embase via Ovid SP <1974 to 2021 Week 04>	1352
Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to February 03, 2021>	2648
INAHTA	0
ClinicalTrials.Gov	7
WHO ICTRP	7

Cochrane Library
Date Run: 05/02/2021 16:48:42 #1 [mh "Vascular Surgical Procedures"[mj]] or (Angiograph* or Angioplast* or Angioscop* or Catheter* or CABG or Coronary or PCI):ti,ab 85377 #2 [mh "Contrast Media"[mj]/ae] or (Contrast or Radiocontrast or Radiopaque):ti,ab 39837 #3 [mh "Acute Kidney Injury"[mj]/ci] or (Acute Renal or Acute Kidney or AKI or CI-AKI or CIAKI or Nephrotoxic* or Nephropath*):ti,ab 19836 #4 DyeVert* or "Osprey Medical" 10 #5 (#1 AND #2 AND #3) OR #4 in Cochrane Reviews, Cochrane Protocols, Trials 1105
Embase via Ovid SP
1 exp *Vascular Surgery/ or (Angiogra* or Angioplast* or Angioscop* or Catheter* or CABG or Coronary or PCI).ti,ab. (1166788) 2 *Contrast Medium/ae or ((Contrast or Radiocontrast or Radiopaque) and Volume*).ti,ab. (70844) 3 *Acute Kidney Failure/si or Contrast Induced Nephropathy/ or (Acute Renal or Acute Kidney or AKI or CI-AKI or CIAKI or Nephrotoxic* or Nephropath*).ti,ab. (188751) 4 (DyeVert* or "Osprey Medical").mp. (30) 5 (1 and 2 and 3) or 4 (1464) 6 limit 5 to (conference abstracts or embase) (1352)
MEDLINE via Ovid SP
1 exp *Vascular Surgical Procedures/ or (Angiograph* or Angioplast* or Angioscop* or Catheter* or CABG or Coronary or PCI).ti,ab. (814611) 2 *Contrast Media/ae or (Contrast or Radiocontrast or Radiopaque).ti,ab. (1035375) 3 *Acute Kidney Injury/ci or (Acute Renal or Acute Kidney or AKI or CI-AKI or CIAKI or Nephrotoxic* or Nephropath*).ti,ab. (131908) 4 (DyeVert* or "Osprey Medical").mp. (12) 5 (1 and 2 and 3) or 4 (2648)

INAHTA
DyeVert (0)
ClinicalTrials.Gov
DyeVert (7)
WHO ICTRP
DyeVert (7)


Identification
Screening
Eligibility
Included
Records identified through database searching (n = 5120)
Additional records identified from company submission (n = 19)
Duplicates records removed (n = 1320)
Records screened (n = 3819)
Records excluded (n = 3788)
Full-text articles assessed for eligibility (n = 31)
Full-text articles excluded, with reasons (n = 10)
1 sent to economist
2 commentaries
4 abstracts associated with other full papers
1 terminated trial record
1 trial record associated to a published paper
1 ongoing trial
Studies included in synthesis (n = 21)
19 in company submission
2 completed trial records
Studies included in quantitative synthesis (meta-analysis) (n = 15)

Appendix B

PICO analysis of each study submitted by the company and all of those identified by extra EAC searches, description of bias for each study, detailed tables of results (if applicable).

Examples: these are from recent assessment reports and for example only. Use whatever is appropriate to the evaluation in question.

Unique ID	A1	**Study ID**	Desch et a. 2018	**Assessor**	
Ref or Label		**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	non-adherence to their assigned intervention by trial participants
Experimental	Angiography with DyeVert	**Comparator**	Angiography without DyeVert	**Source**	Journal article(s)
Outcome		**Results**		**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Permuted block randomisation stratified by access site (radial/femoral) via a web-based system using a computer-generated list of random numbers.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	

			Blinding of physicians was not feasible due to visual requirements of tubing set. Patients were not informed about treatment allocation.
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	Baseline characteristics did not differ significantly.
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	PN	
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	NA	
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	NA	
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?		
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	94/96 patients.

Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	Objective measure. The starting volume level on the CM source bottle was marked to indicate the CM volume starting point. Following diagnostic coronary angiography, the end volume on the CM source bottle was marked to indicate the CM volume ending point and the amount of remaining CM within the syringe was documented. The total volume of CM used from the bottle was then measured using a graduated cylinder.
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PN	

	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 ... multiple eligible analyses of the data?	PN	
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Low**	

Table 9: Summary of the strengths and weaknesses of the trial incorporating internal and external validity

Gurm et al. 2019a

	Strengths	Weaknesses
Study design	Multicentre. Primary analysis was additionally performed using all cases (inclusive of the excluded cases).	Per protocol analysis; 9 participants were excluded. Single arm. Used objective performance criterion based on published literature instead of a concurrent control group.
Patient selection	Appears to reflect eligible population.	Might not reflect UK population
Randomisation	NA	Not randomised. Single arm.
Blinding	Blinding not mentioned. Objective performance criterion used.	Not feasible to blind treating clinicians.
Patient attrition	Reasons for patient exclusion documented.	NA
Reporting of outcomes	Primary analysis pre-specified in protocol.	Data on CI-AKI was based only on available subject data based on standard of care practices rather than coming from protocol-required post-procedure laboratory data.
Statistical analysis	Defined a priori. Power calculation for sample size for primary outcome performed.	NA
Study company	NA.	Study was funded by company. Three lead investigators paid consultants of company.

Briguori et al. 2020

	Strengths	Weaknesses
Study design	Comparative, propensity-matched controlled	Small sample size. Study was a single-centre, observational, non-randomized design
Patient selection	Well described inclusion and exclusion criteria. Appears to reflect eligible population. Propensity score matching.	Might not reflect UK population
Randomisation	Propensity scored matching.	Non randomised.
Blinding	Not blinded.	Not feasible to blind patients or treating/assessing clinicians.
Patient attrition	Patients were selected retrospectively, no attrition. Clinical and biochemical characteristics were well matched between the two groups	Retrospective.
Reporting of outcomes	Primary analysis pre-specified in protocol. AKI assessed according to the Acute Kidney Injury Network criteria	Study not powered to detect differences in hard clinical endpoints (dialysis and death).
Statistical analysis	Statistical protocol outlined. Method for propensity scored matching was outlined.	Power calculation not discussed in paper, though study mentions that study not powered to detect differences in hard clinical endpoints (dialysis and death).
Study company	The authors declared no potential conflict of interest.	None.

Bruno et al. 2019

	Strengths	Weaknesses
Study design	None.	Feasibility study. Very small sample size (n=9). No comparator.
Patient selection	Appears to reflect eligible population.	Might not reflect UK population No specific exclusion criteria
Randomisation	No randomisation.	No randomisation.
Blinding	Blinding not discussed.	Not feasible to blind patients or treating/assessing clinicians. Blinding not discussed.
Patient attrition	Retrospective. No patient attrition.	Retrospective. No patient attrition.
Reporting of outcomes	Results (amount of average CM savings) align with those of previous studies	Estimation of reduction in CM dose based on contrast collection bag demarcations.
Statistical analysis	No statistical analyses.	No statistical analyses.
Study company	Six lead investigators declared no conflict of interest.	One author received a speaking fee by Osprey Medical. Funding provided by Osprey Medical, Inc.

Sapontis et al. 2017

	Strengths	Weaknesses
Study design	Multicentre. Prospective.	Pilot study with moderate sample size. Single arm.
Patient selection	Appears to reflect eligible population.	Might not reflect UK population
Randomisation	NA	Not randomised. Single arm.
Blinding	None.	Lack of use of an independent, blinded reviewer for image assessment.
Patient attrition	None reported.	NA
Reporting of outcomes	Primary analysis pre-specified in protocol.	NA
Statistical analysis	Defined a priori. Power calculation for sample size for primary outcome performed.	NA
Study company	All but one author had no conflicts of interest to declare.	Study was funded by company. One author is a consultant to Osprey Medical, Inc.

Corcione et al. 2017

	Strengths	Weaknesses
Study design	None.	Retrospective. Small sample size. Single arm.
Patient selection	Appears to reflect eligible population.	Might not reflect UK population
Randomisation	NA	Not randomised. Single arm.
Blinding	Blinding not mentioned.	Not feasible to blind treating clinicians.
Patient attrition	None.	NA
Reporting of outcomes	Outcomes corroborated larger studies.	Unclear if study was adequately powered.
Statistical analysis	NA	Unclear if study was adequately powered.
Study company	NA	It is unclear how the study was funded.

Tajti et al. 2019

	Strengths	Weaknesses
Study design	Unique in using DyeVert alongside CTO-PCO. Comparative.	Retrospective, single-centre.
Patient selection	Baseline patient characteristics broadly similar. Reasonably large population.	Small population (may reflect infrequent use of OCT in practice).
Randomisation	NA	Not randomised.
Blinding	None	Not feasible to blind treating clinicians.
Patient attrition	None.	Retrospective (no attrition).
Reporting of outcomes	Procedure time reported.	Median CMV used rather than mean.
Statistical analysis	Defined a priori.	None.
Study company	Funding not clear.	Funding not clear.

Zimin et al. 2020.

	Strengths	Weaknesses
Study design	Prospective, multicentre, feasibility study. Unique in using DyeVert alongside Optical coherence tomography. Comparative, uses most up-to-date model.	Non-randomised, feasibility study. No clinical follow up.
Patient selection	Procedural characteristics were similar between groups.	Small population (may reflect infrequent use of OCT in practice).
Randomisation	NA	Not randomised.
Blinding	None	Not feasible to blind treating clinicians.
Patient attrition	Reasons for patient exclusion documented.	Images were excluded if artifacts present.
Reporting of outcomes	Primary analysis pre-specified in protocol.	None.
Statistical analysis	Defined a priori.	No sample size calculated.
Study company	NA.	Study was partially funded by company.

Appendix C

Study Code, Title & Location	Study Start Date	Estimated Completion Date	Target Sample Size	Inclusion Criteria	Comparator	Study Design	Primary Outcome
NCT04279457 Single-Center Prospective Study to Investigate the Difference in the Incidence of Contrast-Induced Nephropathy in High-Risk Patients With the Use of the Dye-Vert Plus System (Dye-Vert Plus). The US	03/02/2020	03/02/2022	1802	- 18 years of age or older - Scheduled to undergo CAG and/or PCI - Baseline estimated glomerular filtration rate (eGFR) of ≥20 and ≤60 mL/ min/1.73 m2 - Serum creatinine > 1.5mg/dl - Obtaining a Cardiac catheterization. - HTN/Diabetes - Inpatient and outpatient	Standardized Hydration	RCT	Monitoring of AKI [Time Frame: 3 days] Determined by GFR level
NCT03825094 DyeVert™ System for Contrast Monitoring in At-Risk Patients Undergoing Angiography: A Real-World	07/05/2019	Dec 2023	10000	- DyeVert Group Patients: Patient underwent a diagnostic and/or interventional angiography procedure in which the DyeVert System was used in a majority of the case	Non-comparative	Retrospective, observational, cohort study	Evaluate contrast media volume (CMV) threshold setting practices and contrast media (CM) usage during index cath lab procedures in which the DyeVert System was used

Registry (DyeMINISH) The US.				- Patient is willing and able to provide appropriate informed consent (if required)			
NCT04714736 DyeVert System and Contrast-induced Acute Kidney Injury (REMEDIALIV) The US	10/02/2020	31/12/2023	348	Urgent or immediate (within 2 hours) coronary procedure with iodinated contrast media administration in the setting of an acute coronary syndrome	Coronary angiography using conventional manual injection syringe	RCT	Rate of contrast-induced Acute Kidney Injury (CI-AKI). [Time Frame: 30 days]

Appendix D

Results of the Company Meta-analyses

1) Pooled estimate of the relative risk of CI-AKI in the intervention (DyeVert) versus control group among 4 double-arm studies, calculated as **0.59 (CI%95: 0.38-0.89)**

Meta-analysis: relative risk

Variable for studies	Studies
1. Intervention groups	
Variable for total number of cases	DyeVert_n
Variable for number of positive cases	DyeVert_AKI
2. Control groups	
Variable for total number of cases	Control_n
Variable for number of positive cases	Control_AKI

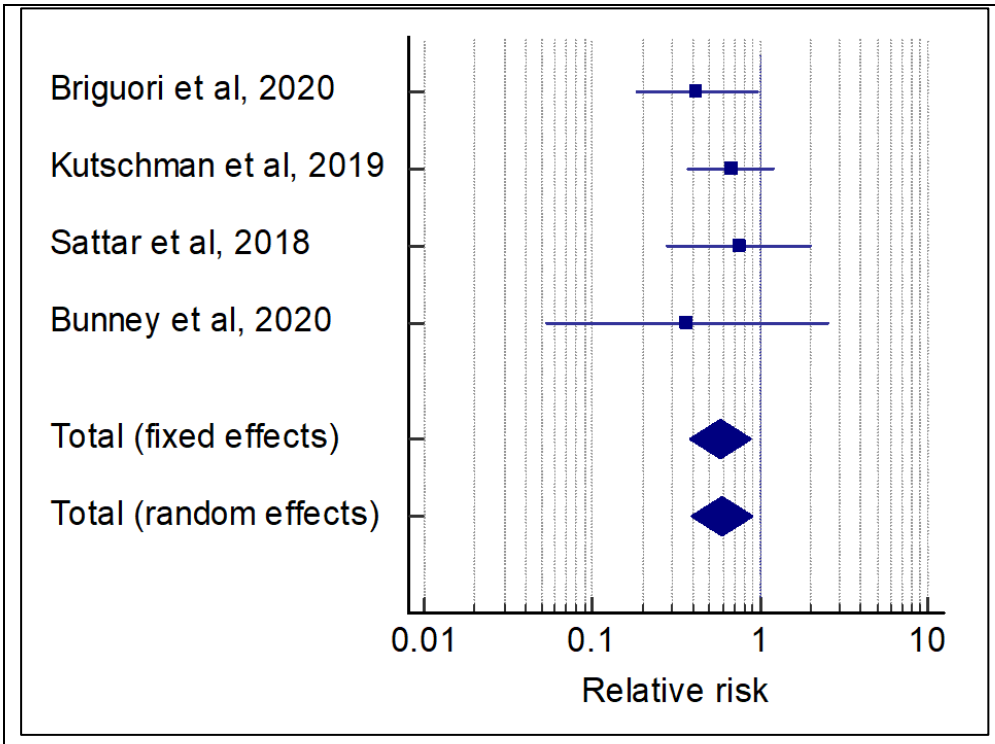
Study	Intervention	Controls	Relative risk	95% CI	z	P	Weight (%)	
							Fixed	Random
Briguori et al, 2020	7/90	17/90	0.421	0.185 to 0.956			25.89	25.89
Kutschman et al, 2019	17/258	25/243	0.670	0.374 to 1.199			51.45	51.45
Sattar et al, 2018	5/41	11/68	0.753	0.282 to 2.013			18.02	18.02
Bunney et al, 2020	1/29	71/770	0.369	0.0531 to 2.562			4.64	4.64
Total (fixed effects)	30/418	124/1171	0.579	0.381 to 0.879	-2.565	0.010	100.00	100.00
Total (random effects)	30/418	124/1171	0.590	0.389 to 0.896	-2.477	0.013	100.00	100.00

Test for heterogeneity

Q	1.3033
DF	3
Significance level	P = 0.7284
I^2 (inconsistency)	0.00%
95% CI for I^2	0.00 to 70.28

Publication bias

Egger's test	
Intercept	-0.7111
95% CI	-5.0074 to 3.5853
Significance level	P = 0.5503
Begg's test	
Kendall's Tau	-0.3333
Significance level	P = 0.4969



2) Pooled estimate of the rate of CI-AKI in the intervention group (DyeVert) among 4 double-arm studies, calculated as **7.71% (CI%95: 5.36%-10.44%)**

Meta-analysis: proportion

Variable for studies	Studies
Variable for total number of cases	DyeVert_n
Variable for number of positive cases	DyeVert_AKI

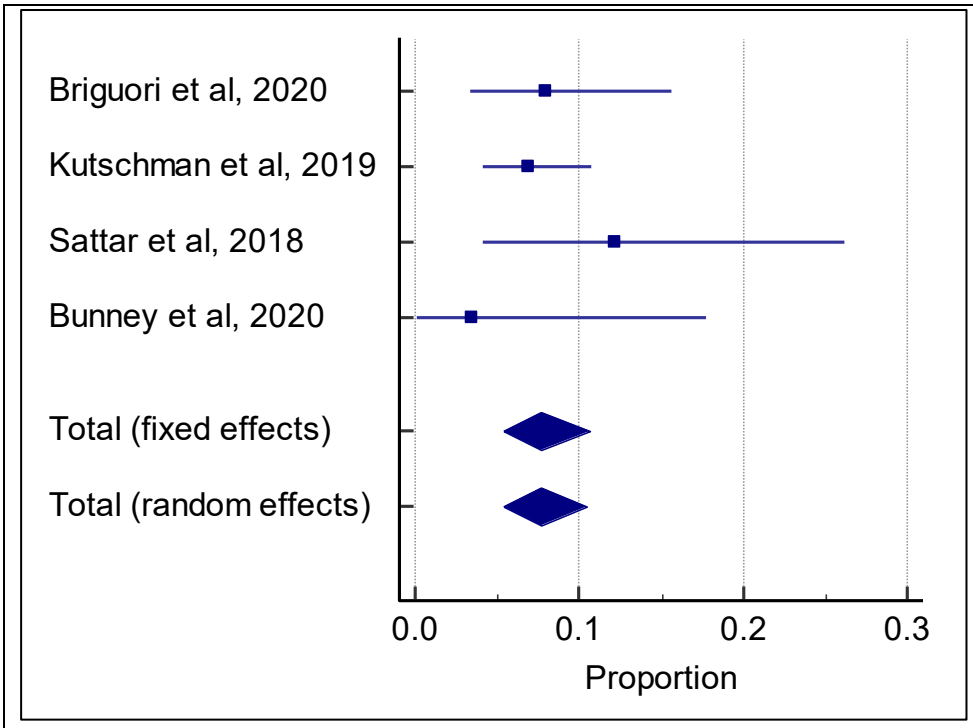
Study	Sample size	Proportion (%)	95% CI	Weight (%)	
				Fixed	Random
Briguori et al, 2020	90	8.000	3.328 to 15.652	21.56	21.56
Kutschman et al, 2019	258	6.900	4.127 to 10.711	61.37	61.37
Sattar et al, 2018	41	12.200	4.084 to 26.211	9.95	9.95
Bunney et al, 2020	29	3.450	0.0874 to 17.767	7.11	7.11
Total (fixed effects)	418	7.710	5.351 to 10.682	100.00	100.00
Total (random effects)	418	7.710	5.361 to 10.444	100.00	100.00

Test for heterogeneity

Q	1.9621
DF	3
Significance level	P = 0.5803
I^2 (inconsistency)	0.00%
95% CI for I^2	0.00 to 80.26

Publication bias

Egger's test	
Intercept	0.5620
95% CI	-4.4335 to 5.5574
Significance level	P = 0.6762
Begg's test	
Kendall's Tau	0.0000
Significance level	P = 1.0000



3) Pooled estimate of the rate of CI-AKI in the control group among 4 double-arm studies, calculated as **12.55% (CI%95: 8.74%-16.93%)**

Meta-analysis: proportion

Variable for studies	Studies
Variable for total number of cases	Control_n
Variable for number of positive cases	Control_AKI

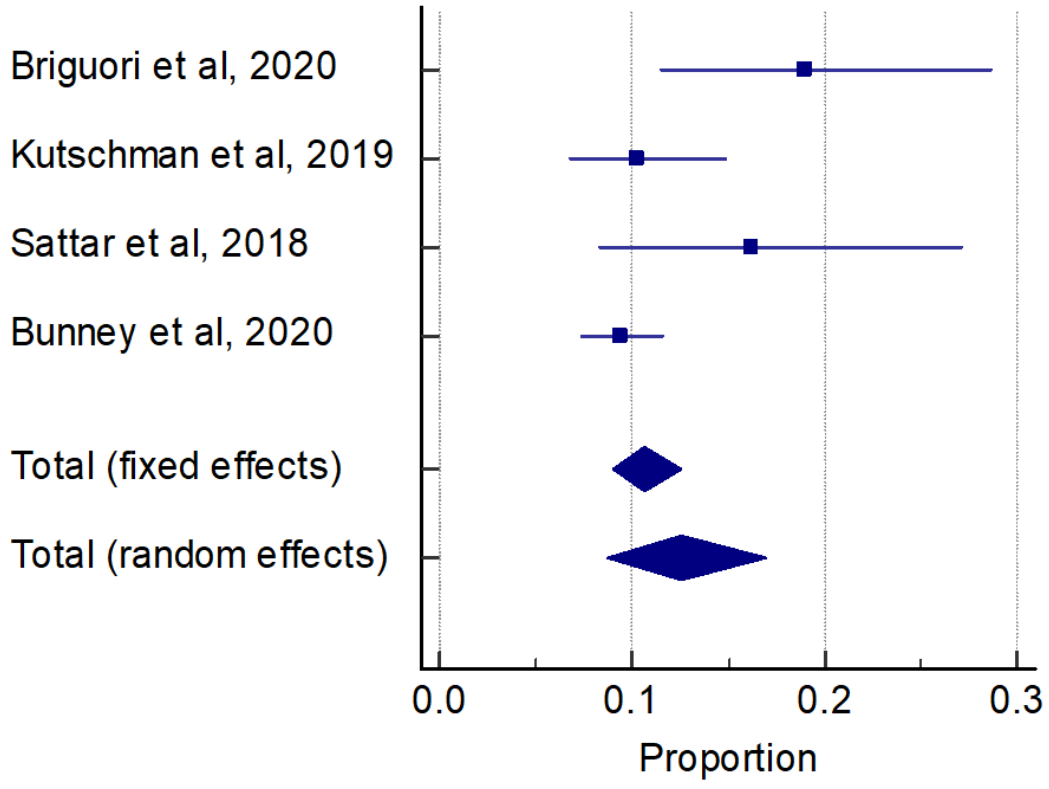
Study	Sample size	Proportion (%)	95% CI	Weight (%)	
				Fixed	Random
Briguori et al, 2020	90	19.000	11.495 to 28.636	7.74	19.16
Kutschman et al, 2019	243	10.300	6.779 to 14.826	20.77	28.62
Sattar et al, 2018	68	16.200	8.379 to 27.131	5.87	16.41
Bunney et al, 2020	770	9.350	7.388 to 11.630	65.62	35.81
Total (fixed effects)	1171	10.677	8.969 to 12.585	100.00	100.00
Total (random effects)	1171	12.552	8.745 to 16.934	100.00	100.00

Test for heterogeneity

Q	8.9892
DF	3
Significance level	P = 0.0294
I^2 (inconsistency)	66.63%
95% CI for I^2	2.38 to 88.59

Publication bias

Egger's test	
Intercept	3.1018
95% CI	-0.6136 to 6.8172
Significance level	P = 0.0695
Begg's test	
Kendall's Tau	0.6667
Significance level	P = 0.1742



4) [redacted]

Meta-analysis: continuous measure

Variable for studies	Study
1. Intervention groups	
Variable for number of cases	DyeVert_n
Variable for mean	DyeVert_m
Variable for SD	DyeVert_sd
2. Control groups	
Variable for number of cases	Control_n
Variable for mean	Control_m
Variable for SD	Control_sd

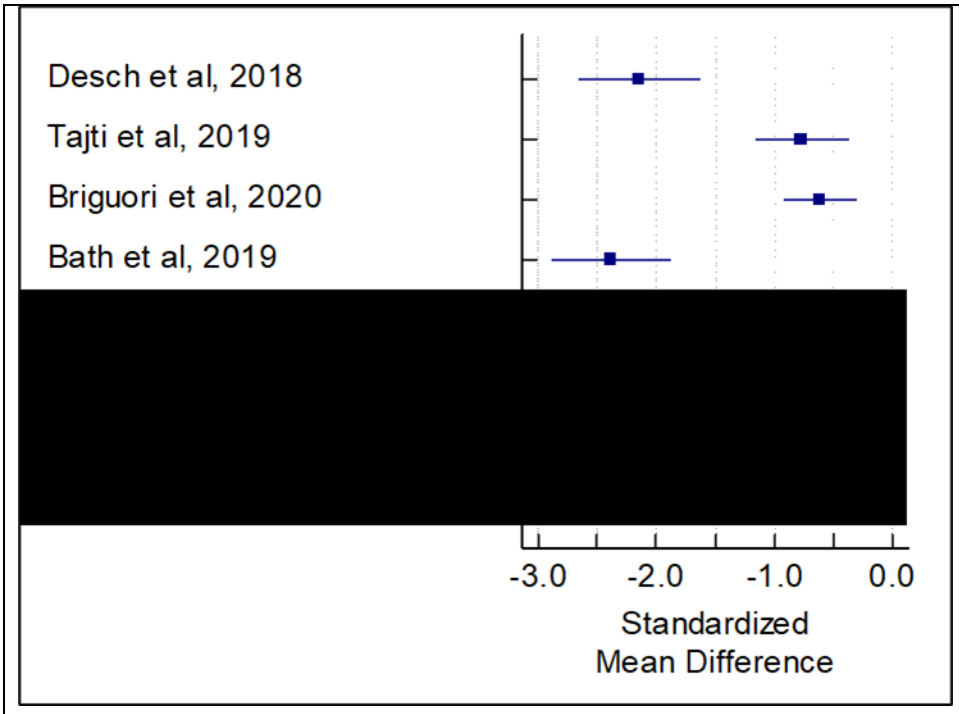
Study	N1	N2	Total	SMD	SE	95% CI	t	P	Weight (%)	
									Fixed	Random
Desch et al, 2018	48	48	96	-2.146	0.255	-2.652 to -1.640			9.16	19.31
Tajti et al, 2019	39	91	130	-0.769	0.196	-1.157 to -0.381			15.48	20.05
Briguori et al, 2020	90	90	180	-0.617	0.152	-0.917 to -0.317			25.79	20.51
Bath et al, 2019	49	59	108	-2.389	0.252	-2.888 to -1.891			9.41	19.36
[redacted]										

Test for heterogeneity

Q	84.2520
DF	4
Significance level	P < 0.0001
I^2 (inconsistency)	95.25%
95% CI for I^2	91.54 to 97.34

Publication bias

Egger's test	
Intercept	-13.6890
95% CI	-22.4299 to -4.9481
Significance level	P = 0.0155
Begg's test	
Kendall's Tau	-0.8000
Significance level	P = 0.0500



5) Pooled estimate of the standardized mean difference in absolute contrast volume (mL) in the intervention and control group calculated as **-1.463 (CI%95: -2.339: -0.588)** among 4 **published** double-arm studies. Two double-arm studies (Bunney et al, 2020 and Sattar et al, 2018 excluded from the meta-analysis because they did not report the standard deviation of mean in the abstract)

Meta-analysis: continuous measure

Variable for studies	Study
1. Intervention groups	
Variable for number of cases	DyeVert_n
Variable for mean	DyeVert_m
Variable for SD	DyeVert_sd
2. Control groups	
Variable for number of cases	Control_n
Variable for mean	Control_m
Variable for SD	Control_sd

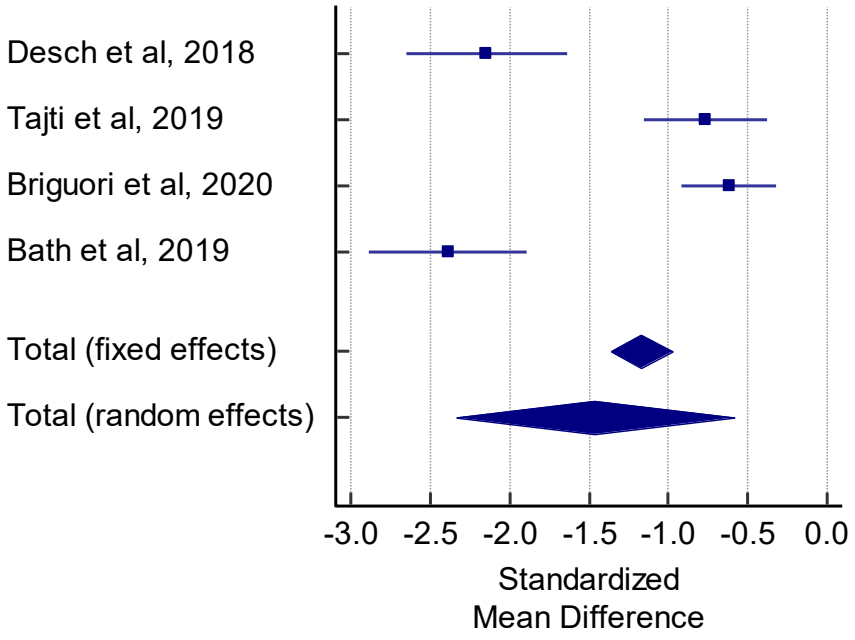
Study	N1	N2	Total	SMD	SE	95% CI	t	P	Weight (%)	
									Fixed	Random
Desch et al, 2018	48	48	96	-2.146	0.255	-2.652 to -1.640			15.31	24.45
Tajti et al, 2019	39	91	130	-0.769	0.196	-1.157 to -0.381			25.87	25.27
Briguori et al, 2020	90	90	180	-0.617	0.152	-0.917 to -0.317			43.09	25.78
Bath et al, 2019	49	59	108	-2.389	0.252	-2.888 to -1.891			15.73	24.50
Total (fixed effects)	226	288	514	-1.169	0.0998	-1.365 to -0.973	-11.722	<0.001	100.00	100.00
Total (random effects)	226	288	514	-1.463	0.446	-2.339 to -0.588	-3.282	0.001	100.00	100.00

Test for heterogeneity

Q	55.5661
DF	3
Significance level	P < 0.0001
I^2 (inconsistency)	94.60%
95% CI for I^2	89.25 to 97.29

Publication bias

Egger's test	
Intercept	-16.1696
95% CI	-34.7635 to 2.4242
Significance level	P = 0.0646
Begg's test	
Kendall's Tau	-0.6667
Significance level	P = 0.1742



6) [redacted]

Variable for studies	Studies
Variable for total number of cases	n
Variable for number of positive cases	CMV

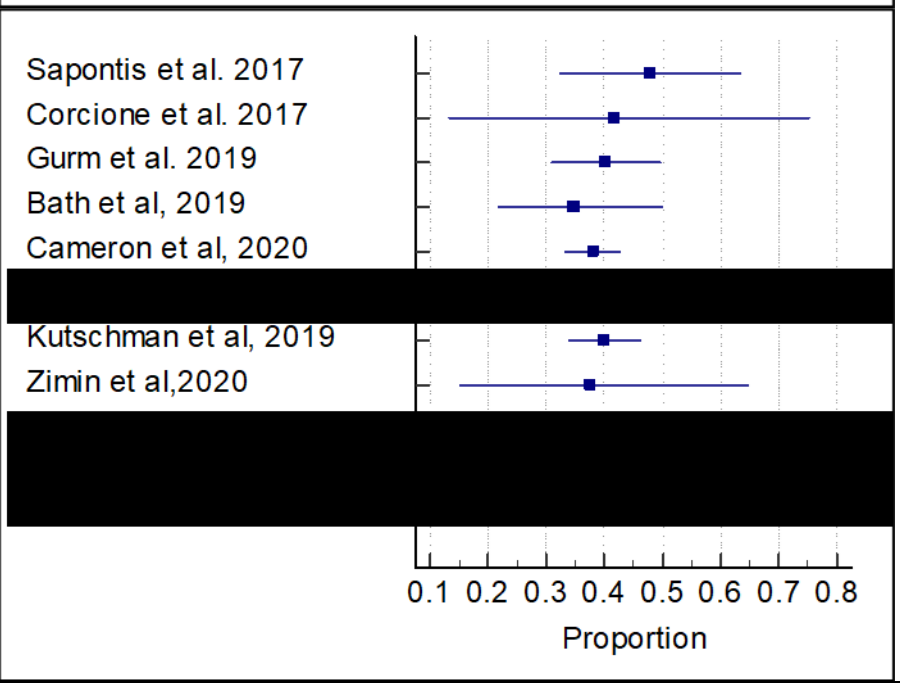
Study	Proportion (%)	95% CI
Sapontis et al. 2017	47.700	32.436 to 63.285
Corcione et al. 2017	41.800	13.260 to 75.189
Gurm et al. 2019	40.100	31.032 to 49.695
Bath et al, 2019	34.900	21.848 to 49.849
Cameron et al, 2020	38.000	33.354 to 42.815
[redacted]		
Kutschman et al, 2019	40.000	33.974 to 46.258
Zimin et al,2020	37.500	15.198 to 64.565
[redacted]		

Test for heterogeneity

Q	3.2965
DF	7
Significance level	P = 0.8563
I^2 (inconsistency)	0.00%
95% CI for I^2	0.00 to 31.87

Publication bias

Egger's test	
Intercept	0.4048
95% CI	-0.8492 to 1.6588
Significance level	P = 0.4597
Begg's test	
Kendall's Tau	0.2143
Significance level	P = 0.4579



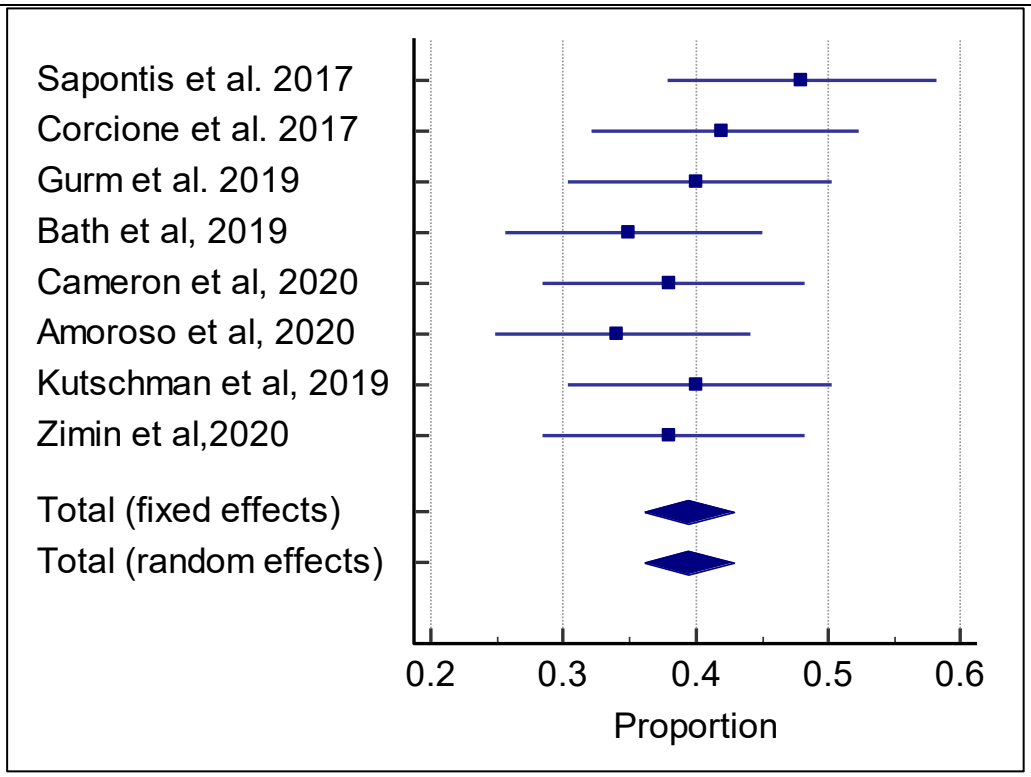
7) Pooled estimate of the contrast volume saving (%) in the intervention group among 8 **published** single-arm studies calculated as **39.43% (CI%95: 36.09%-42.82%)**

Variable for studies	Study
Variable for total number of cases	n
Variable for number of positive cases	contrast_volume_saving

Study	Proportion (%)	95% CI
Sapontis et al. 2017	48.000	37.901 to 58.221
Corcione et al. 2017	42.000	32.199 to 52.288
Gurm et al. 2019	40.000	30.329 to 50.279
Bath et al, 2019	34.900	25.638 to 45.082
Cameron et al, 2020	38.000	28.477 to 48.254
Amoroso et al, 2020	34.000	24.822 to 44.153
Kutschman et al, 2019	40.000	30.329 to 50.279
Zimin et al,2020	38.000	28.477 to 48.254
Total (fixed effects)	39.434	36.047 to 42.899
Total (random effects)	39.434	36.092 to 42.827

Test for heterogeneity

Q	5.5532
DF	7
Significance level	P = 0.5928
I^2 (inconsistency)	0.00%
95% CI for I^2	0.00 to 59.56


Sapontis et al. 2017
Corcione et al. 2017
Gurm et al. 2019
Bath et al, 2019
Cameron et al, 2020
Amoroso et al, 2020
Kutschman et al, 2019
Zimin et al,2020
Total (fixed effects)
Total (random effects)
0.2
0.3
0.4
0.5
0.6
Proportion

8) [redacted]

Meta-analysis: proportion

Variable for studies	Author
Variable for total number of cases	n
Variable for number of positive cases	Image_quality

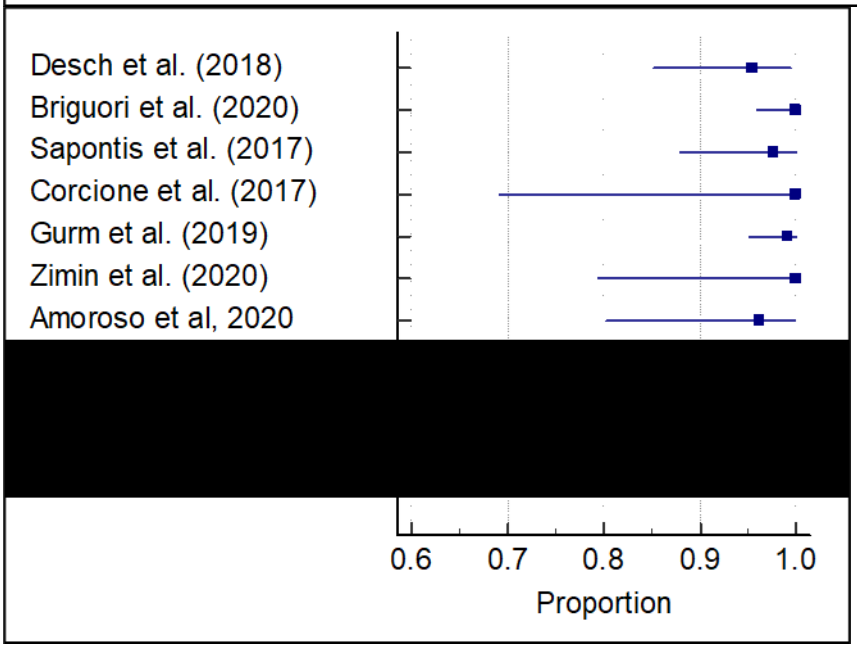
Study	Sample size	Proportion (%)	95% CI	Weight (%)	
				Fixed	Random
Desch et al. (2018)	48	95.500	85.262 to 99.382	9.78	9.78
Briguori et al. (2020)	90	100.000	95.984 to 100.000	18.16	18.16
Sapontis et al. (2017)	44	97.727	87.976 to 99.942	8.98	8.98
Corcione et al. (2017)	10	100.000	69.150 to 100.000	2.20	2.20
Gurm et al. (2019)	114	99.123	95.209 to 99.978	22.95	22.95
Zimin et al. (2020)	16	100.000	79.409 to 100.000	3.39	3.39
Amoroso et al, 2020	26	96.154	80.363 to 99.903	5.39	5.39

Test for heterogeneity

Q	6.7842
DF	7
Significance level	P = 0.4517
I^2 (inconsistency)	0.00%
95% CI for I^2	0.00 to 66.90

Publication bias

Egger's test	
Intercept	-0.6408
95% CI	-3.0093 to 1.7277
Significance level	P = 0.5326
Begg's test	
Kendall's Tau	0.0000
Significance level	P = 1.0000



9) Pooled estimate of the image quality (%) among 7 **published** clinical studies calculated as 98.20% (CI%95: 96.54%-99.33%)

Variable for studies	Author
Variable for total number of cases	n
Variable for number of positive cases	Image_quality

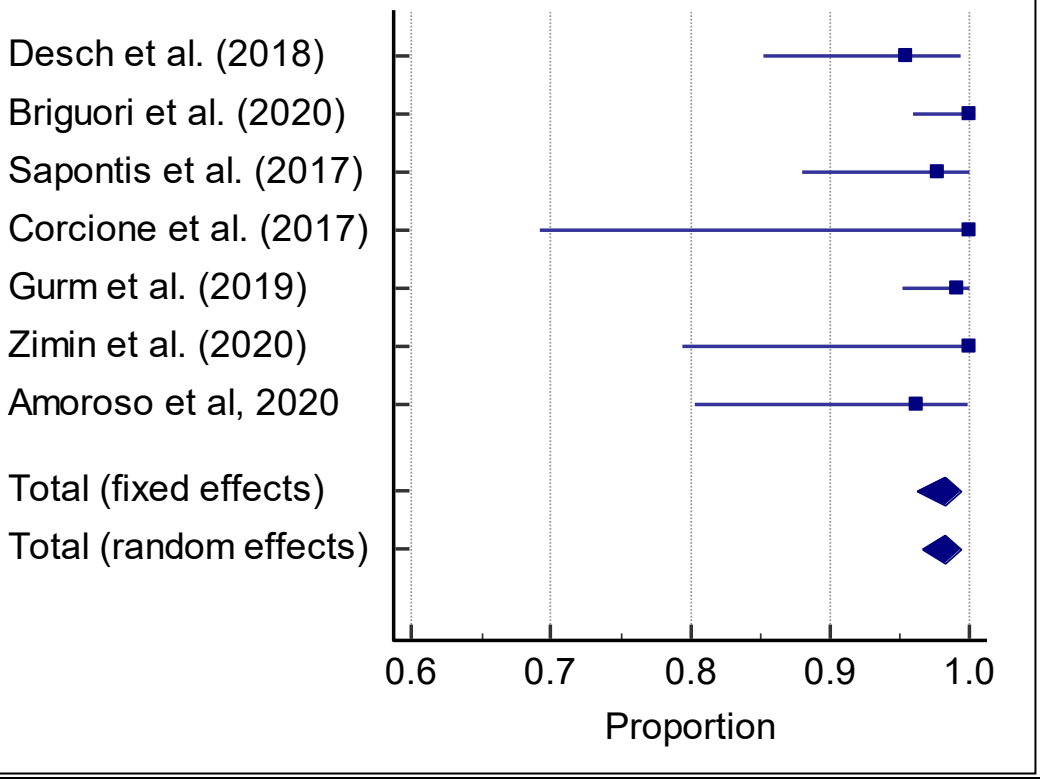
Study	Sample size	Proportion (%)	95% CI	Weight (%)	
				Fixed	Random
Desch et al. (2018)	48	95.500	85.262 to 99.382	13.80	13.94
Briguori et al. (2020)	90	100.000	95.984 to 100.000	25.63	25.49
Sapontis et al. (2017)	44	97.727	87.976 to 99.942	12.68	12.82
Corcione et al. (2017)	10	100.000	69.150 to 100.000	3.10	3.17
Gurm et al. (2019)	114	99.123	95.209 to 99.978	32.39	31.93
Zimin et al. (2020)	16	100.000	79.409 to 100.000	4.79	4.90
Amoroso et al, 2020	26	96.154	80.363 to 99.903	7.61	7.75
Total (fixed effects)	348	98.222	96.239 to 99.324	100.00	100.00
Total (random effects)	348	98.207	96.542 to 99.337	100.00	100.00

Test for heterogeneity

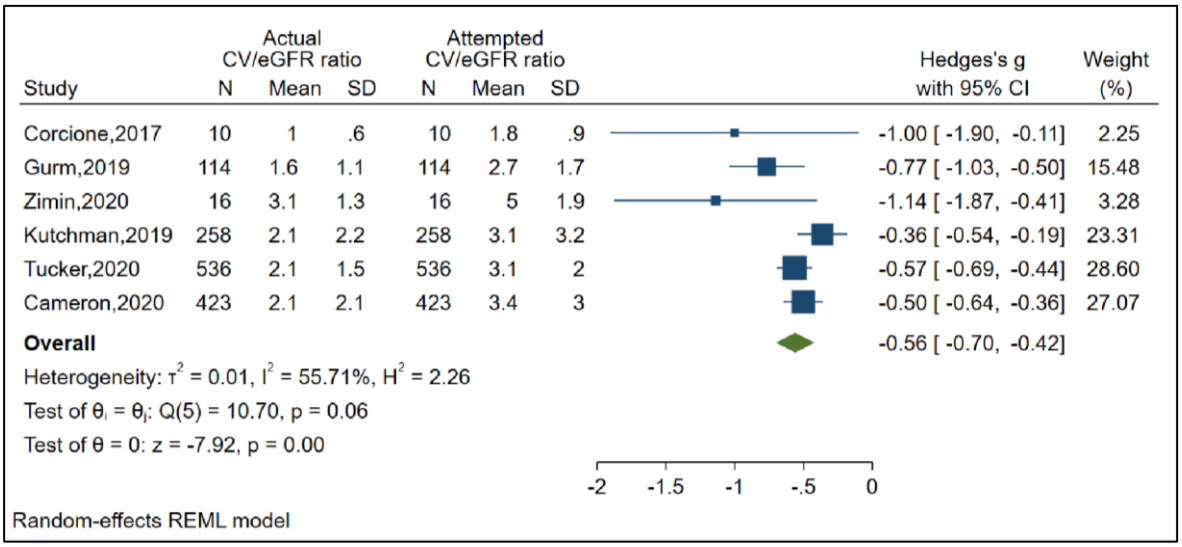
Q	6.1062
DF	6
Significance level	P = 0.4114
I^2 (inconsistency)	1.74%
95% CI for I^2	0.00 to 71.79

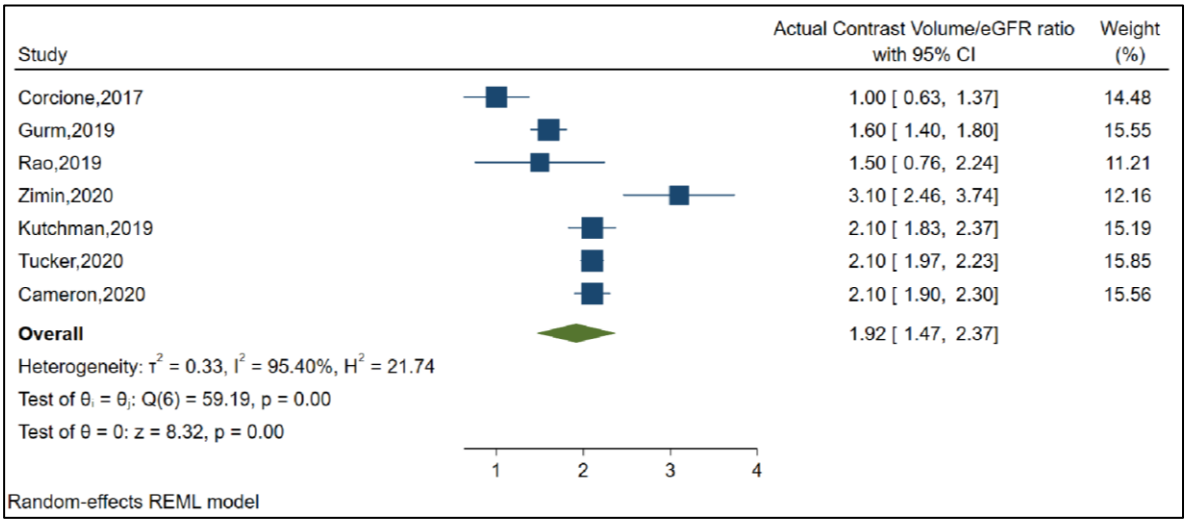
Publication bias

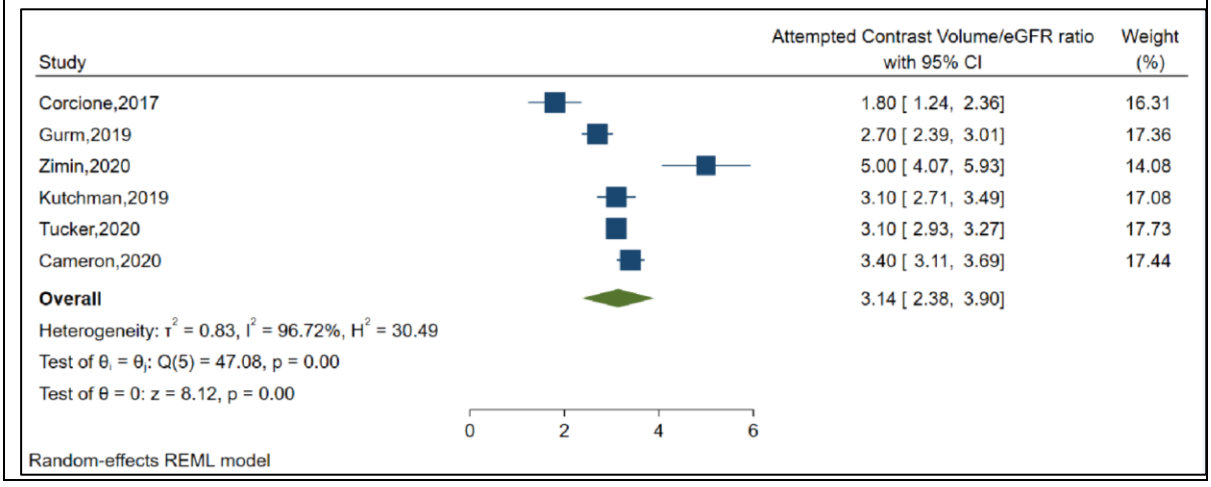
Egger's test	
Intercept	-1.2793
95% CI	-3.9244 to 1.3659
Significance level	P = 0.2689
Begg's test	
Kendall's Tau	-0.1429
Significance level	P = 0.6523



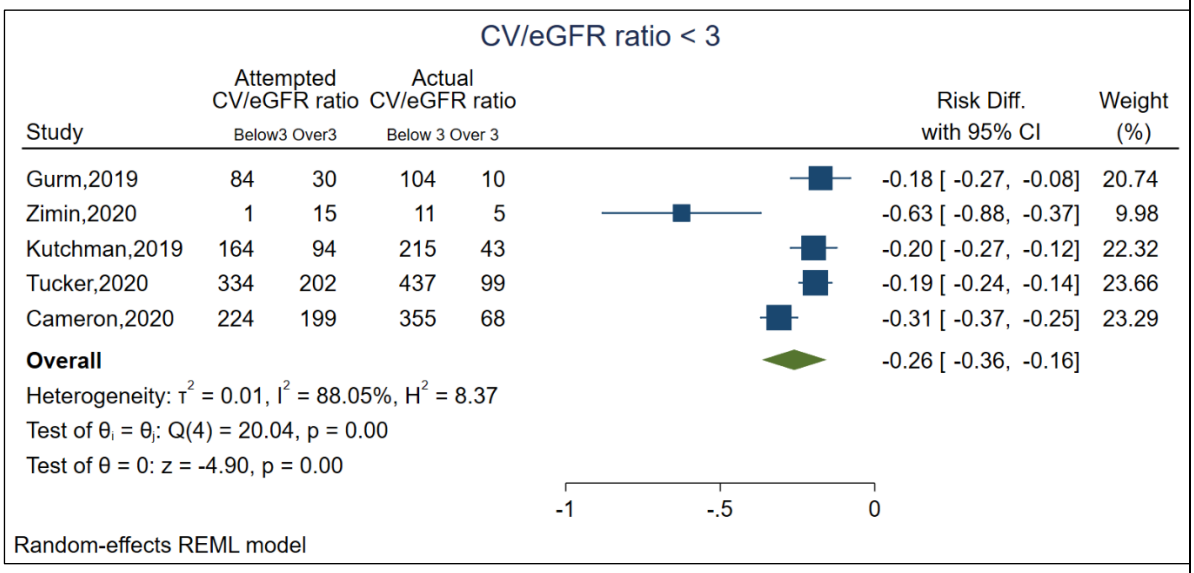
10) Pooled estimate of actual versus attempted CV/eGFR ratio

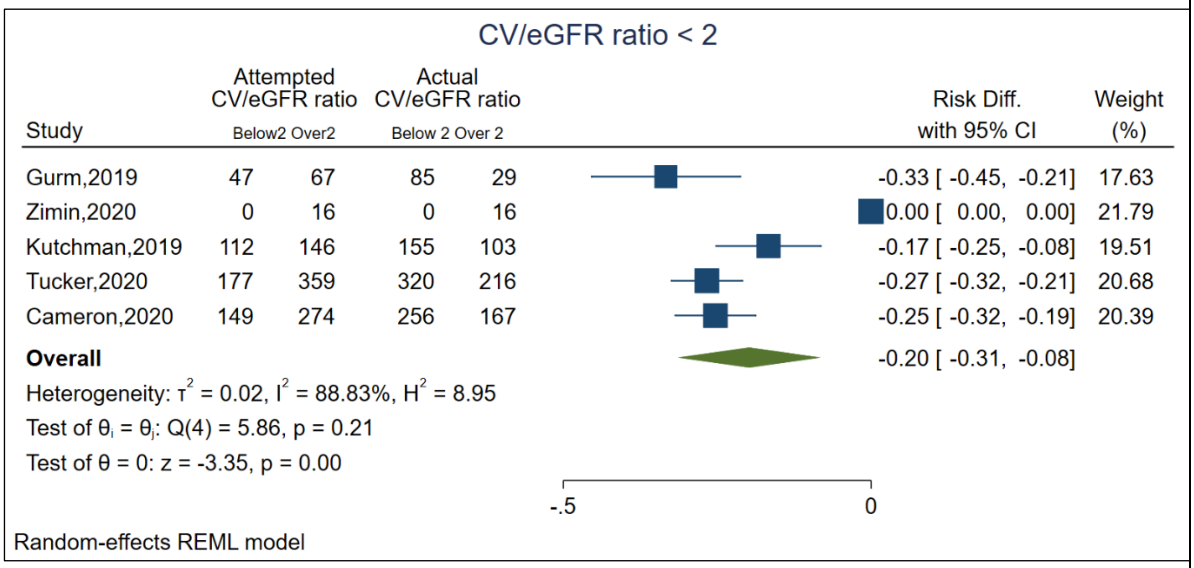


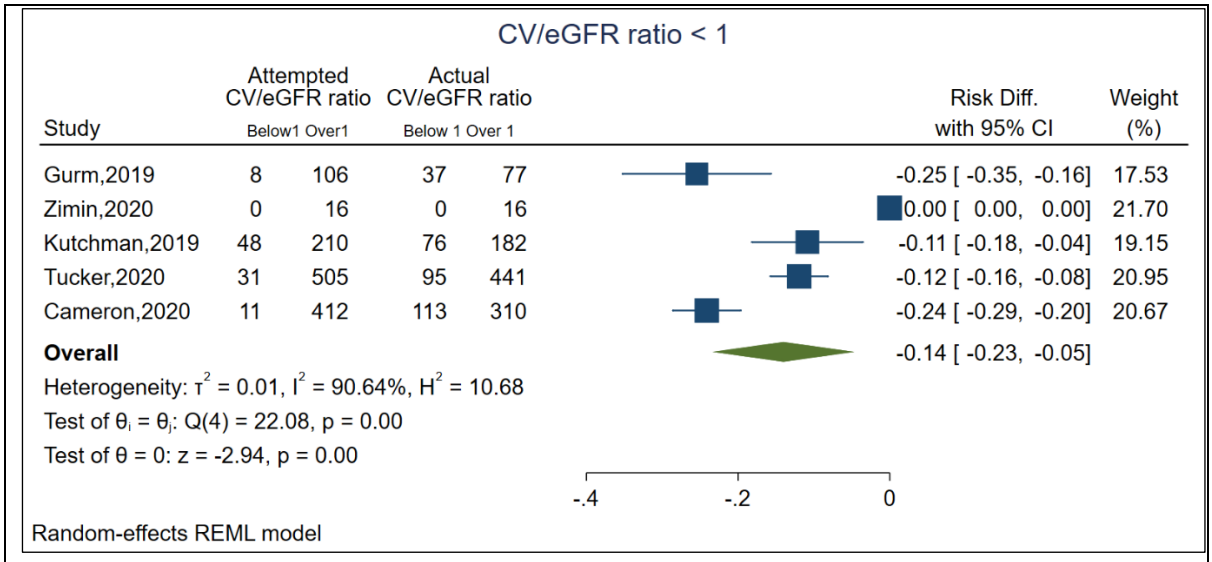




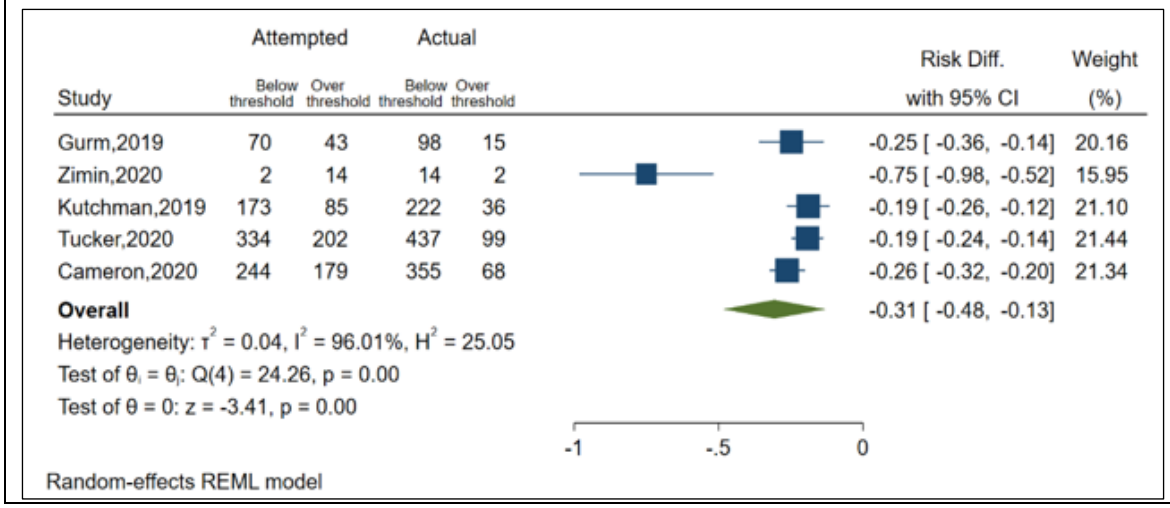
11) Pooled estimate of actual versus attempted CV/eGFR ratios by CV/eGFR group







12) Pooled estimate of contrast threshold management



NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

DyeVert for reducing contrast media in coronary and peripheral angiography

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Centre (EAC) report. It includes **brief** descriptions of the key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues the Committee may wish to discuss. It should be read along with the company submission of evidence and with the EAC assessment report. The overview forms part of the information received by the Medical Technologies Advisory Committee when it develops its recommendations on the technology.

Key issues for consideration by the Committee are described in section 6, following the brief summaries of the clinical and cost evidence.

This report contains information that has been supplied in confidence and will be redacted before publication. This information is highlighted in yellow. This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Comments from patient organisations
- Appendix D: Decision problem from the scope

1 The technology

DyeVert Contrast Reduction System (DyeVert Systems; Osprey Medical Inc) is a non-invasive system designed to reduce the amount of contrast media given during coronary and peripheral angiography, within a cardiac catheterisation or vascular radiology suite. There are 2 models of the DyeVert System. DyeVert Plus EZ Contrast Reduction System is compatible with manual contrast injection systems. DyeVert Power XT Contrast Reduction System is compatible with power or automated contrast injection systems. DyeVert Systems reduce the volume of contrast given using a valve that diverts excess contrast medium into a collection bag by providing flow resistance that increases with increased injection pressure. This reduces the total contrast media volume delivered during coronary or peripheral imaging, whilst maintaining adequate image quality. It is designed for people needing coronary or peripheral angiography at risk of acute kidney injury (AKI), including those with moderate to severe chronic kidney disease, diabetes, and heart failure. By reducing the amount of contrast volume given, DyeVert Systems aim to reduce the risk of contrast induced-AKI (CI-AKI).

The DyeVert Plus EZ system comprises 3 main components: a disposable module, a disposable smart syringe, and a reusable monitor. The smart syringe connects to a standard manifold system and is manually operated by the clinician to inject the dye into the module that contains the diversion valve. The monitor displays the total administered volume and total diverted volume (as a percentage of total volume) of contrast media in real-time through Bluetooth communication with the smart syringe. The DyeVert Power XT System consists of 2 components: the DyeVert Power XT assembly, which connects to a power injector, and the contrast collection bag. There is no reusable monitor on the power system, however, the contrast collection bag includes a digital display showing diverted dye volume.

The Plus EZ and Power XT Systems are both class I CE marked devices as of July 2018 and August 2020, respectively, for control, reduction and

modulation of injection of contrast media into the peripheral and cardiovascular system.

2 Proposed use of the technology

2.1 Disease or condition

Contrast induced AKI (CI-AKI) is a sudden deterioration in kidney function within 48 to 72 hours of administering intravenous iodine-based contrast agent, with the individual usually recovering over the following 5 days. Its incidence increases significantly in people with certain risk factors and can be associated with prolonged hospital stay, increased mortality and increased health care costs. The Kidney Disease, Improving Global Outcomes (KDIGO) clinical practice guideline for AKI defines acute kidney injury using any of the following criteria:

- a rise in serum creatinine of 26 micromol/litre or greater within 48 hours
- a 50% or greater rise in serum creatinine known or presumed to have occurred within the past 7 days
- a fall in urine output to less than 0.5 ml/kg/hour for more than 6 hours in adults and more than 8 hours in children and young people
- a 25% or greater fall in eGFR in children and young people within the past 7 days.

Acute kidney injury may result in renal replacement therapy being needed. Valle et al. (2017) reported that CI-AKI is associated with increased risk of death, myocardial infarction, bleeding, and recurrent renal injury.

2.2 Patient group

DyeVert Systems are intended for use in people at risk of CI-AKI as a result of cardiovascular or peripheral angiography. NICE's evidence review on acute kidney injury: prevention, detection and management states that CI-AKI is uncommon in the general population, with an incidence of 1 to 2%. Risk factors for CI-AKI include chronic kidney disease, critical illness, contrast-

enhanced imaging done as an emergency, older age, diabetes, use of nephrotoxic drugs and reduced kidney function (for example, if a person is dehydrated or has congestive heart failure). The risk of CI-AKI has been reported to be as high as 25% in certain people in at risk groups such as those with chronic kidney disease (CKD) and diabetes. Ozkok et al. (2017) reported that the incidence of CI-AKI is higher in people who already have CKD, in those who are critically ill and in people who have contrast enhanced imaging performed as an emergency. Gurm et al. (2016) suggests that a 30% reduction in contrast dye use could prevent 1 in 8 cases of CI-AKI.

2.3 Current management

NICE's guideline on acute kidney injury: prevention, detection and management states that increasing volume of contrast agent given is a risk factor for AKI. This means that people who are going to have contrast agents should be assessed for their risk of AKI for non-emergency imaging and that the risks of developing AKI are part of the routine discussion of risks and benefits of the imaging procedure. CKD should be investigated by measuring estimated glomerular filtration rate (eGFR) or by checking an eGFR result obtained within the past 3 months. Emergency imaging should not be delayed but clinicians should be aware of those who are at increased risk of developing CI-AKI including those with:

- CKD (adults with an eGFR less than 40 ml/min/1.73 m^2 are at particular risk)
- diabetes with CKD
- heart failure
- renal transplant
- aged 75 years or over
- hypovolaemia
- increasing volume of contrast agent

- intra-arterial administration of contrast medium with first-pass renal exposure.

The guideline encourages oral hydration before and after procedures that use intravenous iodine-based contrast media in adults at increased risk of contrast-induced acute kidney injury. It recommends considering intravenous volume expansion with either isotonic sodium bicarbonate or 0.9% sodium chloride if they are at particularly high risk. People at high risk include those that have:

- an eGFR less than 30 ml/min/1.73 m^2
- had a renal transplant
- received a large volume of contrast medium (for example, higher than the standard diagnostic dose or repeat administration within 24 hours)
- intra-arterial administration of contrast medium with first-pass renal exposure.

This guideline also suggests temporarily stopping angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in adults having iodine-based contrast media if they have chronic kidney disease with an eGFR less than 40 ml/min/1.73 m^2. It is recommended that the person's care be discussed with a nephrology team before offering iodine-based contrast media to adults on renal replacement therapy, including people with a renal transplant, but not to delay emergency imaging for this.

2.4 Proposed management with new technology

DyeVert Systems would be used to reduce the total contrast media volume delivered during coronary or peripheral imaging in those identified as being at risk of acute kidney injury. The device is designed to be used in addition to current risk reduction strategies, such as pre and post procedure hydration.

The DyeVert System can be added to the current equipment used for

angiography procedures. The DyeVert systems aim to reduce the volume of contrast given during an angiography procedure and allow intra-procedure contrast volume monitoring.

3 Company claimed benefits and the decision problem

These are described in the scope in Appendix D. Table 1 describes the company's proposed changes to the decision problem.

Table 1: Proposed changes to the decision problem

Decision problem	Variation proposed by company	EAC view of the variation
Special considerations, including those related to equality: People who have an ileostomy and older people are at an increased risk of becoming dehydrated and may need special consideration. Conditions including alcoholism and hypoalbuminemia may also affect the ability to have pre- and post-scan hydration.	Removed consideration of people with an ileostomy, alcoholism, hypoalbuminemia or other comorbidities that may increase the risk of dehydration	The company suggest that the DyeVert system is not recommended as a replacement or substitute for hydration.

4 The evidence

4.1 Summary of evidence of clinical benefit

The company identified 8 full text publications from its literature search. The company also included 9 studies presented as abstracts and or posters and 2 unpublished reports.

The EAC undertook its own literature search (see section 4.1 of the EAC's assessment report). The EAC agreed with the company's clinical evidence

inclusion criteria but reran the search to include economic studies. The EAC's revised search strategies are in Appendix A of the assessment report. The EAC included all of the studies submitted by the company and did not identify any further clinical studies.

Of the included full text studies there was 1 RCT, 3 prospective studies (2 of which were feasibility studies), and 4 retrospective studies (2 of which were comparative). Of the included posters and abstracts, 1 reported results from an RCT and the remaining 8 studies were retrospective (4 of which were comparative). Of the unpublished studies, one is a retrospective comparative study and one is a prospective comparative study.

Table 2: Studies included from the assessment

Studies included in the assessment	
Publication and study design	19 studies included by both: • 1 full text RCT (Desch et al. 2018) • 2 prospective comparative studies (Gurm et al. 2019a, Zimin et al. 2020) • 1 prospective single arm study (Sapontis et al. 2017) • 2 retrospective comparative studies (Briguori et al. 2020, Tajti et al. 2019) • 2 single arm retrospective studies (Bruno et al. 2019, Corcione et al. 2017) • 1 abstract reporting results from an RCT (Bath et al. 2019) • 8 abstracts reporting retrospective studies (Amoroso et al. 2020, Bunney et al. 2019, Cameron et al. 2020, Kutschman et al. 2019a, Kutschman et al. 2019b, Rao 2019, Sattar et al. 2018,Turner & Tucker 2020) • 2 unpublished studies, one retrospective comparative study (anonymous, AiC) and one prospective comparative study (market access evaluation, CiC).

The evidence for DyeVert systems comprises of 2 RCTs, one of which is presented as an abstract, and a further 8 comparative studies. The RCT by Desch et al. (2018) is reported as full text and is considered to be the highest quality study with a low risk of bias. The study was sufficiently powered and

the allocation sequence was random and stratified by access site (femoral or radial). Additionally, the baseline characteristics were not significantly different and image quality was assessed by a blinded independent reviewer. Of the 8 additional full-text studies included, 4 of these studies were retrospective which may limit the validity of their results and only 4 of them were comparative studies (2 prospective and 2 retrospective). Further to this, the EAC stated that all studies were limited by a lack of follow-up data. Most studies only collected results on the day of the procedure or until discharge, where stated. Briguori et al. (2020) did, however, collect data on major adverse events 1 month post procedure. Data on AKI risk reduction was also limited to only one published paper in addition to poster presentations.

The literature showed that using DyeVert led to around 17% to 41% less contrast media being injected compared to standard angiography. Image quality was also consistently maintained (or deemed acceptable) in all studies, where measured.

The study populations were similar in age (mean age of 61 to 72 years) and sex. Most study participants were men, individual studies ranging from 43% (Rao 2019) to 82% (Gurm et al. 2019a) of the participants. Experts confirm that men may be more likely to need angiography procedures which would account for the higher proportion seen. The mean baseline eGFR, where reported, ranged from 43ml/min/1.73m^2 (Gurm et al. 2019a) to 74ml/min/1.73m^2 (Briguori et al. 2019a). This equates to those who have chronic kidney disease (CKD) stage 3 and 2. Experts thought that DyeVert would most benefit those with CKD stage 4 and over. The economic model focuses on people with CKD stage 3 and 4. As a result, the study populations could be at a lower risk of developing CI-AKI on average.

The evidence predominantly covers coronary angiography with only 2 studies (Corcione et al. 2017 and Rao et al. 2019) including 9 individuals having peripheral angiography. The evidence was also limited for the DyeVert Power XT version of the device, with the first version of the device being used in 2

studies (Bruno et al. 2019 and Amoroso et al. 2020). No studies included the current version of the Power XT System.

Further to the published evidence provided, the company submitted 6 separate fixed and random effects meta-analyses. These covered relative risk of CI-AKI in the intervention compared to control group; rate of CI-AKI in the intervention and control groups; mean difference in absolute contrast volume (mL) in the intervention and control group; the contrast volume saving (%) in the intervention group; image quality; actual versus attempted contrast volume to eGFR ratio; and contrast threshold management. The results of key parameters evaluated in the meta-analyses are listed in table 3. The EAC reviewed the meta-analyses and considered them to be statistically robust. However, some of the analyses only included a small number of studies where the studies were deemed to be of low to moderate quality, with some parameters featuring data primarily from abstracts and posters. This means that caution is needed in interpreting the conclusions, especially regarding relative risk of CI-AKI. For some of the meta-analyses (relative risk of CI-AKI and rate of CI-AKI in the intervention and control groups) the sample size in some of the included studies is much greater than in others meaning that they dominate the results.

Table 3 Results of key parameters evaluated in the meta-analyses

Parameter evaluated	**Pooled estimates**
Relative risk of CI-AKI in the DyeVert group versus control group	0.59 (95%CI: 0.38-0.89)
Rate of CI-AKI in the DyeVert group	7.71% (95%CI: 5.36%-10.44%)
Rate of CI-AKI in the control group	12.55% (95%CI: 8.74%-16.93%)

Mean difference in absolute contrast volume (mL) in the DyeVert group compared to control group (when calculated as from 4 published double-arm studies)	-1.463 (95%CI: -2.339: -0.588)
Contrast volume saving (%) in the DyeVert group (when calculated from 8 published single-arm studies)	39.43% (95%CI: 36.09%-42.82%)
Image quality (%) (when calculated from 7 published clinical studies)	98.20% (95%CI: 96.54%-99.33%)

Table 4: Studies considered pivotal to the clinical and economic analysis

Study and design	Participants/ population	Intervention & comparator	Outcome measures and follow up	Results	Withdrawals	Funding	Comments
Desch et al. 2018 Prospective, single-centre, open label RCT.	96 adults scheduled for a diagnostic coronary angiogram due to suspected coronary artery disease or progression of known coronary artery disease Mean age (years): DyeVert: 68.6 Control: 66.2 Male (%): DyeVert: 58.3 Control: 58.3 Germany	Coronary angiography with and without the DyeVert System	Contrast media volume (CMV) reduction, image quality, total fluoroscopy time	Mean CMV: Significantly lower in the DyeVert group (36.9 ± 10.9 ml versus 62.5 ± 12.7 ml, p<0.001); a 41% reduction (EAC calculated). Image Quality: No significant difference in adequate quality images between the DyeVert and Control groups (95.5% vs 95%, p=0.74) Fluoroscopy Time: No significant difference in total fluoroscopy time (3.9 ± 3.9 minutes	2 withdrawals in the DyeVert group due to 1 individual not meeting study inclusion criteria and 1 error in contrast volume data collection	Company funded	This is a well-designed RCT with 1:1 randomisation ratio by permuted block randomisation stratified by access site (radial/femoral). Half of the study cohort underwent angiography using a radial approach. The study was adequately powered based on pilot results and a power of 80%. Blinding was not possible during the procedure. However, patients were not informed on treatment allocation and an independent reviewer assessed image quality.

				versus 3.7 ± 3.5 minutes, p=0.76).			
Briguori et al. 2020 Retrospective, observational, single-centre study.	451 adults with acute coronary syndrome who had urgent or immediate coronary angiography or angioplasty. Mean age (years): DyeVert: 62.5 Control: 63.5 Male (%): DyeVert: 71.0 Control: 76.5 Mean baseline eGFR (mL/min/1.73 m^2): DyeVert: 74 ± 26 Control: 79 ± 28 DyeVert cases were propensity	Angiography and angioplasty with and without the DyeVert PLUS EZ System	Contrast media volume reduction, incidence of acute kidney injury (AKI), correlation between CMV and maximal absolute difference in serum creatinine, length of hospital stay.	CMV: Significantly lower in the DyeVert group than in the Control group (99 [69-136] ml vs. 130 [120-188] ml; p <0.001). Mean CMV saved in DyeVert group: 38 ± 13%. AKI Incidence: 8% (7/90) of the DyeVert group and in 19% (17/90) of the Control group (odds ratio 0.37; p=0.047). Length of in-hospital stay: Longer in the Control group than in the DyeVert group (8	Not reported	Funding not specified	The authors note that the small sample size and the single-centre, observational, non-randomised design are limitations. However, the control group was selected from patients treated in the same centre and matched to the DyeVert group using propensity score matching. No blinding was discussed.

	matched to Controls, n=180 Italy			± 4 vs 6 ± 2 days; p =0.003). Correlation between CMV and maximal absolute difference in serum creatinine: Significant direct correlation between CMV and maximal absolute difference in serum creatinine was observed in the Control group but not in the DyeVert group.			
Sattar et al. 2018 Retrospective, observational, single-centre, real-world data analysis.	109 adults undergoing PCI Mean age (years): DyeVert: 69.5 Control: 71.3	PCI with DyeVert PLUS or standard angiography. 41 adults (38%) had PCI using DyeVert and 68 (62%)	Pre and post procedure serum creatinine, CI-AKI incidence, contrast volume usage	Mean pre and post procedure serum creatinine (SCr): DyeVert: 1.56mg/dl and 1.56mg/dl with mean decrease of 0.002 (p=0.97).	Not reported.	Funding not specified	This was an unblinded observational study. The inclusion criteria were those with CKD stage 3 and over (eGFR <60 mL/min). There was a low overall incidence of AKI during the study, so the sample size was

(poster presentation)	Male (%): DyeVert: 41.0 Control: 65.0 Mean eGFR (mL/min/1.73 m^2): DyeVert: 43.6 Control: 47.7 The US	underwent standard PCI		Without DyeVert: 1.51mg/dl and 1.54mg/dl respectively with mean increase of 0.35 (p=0.44) No significant change in SCr between groups. Incidence of CI-AKI: DyeVert:12.2% Control: 16.2% (p=0.56 pearson Chi Sq, odds ratio 0.71, 95% CI [0.23, 2.24]). Average CMV: DyeVert: 128ml Control: 155 ml 17% reduction (EAC calculated).			too small to detect a significant difference between groups. There was a lack of statistical analysis for some measurements collected including those on the baseline population characteristics and contrast dye usage.
Kutschman et al. 2019b Retrospective, observational, single-centre,	551 participants undergoing diagnostic coronary angiography and/or	DyeVert PLUS & DyeVert PLUS EZ as part of a CMV reduction programme	CMV reduction, AKI incidence, CMV given	Mean CMV given (ml): For PCI: 138 ml and contrast given (ml)/baseline	Not reported	Osprey Medical provided research support services	The results presented for DyeVert were part of a contrast media volume reduction programme and so may not be

real-world data analysis. (poster presentation)	percutaneous coronary interventions. Mean age (years): 66 ± 12 Male (%): 63 Mean eGFR (mL/min/1.73m^2): 64 ± 32 The US			eGFR ratio was 3.8ml/min/1.73m^2. For diagnostic cases: 66 mL and contrast given (mL)/baseline eGFR ratio was 1.7 ml/min/1.73m^2. Mean CMV reduction: 58ml or 40% of the attempted CMV per case AKI Incidence: 33% relative reduction in AKI compared to the cohort in which DyeVert was not used (6.9% vs 10.3%, respectively). In the Protocol Followed cohort, the overall relative reduction in AKI was 61%			representative of real-world practice.

				compared to the Protocol Not Followed cohort (p<0.02).			
Bunney et al. 2019 Retrospective, observational, single-centre, real world registry analysis. (Poster presentation) .	799 adults needing PCI. Mean age (years): DyeVert: 63 Control: 61 Baseline eGFR<60 (%): DyeVert: 55.2 Control: 23.5 The US	PCI with and without either the DyeVert or DyeVert PLUS Control n=770 DyeVert n=29 Those who had DyeVert underwent a higher proportion of complex PCIs with haemodynamic support (20% vs 3.7%).	Contrast media volume, non-risk adjusted rate of AKI	Mean CMV per procedure (ml): DyeVert:194 Control: 192 Non-risk-adjusted AKI rate (%): DyeVert: 3.45 Control: 9.35	Not reported	Funding not specified	This was a retrospective study presented as a poster with limited information and no statistical analysis. More individuals in the DyeVert group had poorer kidney function (baseline eGFR<60).
Abbreviations used: AKI: Acute Kidney Injury; CAG: Coronary Angiography; CI-AKI: Contrast-Induced Acute Kidney Injury; CKD: Chronic Kidney Disease; CM: Contrast Media; CMV: Contrast Media Volume; EAC: External Assessment Centre; eGFR: Estimated Glomerular Filtration Rate; OR: Odds Ratio; PCI: Percutaneous Coronary Intervention; RCT: Randomised Controlled Trial; SCr: Serum Creatinine.							

4.2 Summary of economic evidence

The company included 4 studies in their submission. The EAC conducted its own search (see section 4.1 and Appendix A of the EAC's assessment report) and found no additional economic evidence.

The studies included 1 full text publication (Javanbakht et al., 2020), 1 unpublished US study (Anon, 2020), 1 short article (Kutschman et al., 2019a) and 1 abstract (Turner and Tucker, 2020).

Javanbakht et al. (2020) was a UK-based cost-utility study. The analysis presented a decision tree followed by a Markov model with 6 health states for a hypothetical cohort of people with chronic kidney disease (CKD) stages 3 and 4 undergoing diagnostic coronary angiography (CAG) and percutaneous coronary intervention (PCI) comparing DyeVert PLUS EZ with standard care (a coronary angiographic procedure without DyeVert). This model has a lifetime time horizon with costs and benefits estimated in the decision tree for the first 3 months and in the Markov model for the remainder of the person's lifetime. Individuals in each model state incur associated health and social care costs and quality-adjusted life-years (QALYs). Simulated patients are at risk of death from all causes during any given cycle period. Risk of death is conditional on CKD stage, history of AKI and myocardial infarction (MI), gender, and age. Clinical data used to populate the model were from the literature or informed by expert clinical input. Costs were from the NHS and personal social services perspective. The base-case results showed that the DyeVert leads to a cost saving of £435 and improved effectiveness (+ 0.028 QALYs) over an individual's lifetime compared with current practice. DyeVert was therefore considered a dominant strategy. The EAC considered the model to be well constructed and the input parameters and results are reflective of the real-world and are consistent with the wider literature. The authors acknowledge that the model is limited by assuming that the risk of developing CI-AKI does not change dependent on procedure type (CAG and or PCI).

The remaining three studies report the use of DyeVert as part of CI-AKI reduction initiatives in the US. Kutschman (2019) reports results of 206 people treated with DyeVert undergoing CAG and or PCI. The study states that when the quality initiative (including DyeVert) was used, the initiative was cost saving due to AKI avoidance. However, the cost saving attributable to DyeVert alone is not identified and no details on economic analysis were included in the methods. Turner and Tucker (2020) reported an outcome analysis on a longitudinal, CI-AKI quality improvement programme where the DyeVert System was introduced for people with an eGFR < 60ml/min1.73m^2 or serum creatinine > 1.5 mg/dl. The CI-AKI rate reduced by 10.46%. The result showed the use of DyeVert to be cost-saving. However, there was no information on the economic model used to estimate these results.

De novo analysis

The company's economic model is based on the model used in Javanbakht et al. (2020). This publication closely aligns with the modelling undertaken for NICE CG169 in 2013 (which has subsequently been updated to NG148 in 2019). The company stated that there are a number of changes to the submitted model when compared to their published study. The relative risk of CI-AKI has been updated from 21.4% to 41% to reflect the results from the meta-analysis, all unit costs have been updated, and the baseline risk of CI-AKI was also updated in their scenario analyses.

The analysis included people with stage 3 or 4 CKD having coronary or peripheral angiography or percutaneous coronary intervention compared to current standard care (conventional hand or automated injection of contrast media in the absence of the DyeVert Systems). The risk of developing CI-AKI is considered the same for all coronary and peripheral angiography procedures.

The company's model structure includes a decision tree for the first 3 months followed by a Markov model for the remainder of the individual's lifetime. Following the angiography procedure, individuals may or may not experience

CI-AKI and then enter the Markov model. The Markov model then transitions between health states in 3-month cycles. The model includes the risk of further AKI episodes, myocardial infarction (MI), progression to CKD stage 5 and death. The EAC accepts the structure of the economic model and thinks the population included and comparator is valid and the model structure, cycle lengths and time horizon are appropriate.

Model parameters

Clinical parameters

Key assumptions in the base case analysis:

- The risk of developing CI-AKI after coronary or peripheral angiography and/or percutaneous coronary intervention are the same. This differs from the Javanbakht et al. (2020) which did not include peripheral angiography procedures.

- The baseline risk of CI-AKI is 30% for CKD stage 3 and 4 (Mehran et al. 2004). The EAC considers it unlikely that the baseline risk is this high if individuals are appropriately hydrated. The EAC have revised this risk to 8.74%.

- The age of the cohort is 65 years old based on company analysis of data from Hospital Episode Statistics (HES). This differs from the Javanbakht et al. (2020) which used an age of 72 years.

- Relative risk reduction of CI-AKI due to DyeVert is 0.41 and is based on the company's meta-analysis. The EAC accepts the statistical validity of the meta-analysis but notes that the strength of the included studies is low-to-moderate.

- The risk of adverse events is dependent on previous CI-AKI history. Simulated individuals are at risk of death from all causes during any

model cycle and risk of death is conditional on age, CKD stage, history of AKI and or MI.

- Further angiographies are not considered. The EAC thinks that this is an acceptable simplification but states that multiple uses of DyeVert is likely to underestimate the cost of DyeVert.

Costs and resource use

The main costs included in the model were the costs associated with CKD stage 5, myocardial infarctions and cost of CI-AKI. The cost parameters used in the company's model and changes made by the EAC are described in table 5.

Table 5: Cost parameters used in the economic model and EAC changes

Parameter	Company value	Source	EAC value	EAC comment
CKD stage 3-4/cycle	£260	Company estimation	£260	Unchanged
CKD stage 5 first cycle/cycle	£7,135	NHS reference costs, 2017/18, British National Formulary	£7,111	Error in cost inflation and in estimation of access costs amended
CKD stage 5 subsequent cycles/cycle	£6,113	NHS reference costs, 2017/18, British National Formulary	£5,783	EAC amended cost inflation
Cost of non-fatal MI (initial)/cycle	£6,364	Walker et al. (2016)	£6,727	EAC amended cost inflation
Cost of fatal MI (initial)/cycle	£6,364	Walker et al. (2016)	£2,209	EAC differentiated fatal and non-fatal MI
Cost of MI (subsequent)/cycle	£512	Walker et al. (2016)	£573	EAC amended cost inflation
CI-AKI cost of index admission	£2,834	NHS reference cost 2018/19 LA07H-P	£2,834	Unchanged

CI-AKI cost of extended hospital admission	£1,421	Excess bed day cost NHS reference cost 2017/18 inflated to current prices and Subramanian et al. (2007)	£1,375	EAC amended cost inflation
DyeVert Cost	£350	Company list price	£350	Unchanged
Cost of CAG	£1,786	NHS reference costs 2018/19 (HRG codes: EY40A, EY40B, EY40C, EY40D, EY41A, EY41B, EY41C, EY41D)	£1,786	Unchanged
Cost of PCI	£2,836	NHS reference costs 2018/19 (HRG codes: EY42A, EY42B, EY42C, EY42D, EY43A, EY43B, EY43C, EY43D, EY43E, EY43F)	£2,836	Unchanged

Results

The company's submission reports cost savings of £1350 per person when DyeVert is used. The company has also presented the impact of DyeVert on QALYs, showing a gain of 0.057 QALYs. The EAC's revised base case, found DyeVert to be cost saving by £23 with a QALY gain of 0.013, meaning that DyeVert is a dominant intervention.

Table 6: DyeVert Systems compared to standard care

Cost category	**Company's base-case**				**EAC's base-case**		
	Device	**Comparator**	**Difference***		**Device**	**Comparator**	**Difference***
Device cost per procedure	£350	£0	-£350		£350	£0	-£350

Adverse events (first 3 months of model)	£668	£947	£279		£275	£360	£85
Subsequent disease management	£24,164	£25,586	£1,421		£19,942	£20,230	£288
Total	**£28,701**	**£30,051**	**£1,350**		**£20,567**	**£20,590**	**£23**
QALYS	**6.05**	**6.00**	**0.057**		**6.05**	**6.04**	**0.013**
** A minus sign indicates device is more expensive than the comparator in this cost category.*							

Sensitivity Analysis

The company submitted a deterministic and a probabilistic sensitivity analysis. The deterministic sensitivity analysis results (Figure 3 of the EAC's assessment report) show that baseline probability of CI-AKI following the initial procedure and the risk reduction in experiencing CI-AKI following use of the DyeVert Systems have the biggest impact on cost, with a reduction in these values leading to a reduction in cost savings. The EAC's deterministic one-way sensitivity analysis also found these parameters to have the biggest impact on cost.

The EAC undertook further sensitivity analysis assuming a baseline risk of CI-AKI of 8.74%, a higher rate of 13.89% and a lower rate of 2.74%. For a starting age of 65, as used in the company submission, a lower rate of 2.74% would mean that DyeVert is no longer cost saving. The EAC calculated the breakeven risk of CI-AKI is 8.2%. If the baseline risk of CI-AKI is set to 8.74%, the breakeven cost of DyeVert would be £373. The clinical experts indicated that the probability of CI-AKI in those considered at risk is above 10%. However, they expressed uncertainty of the impact of factors that influence the risk of CI-AKI including volume of contrast media, the type of procedure and CKD stage. Further to this, the EAC undertook sensitivity analysis around the risk reduction of CI-AKI due to DyeVert. They found that the breakeven relative risk reduction was 38.5%. The company stated in their submission a relative risk reduction of 40%, according to data presented in their meta-analysis.

5 Ongoing research

There are 3 ongoing studies, 2 of which are RCTs and 1 is a single arm observational study. The EAC viewed that one on-going study DyeVert System and Contrast-induced Acute Kidney Injury (REMEDIALIV), (NCT04714736), which is due to be completed in 2023, could fulfil the need

for longer follow-up as it measures CI-AKI rates for 30 days post-procedure. See section 8.2 of the EAC's assessment report.

6 Issues for consideration by the Committee

Clinical evidence

- NG147 refers to contrast induced AKI and DG37 refers to post contrast associated AKI. Experts have also referred to contrast associated AKI. What is the most appropriate terminology to use based on the association between AKI associated and the use of contrast media?

- There is limited clinical evidence on the use of DyeVert systems during peripheral angiography. How generalisable is the evidence on coronary angiography for peripheral angiography? Would clinical decision-making to use the DyeVert system differ between coronary and peripheral angiography?

- Can the effectiveness of the Power XT device be assumed as equivalent to the PLUS EZ device? Should the devices be considered individually or together as the DyeVert system?

- How certain are the results of the key clinical outcomes associated with the use of the DyeVert systems presented in the clinical studies? Is the length of follow up in the clinical evidence appropriate?

- The experts have advised that DyeVert would be considered for people with CKD stage 4 and over. The clinical studies predominantly include people with CKD stage 2 to 3. Is the data from these populations relevant and does it support clinical decision-making in other populations?

Cost evidence

- The probability of CI-AKI and the relative risk reduction of CI-AKI due to the use of the DyeVert system have the biggest impact on the results of

the cost analysis. Can a CI-AKI risk reduction of 8.74% be considered appropriate and is the relative risk reduction of CI-AKI due to DyeVert based on a meta-analysis robust?

- Clinical experts stated that they would only use the device in people with CKD stage 4 and over. Is the model, capturing those with CKD stage 3 and 4 appropriate and can the results of the cost analysis predict the likely cost impact of use of the DyeVert system in people with CKD stage 4 and over in the NHS?

- What are the implications, if any, of analysing the costs of peripheral angiography and coronary angiography together?

7 Authors

Charlotte Pelekanou, Technical Analyst

Lizzy Latimer, Technical Adviser

NICE Medical Technologies Evaluation Programme

March 2021

Appendix A: Sources of evidence considered in the preparation of the overview

A Details of assessment report:

- Erskine J et al. DyeVert for reducing contrast media in coronary and peripheral angiography, March 2021.

B Submissions from the following sponsors:

- Osprey Medical Inc.

C Related NICE guidance

- Acute Kidney Injury risk assessment, Tests to help assess risk of acute kidney injury for people being considered for critical care admission (ARCHITECT and Alinity i Urine NGAL assays, BioPorto NGAL test and NephroCheck test) NICE diagnostics guidance DG39 (2020). Available from https://www.nice.org.uk/guidance/dg39
- Kidney function test, Point-of-care creatinine devices to assess kidney function before CT imaging with intravenous contrast NICE diagnostics guidance DG37 (2019). Available from https://www.nice.org.uk/guidance/dg37
- Acute kidney injury, Acute kidney injury: prevention, detection and management NICE guideline NG148 (2019). Available from https://www.nice.org.uk/guidance/ng148
- Acute kidney injury, Acute kidney injury (2014) NICE quality standard QS76 (2014). Available from https://www.nice.org.uk/guidance/qs76

D References

Amoroso G, Jung C, Abell C. (2020) First European experience using a novel contrast reduction system during coronary angiography with automated contrast injection. EuroIntervention. 16(Suppl):387.

Bath A, Bobba K, Gautam S, et al. (2019) Use of DyeVert PLUS to reduce contrast exposure in high-risk patients undergoing coronary angiography. Journal of the American College of Cardiology. 73(9 Supplement 1):1193.

Briguori C, Golino M, Porchetta N, et al. (2020) Impact of a contrast media volume control device on acute kidney injury rate in patients with acute coronary syndrome. Catheterization and cardiovascular interventions.

Bruno RR, Nia AM, Wolff G, Erkens et al. (2019) Early clinical experiences with a novel contrast volume reduction system during invasive coronary angiography. IJC Heart and Vasculature.;23:100377.

Bunney R, Saenger E, Shah C et al. (2019) Contemporary use of contrast dye reduction technology in a tertiary academic hospital: patient characteristics and acute kidney injury outcomes following percutaneous coronary interventions. American College of Cardiology (ACC) Quality Summit; March 2019; New Orleans, LA.

Cameron A, Espinosa T. (2020) Reducing Contrast-Induced Acute Kidney Injury in a Cardiac Catherization Laboratory: A Quality Improvement Initiative. Society for Cardiac Angiography & Interventions Scientific Sessions Virtual Conference Catheterization and Cardiovascular Interventions. 95(Suppl 2):S25-S6.

Corcione N, Biondi-Zoccai G, Ferraro P et al. (2017) Contrast Minimization With the New-Generation DyeVert Plus System for Contrast Reduction and Real-Time Monitoring During Coronary and Peripheral Procedures: First Experience. The Journal of invasive cardiology. 29(8):259-62.

Desch S, Fuernau G, Pöss J, et al. (2018) Impact of a novel contrast reduction system on contrast savings in coronary angiography – The DyeVert randomised controlled trial. International Journal of Cardiology. 257:50-53.

Gurm HS, Mavromatis K, Bertolet B et al. (2019) Minimizing radiographic contrast administration during coronary angiography using a novel contrast

reduction system: A multicenter observational study of the DyeVertTM plus contrast reduction system. Catheterization and Cardiovascular Interventions. 93(7):1228-35.

Javanbakht M, Hemami M, Mashayekhi A, et al. (2020) DyeVert™ PLUS EZ System for Preventing Contrast-Induced Acute Kidney Injury in Patients Undergoing Diagnostic Coronary Angiography and/or Percutaneous Coronary Intervention: A UK-Based Cost–Utility Analysis. PharmacoEconomics - Open. 4(3):459-472.

KDIGO. (2012) Kidney International Supplements(2012)2,2; doi:10.1038

Kutschman R. (2019) Clinical and Economic Outcomes of a Comprehensive Clinical Quality Initiative for Reducing Acute Kidney Injury in Chronic Kidney Disease Patients Undergoing Coronary Angiography. Journal of the American College of Cardiology. 74(13 Supplement):B605.

Kutschman R, Davison L, Beyer J. (2019) Comprehensive clinical quality initiative for reducing acute kidney injury in at-risk patients undergoing diagnostic coronary angiogram and/or percutaneous coronary interventions. Catheterization and Cardiovascular Interventions. 93(Supplement 2):S150.

Mehran, R., Aymong, e. D., Nikolsky, e., et al. (2004). A simple risk score for prediction of contrast induced nephropathy after percutaneous coronary intervention: development and initial validation. J Am Coll Cardiol, 44, 1393-9.

NICE. (2019) Acute kidney injury: prevention, detection and management (NG148). Available at https://www.nice.org.uk/guidance/ng148

Rao S. (2019) DyeVert Plus Contrast Reduction System Use in Patients Undergoing Highly Complex Peripheral Vascular Interventions. Journal of Vascular and Interventional Radiology. 30:e16.

Sapontis J, Barron G, Seneviratne S et al. (2017) A first in human evaluation of a novel contrast media saving device. Catheterization and cardiovascular

interventions: official journal of the Society for Cardiac Angiography & Interventions. 90(6):928-34.

Sattar A, Darby M, Schnatz R, et al. (2019). Impact of using DyeVert PLUS on incidence of acute kidney injury after cardiac catheterization with coronary interventions in high-risk patients. American College of Cardiology Annual Meeting; April 2018; Charleston, WV. 2018.

Tajti P, Xenogiannis I, Hall A et al. (2019) Use of the DyeVert System in Chronic Total Occlusion Percutaneous Coronary Intervention. The Journal of invasive cardiology. 31(9):253-9.

Turner C, Tucker PA. (2020) Real-world impact of a quality improvement program for AKI prevention in the cardiac cath LAB. Catheterization and Cardiovascular Interventions. 95(Supplement 2): S112-S3.

Valle JA, McCoy LA, Maddox TM, et al. (2017) Longitudinal risk of adverse events in patients with acute kidney injury after percutaneous coronary intervention: insights from the national cardiovascular data registry. Catheterization and Cardiovascular Interventions 10(4): e004439. doi:10.1161/CIRCINTERVENTIONS.116.004439.

Walker, S., Asaria, M., Manca, A et al. (2016). Long-term healthcare use and costs in patients with stable coronary artery disease: a population-based cohort using linked health records (CALIBER). Eur Heart J Qual Care Clin Outcomes, 2, 125-40.

Zimin VN, Jones MR, Richmond Iv et al. (2020) A feasibility study of the DyeVert TM plus contrast reduction system to reduce contrast media volumes in percutaneous coronary procedures using optical coherence tomography. Cardiovascular revascularization medicine: including molecular interventions.

Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their Specialist Society, Royal College or Professional Body. The advice received is their individual opinion and does not represent the view of the society.

Dr Yahya al-Najjar

Consultant Interventional Cardiologist, Manchester University NHS Foundation Trust.

Professor Azfar Zaman

Consultant Cardiologist, Freeman Hospital - Newcastle Hospitals NHS Foundation Trust.

Dr Sudhir Rathore

Consultant Cardiologist, NHS Frimley Health Foundation Trust.

Dr Bella Hausen

Interventional Radiology and Vascular Consultant, Lancashire University Teaching Health Trusts NHS.

Dr Daniel Conroy

Consultant Radiologist, Belfast Health and Social Care Trust.

Dr Mark Devonald

Consultant Nephrologist, Liverpool University Hospitals Foundation Trust.

Please see the clinical expert statements included in the pack for full details.

Appendix C: Comments from patient organisations

Advice and information was sought from patient and carer organisations. The following patient and carer organisations responded:

The following patient organisations were contacted and no response was received.

- British Cardiac Patients Association (BCPA)
- British Heart Foundation (BHF)
- Diabetes UK
- Kidney Care UK
- Kidney Research UK
- Pumping Marvellous

Appendix D: decision problem from scope

Population	People at risk of contrast-induced acute kidney injury (CI-AKI) who need coronary or peripheral angiography with contrast media.
Intervention	DyeVert Systems used as an adjunct to standard NHS clinical practice.
Comparator(s)	Conventional hand or automated injection of contrast agent.
Outcomes	The outcome measures to consider include: • CI-AKI incidence • CI-AKI severity • Measures of renal function, such as serum creatinine concentration, estimated glomerular filtration rate and urine output • Volume of contrast agent received and diverted • Image quality • Length of hospital stay and rates of re-admission as a result of CI-AKI or acute heart failure (suspected cause by contrast agent) • Rate of acute heart failure with suspected cause by contrast agent • Rate of renal replacement therapy, intensive care transfer or mortality as a result of CI-AKI • Device-related adverse events.
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which can include scenarios in which different numbers and combinations of devices are needed.
Subgroups to be considered	Identifiable subgroups who may be at particularly high risk of developing CI-AKI.
Special considerations, including those related to equality	People with chronic kidney disease, heart failure, diabetes, and renal transplant would be more at risk of CI-AKI. Kidney disease occurs more frequently in males, people over the age of 60, and those of African-Caribbean, African or South-Asian family origin. People who have an ileostomy and older people are at an increased risk of becoming dehydrated and may need special consideration. Conditions including alcoholism and hypoalbuminemia may also affect the ability to have pre- and post-scan hydration.

Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristic?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No
Any other special considerations	Not applicable	

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance scope

DyeVert Systems for reducing contrast media in coronary and peripheral angiography

1 Technology

1.1 Description of the technology

DyeVert Contrast Reduction System (DyeVert Systems; Osprey Medical Inc) is a non-invasive system designed to reduce the amount of contrast media given during coronary and peripheral angiography, within a cardiac catheterisation or vascular radiology suite. There are 2 DyeVert Systems models. DyeVert Plus EZ Contrast Reduction System is compatible with manual contrast injection systems. DyeVert Power XT Contrast Reduction System is compatible with power or automated contrast injection systems.

DyeVert Systems reduces contrast given using a modifiable valve which responds to injection pressure and fluid pathway resistance. This reduces the total contrast media volume delivered during coronary or peripheral imaging, whilst maintaining adequate image quality.

It is designed for people at risk of acute kidney injury (AKI), including those with moderate to severe chronic kidney disease, diabetes, and heart failure. By reducing the amount of contrast volume given, DyeVert Systems aims to reduce the risk of contrast induced-AKI (CI-AKI).

The DyeVert PLUS EZ System consists of:

- A disposable module, which attaches to an injection port, has a standard valve which allows for opening and closing the system to the manifold, a

reservoir for storing excess dye and a contrast collection bag for disposing of diverted contrast at the end of the procedure.

- A disposable smart syringe which connects to the manifold to deliver dye injections.

- A reusable monitor which shows real-time dye delivery amounts including volume per injection, cumulative volume delivered and volume remaining until threshold dose is reached. The monitor also allows predefined maximum contrast media thresholds to be entered and provides a historical contrast use summary.

The DyeVert PLUS EZ disposable module is positioned between the manual syringe (smart syringe) and the injection port (manifold). The clinician controls the injection of contrast manually using the smart syringe. Excess contrast not needed for diagnostic or therapeutic purposes is removed. The clinician is still in control of the amount of dye given and the redirection valves can be closed to give more contrast. The monitor display can help inform the clinician's decisions about how much dye to give.

The DyeVert Power XT Contrast Reduction System consists of a disposable module and smart bag. The disposable module, which has a diversion line and 2 catheter size-dependent diversion valves, attaches to the automated injector connection and the angiographic catheter used to deliver contrast media into the vascular system. The smart bag collects and digitally displays diverted contrast media volume in real-time throughout the procedure.

1.2 Relevant diseases and conditions

DyeVert Systems is intended for use in people at risk of CI-AKI as a result of cardiovascular or peripheral angiography.

NICE's evidence review on acute kidney injury: prevention, detection and management states that CI-AKI is uncommon in the general population, with an incidence of 1 to 2%. CI-AKI occurs within 72 hours of receiving iodinated contrast media, with the individual usually recovering over the following 5

days. Its incidence increases significantly in people with certain risk factors and is associated with prolonged hospital stay, increased mortality and increased health care costs. The risk of CI-AKI has been reported to be as high as 25% in certain people in at risk groups such as those with chronic kidney disease (CKD) and diabetes.

Ozkok et al (2017) reported that the incidence of CI-AKI is higher in people who already have CKD, in those who are critically ill and in people who have contrast enhanced imaging performed as an emergency. Short and long-term mortality rates have been found to be significantly higher in people with CI-AKI compared with those without CI-AKI. A history of CI-AKI may be associated with the development of CKD and progression to end stage renal disease. Prasad et al (2020) found that CI-AKI led to an increased risk of in-hospital mortality and hospital readmission. This incidence was higher in people with CKD. Gurm et al (2016) suggests that a 30% reduction in contrast dye use could prevent 1 in 8 cases of CI-AKI.

1.3 Current management

NICE's guideline on acute kidney injury: prevention, detection and management states that increasing volume of contrast agent given is a risk factor for AKI. This means that people who are going to have contrast agents should be assessed for their risk of AKI for non-emergency imaging and that the risks of developing AKI are part of the routine discussion of risks and benefits of the imaging procedure. CKD should be investigated by measuring estimated glomerular filtration rate (eGFR) or by checking an eGFR result obtained within the past 3 months. Emergency imaging should not be delayed but clinicians should be aware of those who are at increased risk of developing CI-AKI including those with:

- CKD (adults with an eGFR less than 40 ml/min/1.73 m^2 are at particular risk)
- diabetes with CKD
- heart failure

- renal transplant
- aged 75 years or over
- hypovolaemia
- increasing volume of contrast agent
- intra-arterial administration of contrast medium with first-pass renal exposure.

NICE's diagnostic guideline on point-of-care creatinine devices to assess kidney function before CT imaging with intravenous contrast states that the threshold for eGFR at which there is a risk of developing CI-AKI varies across different guidelines. These thresholds range between an eGFR less than 30 ml/min/1.73 m^2 (The Royal Australian and New Zealand College of Radiologists iodinated contrast guidelines, which have been endorsed by the Royal College of Radiologists) and an eGFR less than 60 ml/min/1.73 m^2 (Prevention of Contrast Induced Acute Kidney Injury (CI-AKI) In Adult Patients). Clinical experts suggested that people with an eGFR of less than 30 ml/min/1.73 m^2 are at highest risk of developing CI-AKI.

NICE's guideline on acute kidney injury: prevention, detection and management encourages oral hydration before and after procedures that use intravenous iodine-based contrast media in adults at increased risk of contrast-induced acute kidney injury. It also recommends considering intravenous volume expansion with either isotonic sodium bicarbonate or 0.9% sodium chloride if they are at particularly high risk. People at high risk include those that have:

- an eGFR less than 30 ml/min/1.73 m^2
- had a renal transplant
- received a large volume of contrast medium (for example, higher than the standard diagnostic dose or repeat administration within 24 hours)

- intra-arterial administration of contrast medium with first-pass renal exposure.

This guideline also suggests temporarily stopping angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in adults having iodine-based contrast media if they have chronic kidney disease with an eGFR less than 40 ml/min/1.73 m^2. It is recommended that the person's care be discussed with a nephrology team before offering iodine-based contrast media to adults on renal replacement therapy, including people with a renal transplant, but not to delay emergency imaging for this.

The Kidney Disease, Improving Global Outcomes (KDIGO) clinical practice guideline for AKI recommends using either iso-osmolar or low-osmolar iodinated contrast media (rather than high-osmolar) in people at increased risk of CI-AKI. The European Society of Urogenital Radiology guidelines on contrast media recommends that the lowest dose of contrast medium consistent with a diagnostic result be used and that low or iso-osmolar contrast media be selected. For at-risk people, the guidelines also recommend considering an alternative imaging method without iodinated contrast media as well as preventative hydration.

1.4 Regulatory status

The DyeVert PLUS EZ Contrast Reduction System and DyeVert Power XT Contrast Reduction System first received their CE mark in August 2014 as a class I device for control, reduction and modulation of injection of contrast media into the peripheral and cardiovascular system.

1.5 Claimed benefits

The benefits to patients claimed by the company are:

- Reduction in CI-AKI incidence
- Contrast agent volume monitoring
- Maintaining good image quality

- Total contrast media volume reduction (on average 40%) because of diversion of contrast agent on each injection
- Contrast agent reflux reduction
- More likely to get contrast administration at or below the maximum contrast media dose
- Reduction in CI-AKI associated morbidity, in-hospital mortality and post-procedure readmissions.

The benefits to the healthcare system claimed by the company are:

- Real-time contrast media dose monitoring relative to the maximum dose target and recording
- Reduced number of bed stays or length of stay in hospital post percutaneous coronary intervention and angiography
- Reduced costs for treating CI-AKI
- Reduced associated treatment costs including drugs or readmissions due to lower long-term adverse events worsening chronic kidney disease, developing major adverse kidney events, end stage renal disease, and major cardiovascular events
- Reduced clinical staff time.
- Improved adherence to recommended guidelines for contrast minimisation as part of an initiative to reduce CI-AKI
- Improved access of coronary and peripheral angiography to people with CI-AKI risk factors.

2 Decision problem

Population	People at risk of contrast-induced acute kidney injury (CI-AKI) who need coronary or peripheral angiography with contrast media.
Intervention	DyeVert Systems used as an adjunct to standard NHS clinical practice.
Comparator(s)	Conventional hand or automated injection of contrast agent.
Outcomes	The outcome measures to consider include: • CI-AKI incidence • CI-AKI severity

	• Measures of renal function, such as serum creatinine concentration, estimated glomerular filtration rate and urine output • Volume of contrast agent received and diverted • Image quality • Length of hospital stay and rates of re-admission as a result of CI-AKI or acute heart failure (suspected cause by contrast agent) • Rate of acute heart failure with suspected cause by contrast agent • Rate of renal replacement therapy, intensive care transfer or mortality as a result of CI-AKI • Device-related adverse events.	
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which can include scenarios in which different numbers and combinations of devices are needed.	
Subgroups to be considered	Identifiable subgroups who may be at particularly high risk of developing CI-AKI.	
Special considerations, including those related to equality	People with chronic kidney disease, heart failure, diabetes, and renal transplant would be more at risk of CI-AKI. Kidney disease occurs more frequently in males, people over the age of 60, and those of African-Caribbean, African or South-Asian family origin. People who have an ileostomy and older people are at an increased risk of becoming dehydrated and may need special consideration. Conditions including alcoholism and hypoalbuminemia may also affect the ability to have pre- and post-scan hydration.	
Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristic?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No
Any other special considerations	Not applicable	

3 Related NICE guidance

Published

- Tests to help assess risk of acute kidney injury for people being considered for critical care admission (ARCHITECT and Alinity i Urine NGAL assays, BioPorto NGAL test and NephroCheck test) (2020) NICE diagnostics guidance DG39
- COVID-19 rapid guideline: acute kidney injury in hospital (2020) NICE guideline NG175
- Point-of-care creatinine devices to assess kidney function before CT imaging with intravenous contrast (2019) NICE diagnostics guidance DG37
- Acute kidney injury: prevention, detection and management (2019) NICE guideline NG148
- Acute kidney injury (2014) NICE quality standard QS76

4 External organisations

4.1 Professional

The following organisations have been asked to comment on the draft scope:

- British Association for Nursing Cardiovascular Care
- British Cardiovascular Intervention Society
- British Heart Foundation
- British Institute of Radiology
- British Renal Society
- British Society for Heart Failure
- British Society of Cardiac Radiology
- British Society of Cardiovascular Imaging
- British Society of Interventional Radiologists
- National Kidney Federation
- Renal Association
- Royal College of Radiologists
- Society for Cardiological Science and Technology

- Society for Vascular Technology
- The Society for Cardiothoracic Surgery
- The Vascular Society of Great Britain and Ireland.

4.2 Patient

NICE's Public Involvement Programme contacted the following organisations for patient commentary and asked them to comment on the draft scope:

- British Cardiac Patients Association (BCPA)
- British Heart Foundation (BHF)
- Diabetes UK
- Kidney Care UK
- Kidney Research UK
- Pumping Marvellous

NICE National Institute for Health and Care Excellence

Adoption report: GID-MT550 DyeVert for reducing contrast media in coronary and peripheral angiography

Summary – MTAC1

Adoption levers

- Accurate quantification of contrast volume delivered is useful (vs visual estimations).
- The modifiable valve and pressure divert component is unique.
- If proven to work in reducing CI-AKI, clinicians see a place for it.

Adoption barriers

- Contributors found it difficult to understand:
  - how the device works
  - the benefits of using it over simply using less contrast.
- Need to decide in advance of procedure whether manual or pump powered injection required (vs current practice where both may be used concurrently).
- Environmental impact of plastic waste.
- Emerging techniques require no contrast which will negate need for this device.
- Lack of relevant patient information communicated between clinicians to aid patient selection.
- Savings may not realised within the purchasing department budget.

1 Introduction

The adoption team has collated information from healthcare professionals working within NHS organisations, who have experience of using DyeVert systems or are experts in coronary or peripheral angiography, cardiology or nephrology.

This report has been developed for the medical technologies advisory committee (MTAC) to provide context from current practice and an insight into the potential levers and barriers to adoption. It does not represent the opinion of NICE or MTAC.

2 Contributors

The adoption team spoke to 6 NHS clinicians; a consultant nephrologist, 3 consultant cardiologists, 1 interventional cardiologist, 1 professor of vascular surgery and 1

interventional radiologist (peripheral angiography). The interventional cardiologist is a current user of the technology and one consultant cardiologist had previous experience of the device from a company trial.

3 Current practice in clinical area

Prior to cardiac and peripheral angiography, contributors routinely measure estimated glomerular filtration rate (eGFR) as a marker of renal function to evaluate risk of contrast-induced acute kidney injury (CI-AKI) in patients undergoing angiography.

Contrast media is essential to obtain adequate quality images during diagnostic and interventional angiography.

In peripheral vs. coronary angiography the contrast would be more dilute when it reaches the kidneys. Despite this, it was reported that contrast volume should still be minimised for at risk patients.

Cardiolology and vascular contributors did not routinely seek nephrology advice, however, one contributor reported that if eGFR was very low (15-20 ml/min/1.73m^2) he would consult a nephrologist.

For those identified at risk of CI-AKI, contributors were following NICE guidelines and routinely:

- Promote oral/hydration (if appropriate) and/or administer intravenous preventative hydration (before and/or after the procedure).
- Stop medications (ACEi, ARBs and NSAIDs)
- Try to use the minimum contrast medium possible while ensuring adequate image quality.
- Use either low osmolar contrast (if available) or iso osmolar contrast if not.

Administering intravenous hydration was noted as time consuming and costly.

Based on contributors' experience, both manual injector and powered pump techniques may be used to administer contrast, but the latter is mainly used in peripheral angiography. One contributor reported a preference of using a pump injector during peripheral angiography as this avoids radiation exposure but identified that contrast media can get wasted if the pump activates but imaging is set incorrectly, meaning more contrast would be needed. This is particularly undesirable in high-risk patients when trying to minimise contrast used. It is possible to use both manual and pump injectors concurrently if desired.

NHS England published a Patient Safety Alert in 2015, stating that contrast medium must be administered from a closed system. During angiography, the volume of contrast received is recorded.

The volume of contrast media required varies from patient to patient and depends on patient size, artery size and nomenclature (e.g. degree of calcification), size of equipment (e.g. catheters, guidewires, stents) and operator skill. It was reported that inexperienced operators tend to use more contrast.

For coronary angiography, one contributor reported using pre-filled syringes holding 120-150mls of contrast which must be discarded after each use, regardless of how much is used.

Another contributor reported standard practice in his trust is using glass bottles of contrast (100ml, 250ml or 500ml). Average volumes used are 100ml during diagnostic angiography and 200-250ml during interventional cases. The contrast volume used is estimated from the amount of contrast left in the bottle and recorded in the notes. There is less waste with this approach as residual contrast can be used on another patient and glass bottles recycled.

One contributor reported the usual volume of contrast used in peripheral angiography was between 50-150ml.

All contributors were aware of standard (iso-osmolar e.g. Omnipaque) and 'renal-friendly' (low osmolar e.g. Visipaque) contrasts. There was variation around who would select or influence the type of contrast used depending on the service. Higher osmolar contrasts are selected for larger patients. Carbon dioxide gas was reported as a (mainly historically) alternative to using iodinated contrast.

4 Use of DyeVert in practice

At the time of writing, DyeVert Plus EZ is in use in 3 NHS hospitals in England. The DyeVert Power XT contrast reduction system is not currently in use in the NHS. One contributor has used the device at least once a month themselves and in total, the device has been used 30-40 times in their Trust.

Another contributor undertook a trial of DyeVert Plus EZ in early 2020. This involved using the device for 4-6 cases (non-selected non-high-risk patients). After training (and an instructional video) it was reportedly easy to set up, with removal of 'pull out' tabs that enable automatic digital (via Bluetooth) connection between the syringe

and the monitor. This user was unable to conduct a proper evaluation or progress on to a formal trial due to the COVID-19 pandemic.

5 Reported benefits

The potential benefits of adopting DyeVert Plus EZ as reported to the adoption team by the 2 healthcare professionals with experience of using the technology are:

- Enables accurate monitoring of volume of contrast injected.
- Reduced contrast administered to patients.
- Cost savings anticipated in relation to less wasted contrast.
- Reduced overspill of contrast dye into the aorta (which reduces volume of contrast entering the circulation), provided the catheter tip is accurately placed.

Potential benefits (if it reduces CI-AKI) of non-users were reported as:

- Reduced patient morbidity
- Reduced length of stay
- Reduced healthcare costs

6 Insights from the NHS

The current and previous users of DyeVert Plus EZ were in coronary angiography. The remaining contributors discussed the potential use of DyeVert Plus EZ either in coronary or peripheral angiography.

Area of application in NHS

DyeVert Plus EZ is intended for use in the catheter laboratory where coronary and peripheral angiography (both requiring the use of contrast media) take place. This could include diagnostic or interventional angiography. It is not intended for use in CT coronary angiography.

Care pathway

The patient indications are the same whether angiography is a planned or emergency procedure.

In planned care the patient's eGFR, medical history and hydration status (+/- input from a nephrologist) influence volume and potentially type of contrast given. In emergency care, the patient's medical history and eGFR may not be available but a risk vs. benefit decision would be made by the relevant team.

Patient selection

The company states the DyeVert Plus EZ is suitable for all patients considered at risk of CI-AKI.

They report that good communication between the referring clinician and interventional radiologist on CI-AKI risk is essential to aid patient selection. This may not always happen. Documented process and protocols could help address this barrier, as well as the use of a sticker that can be used on the referral to identify appropriate patients.

The previous user (informal trial) did not pre-select patients according to CI-AKI risk status but would do so if using in routine practice. The current user does pre-select patients considered at high risk of CI-AKI and only uses DyeVert Plus EZ in these cases.

Contributors were aware of the risk factors for CI-AKI and stated these include people with chronic kidney disease (CKD), diabetes, heart failure, age (>75) and previous kidney transplant. One contributor shared local guidance specifying additional exposure risk factors, including; AKI, sepsis, hypovolaemia, toxins (e.g., NSAIDs, gentamycin) and IV or intra-arterial contrast in previous 48hours. Another contributor also included people at risk of CKD as high risk.

Practical Application

The company state DyeVert Plus EZ takes 2-3 minutes to set up. Users agreed it was easy to set up after training, but one had some difficulty priming the device at first. Users like the monitor and ability to see exactly how much contrast has been administered. This was considered a key benefit over current practice.

The current user reported that in a small number of cases (less than 5%) where DyeVert Plus EZ is used, images might be suboptimal making it necessary to adjust the force of the injection to obtain adequate quality images. A protocol has been developed in their department to guide its use.

Operator variation was considered to be a key factor influencing the volume of contrast administered during angiography (with or without DyeVert Plus EZ). Operators include doctors, nurses or trainee doctors with varying skill levels. Some were reportedly more cautious and others less so. Catheter tip position was also reportedly important to minimise contrast volume and obtain adequate imaging.

The previous user said that the device limits the operator's tactile feedback from injection of contrast. During complex cases it may be necessary to carefully 'titrate' the amount of contrast injected for particular images, and this user reported that Dyevert made this more difficult. He also reported that if more contrast was required, for example in very large calibre arteries, or patients with hyperdynamic circulation, the system resists. Advice from the company was to push harder on the syringe in those cases to 'override' the Dyevert,

The previous user reported it remains unclear how the device can 'divert' contrast if injecting hard inadvertently but will deliver contrast to the patient if deliberately injecting hard.

Diverted contrast with DyeVert Plus EZ was reported as not true waste as without it, this would have been administered to the patient.

DyeVert Plus EZ and DyeVert Power XT can be used concurrently. However, this may be an adoption barrier for angiographers as it would require two different device configurations for the same patient.

Clinician confidence/acceptance

Reducing the incidence of CI-AKI was important to all contributors and they were keen to see any evidence to support this for DyeVert. Definition of AKI was considered important with at least two contributors referring to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria of this. Two contributors stated that transient, slightly elevated creatinine, that is often asymptomatic, was not synonymous with CI-AKI and that evaluation of evidence should take this into account.

Contributors agreed that using less contrast was advantageous, but non-users were unsure how the product worked despite having read the NICE MedTech Innovation Briefing and viewed the company demonstration video. They were unclear about how and why it diverts the contrast and the value of this over simply using less contrast to start with.

All non-users said they would need to see evidence that it works before they would consider its use.

Patient experience

Clinicians described the negative impact that CI-AKI has on patients, resulting in longer hospital stays, more symptoms, long term dialysis and mortality.

The company states that the patient interface during angiographic procedures is not altered with addition of DyeVert Systems.

Cost and procurement

While there are potential system savings associated with reduction in CI-AKI, contributors reported that in most cases the purchasing budget holder will not realise savings even if there are downstream cost savings. This may be a barrier to adoption, however if DyeVert is shown to reduce length of stay in cardiology departments, local cost savings may be direct.

Training and compliance

The company report that no formal training is offered but that they usually provide face-to-face, group training on connecting and using their systems during product evaluation. This is available for radiographers, nursing staff and other catheter laboratory operatives as required.

The company does have additional tools such as YouTube videos demonstrating priming of the device. In addition, the DyeVert Plus EZ system has a priming video that is part of the display software that the user can select and watch in real time during device set up.

Maintenance

No problems were reported relating to maintenance of the monitor while under loan. Any malfunctions would be resolved by the company with a replacement monitor if required.

Emerging techniques require no contrast

Emerging techniques including intracoronary imaging and intravascular ultrasound require minimal contrast media and would negate the need for contrast saving devices. This was cited as a potential barrier for the adoption of DyeVert Systems.

Environmental impact

Contributors were concerned about the additional disposable plastic involved in using DyeVert Plus EZ.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

GID-MT550 DyeVert for reducing contrast media in coronary and peripheral angiography

Company evidence submission

Part 1: Decision problem and clinical evidence

Company name	Osprey Medical Inc.
Submission date	25 January 2021
Regulatory documents attached	1. CE Certificate, CE 615030 2. Declaration of Conformity 3. IFU, 8287 DyeVert Plus EZ Contrast Reduction System 4. IFU, 8300 DyeVert Power XT Contrast Reduction System 5. IFU, 8161 Display, Contrast Monitoring 6. IFU, 8280 Smart Monitor 7. IFU, 8259 Smart Syringe, Replacement
Contains confidential information	Yes

Contents

1 Statement of the Decision Problem

	Scope issued by NICE	Variation from scope (if applicable)	Rationale for variation
Population	People at risk of contrast-induced acute kidney injury (CI-AKI) who need coronary and peripheral angiography with contrast media	None	N/A
Intervention	DyeVert™ Contrast Reduction Systems used as an adjunct to standard NHS clinical practice	None	N/A
Comparator(s)	Conventional hand or automated injection of contrast media	None	N/A
Outcomes	CI-AKI incidence CI-AKI severity Measures of renal function, such as serum creatinine concentration, estimated glomerular filtration rate and urine output. Volume of contrast agent received and diverted. Image quality. Length of hospital stay and rates of re-admission as a result of CI-AKI or acute heart failure (suspected cause by contrast agent). Rate of acute heart failure with suspected cause by contrast agent. Rate of renal replacement therapy, intensive care transfer or mortality as a result of CI-AKI. Device-related adverse events.	None	N/A
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which can include scenarios in which different numbers and combinations of devices are needed.	None	N/A

Subgroups to be considered	Other identifiable subgroups who may be at particularly high risk for developing CI-AKI	None	N/A
Special considerations, including issues related to equality	People with chronic kidney disease, heart failure, diabetes, and renal transplant would be more at risk of CI-AKI. Kidney disease occurs more frequently in males, people over the age of 60, and those of African-Caribbean, African or South-Asian family origin. People who have an ileostomy or older people are at an increased risk of becoming dehydrated and may need special consideration. Conditions including alcoholism and hypoalbuminemia may also affect the ability to have pre- and post-scan hydration.	Removed consideration of people with an ileostomy, alcoholism, hypoalbuminemia or other comorbidities that may increase the risk of dehydration.	The subject system does not provide or alter hydration. The proposed system is not intended to be a substitute to hydration. Osprey Medical recognizes that those that may not be able to benefit from hydration currently do not have alternative treatments in the prevention of CI-AKI at this time.

2 Description of Technology

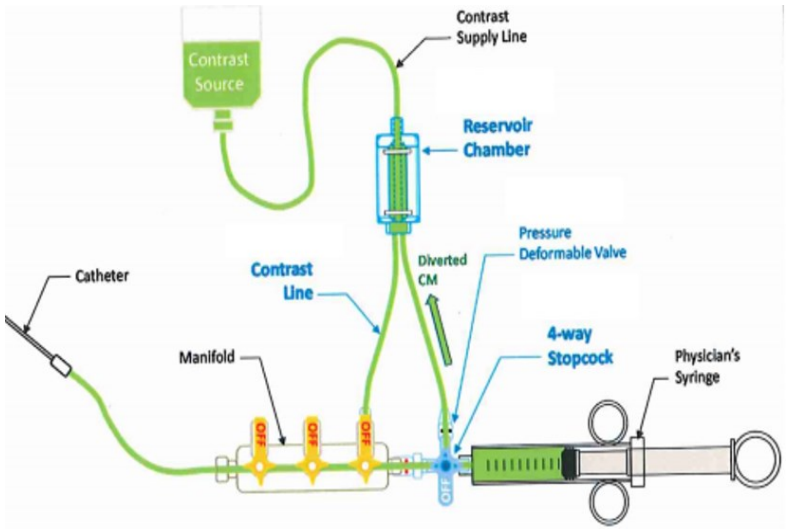
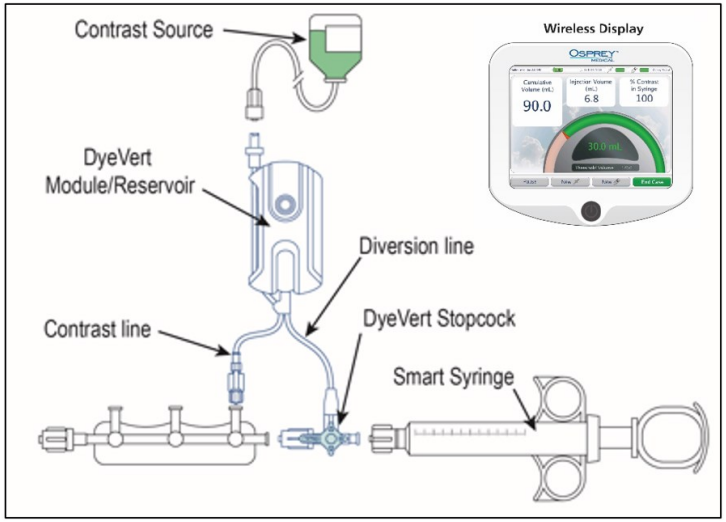
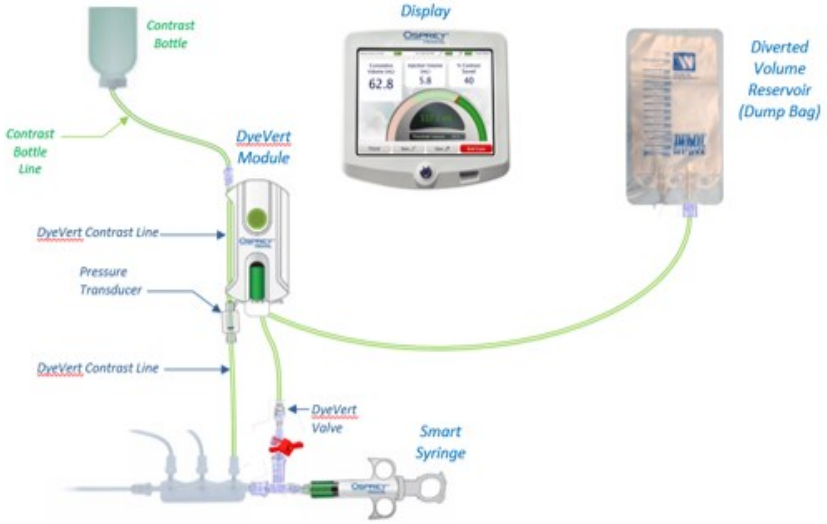
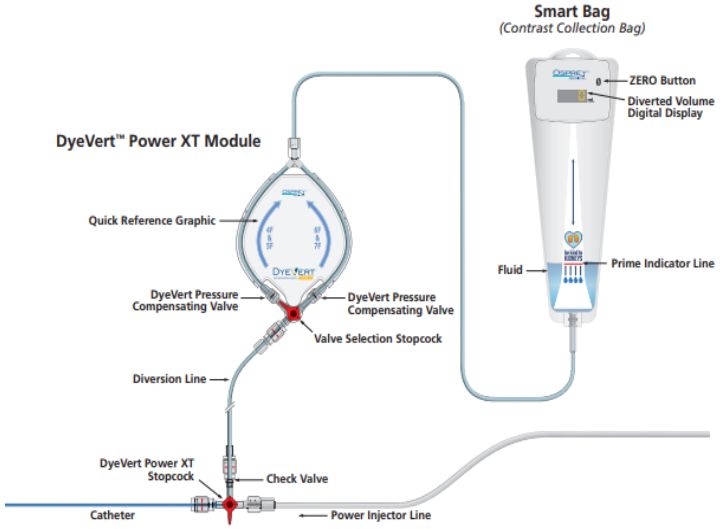
Brand name	DyeVert™ Plus EZ and DyeVert™ Power XT Contrast Reduction Systems
Approved name	DyeVert™ Plus EZ and DyeVert™ Power XT Contrast Reduction Systems
CE mark class and date of authorisation	DyeVert™ Plus EZ Contrast Reduction System: Class I, sterile, measuring Annex IX, Rule 1 and active, Annex IX, Rule 12 Date of Authorization: (current version) 12 July 2018 DyeVert Power XT Contrast Reduction System: Class I, sterile, measuring, Annex IX, Rule 2 and 12 Date of Authorization: (current version) 11 August 2020

Previous Version(s)	Launched	Features
DyeVert System (first generation DyeVert System)	2015	No longer available. First generation of DyeVert System. The current DyeVert Plus EZ System has the identical diversion valve (mechanism of action and principle of operation) of the first generation DyeVert System. Differences include improvements made to the DyeVert

		Plus EZ system to allow for monitoring of contrast administration and ease of priming.
DyeVert Plus System (second generation DyeVert System)	28 Oct 2016	No longer available. The current DyeVert Plus EZ System has the identical diversion valve (mechanism of action and principle of operation) of the second generation DyeVert System. Differences include 'ease of use' improvements. Refer to attached IFU p/n 8175.
DyeVert Power XT System (previous version)	22 Jun 2018	No longer available. The previous version did not provide any monitoring capability. Refer to attached IFU p/n 8285.

The currently commercial devices leverage data on previous configurations of the device as noted in the table above. To ease review, below is a visual comparison and descriptive comparison of the previous versions and the currently commercial versions.

DyeVert Systems – Device Configurations

DyeVert (no longer available)	DyeVert Plus (no longer available)
	
DyeVert Plus EZ	**DyeVert Power XT**
	

DyeVert Systems – Intended Use and Clinical Characteristics

Criteria	DyeVert	DyeVert Plus	DyeVert Plus EZ	DyeVert Power XT
Intended Use	For the controlled infusion of radiopaque contrast media for angiographic procedures			
Conditions of Use	Cardiac catheterization laboratory			
User	Interventional cardiologists, Cath lab staff			
Injection System Compatibility	Manual contrast injection with a control syringe			Automatic contrast injection
Anatomic Areas of Use	Cardiac and peripheral angiography			
Patient Population	Patients at risk of contrast-induced acute kidney injury			

DyeVert Systems – Technical Characteristics

Criteria	DyeVert	DyeVert Plus	DyeVert Plus EZ	DyeVert Power XT
Principles of Operation for Contrast Reduction	Creates a secondary fluid path with pre-determined variable resistance to contrast volume to patient			
Volume and Speed of Contrast Injection	Variable as determined by user			
Mechanism of Action	DyeVert Compensating Diversion Valve			
Syringe	User selected Control Syringe	Smart Syringe (User selected Control Syringe with firmware)		N/A
Module	Diverts contrast	Diverts and monitors contrast		Diverts Contrast
Display	None	Reusable display 15V 2A DC power supply, power cord		Single use Smart Bag digital display Alkaline battery
Contrast Monitoring	None	Real time contrast volume used as compared to a user selected prespecified threshold, real-time contrast diverted/saved		Real time contrast diverted/saved

Criteria	DyeVert	DyeVert Plus	DyeVert Plus EZ	DyeVert Power XT
Compatible Catheter Configurations	Diagnostic 4Fr, 5Fr, 6Fr Guide 5Fr, 6Fr, 7Fr Guide with RX 6Fr, 7Fr Guide with OTW 6Fr, 7Fr			Diagnostic 4Fr, 5Fr, 6Fr Guide 5F Guide with RX 6Fr, 7Fr Guide with OTW 6Fr, 7Fr
Compatible Contrast Media	Contrast agents with the following viscosity @ 20ºC: 8.8 to 26.6 cps (mPa.s)			
Mechanical Connections	ISO594-1, -2 compliant			

Fr=French, OTW=over-the-wire, RX=rapid exchange

Claimed benefit	Supporting evidence	Rationale
Patient benefits		
Accurate, real-time contrast media dose monitoring relative to the maximum dose target and recording	Corcione 2017, Gurm 2019a, Desch 2018, Tajti 2019, Briguori 2020, Zimin 2020, Turner & Tucker 2020, Kutschman 2019a, Kutschman 2019b, Cameron 2020	During the case, the Display actively monitors contrast use during each injection and cumulatively relative to a dose target. The Display notifies the user periodically as the actual contrast used approaches the dose target. These features bring regular awareness to contrast use and contrast use relative to the pre-determined maximum dose, which supports clinical decision making to limit contrast use for each patient.
Total contrast media volume reduction	Corcione 2017, Sapontis 2017, Desch 2018, Locklear 2018, Gurm 2019a, Sattar 2018, Bath 2019, Bruno 2019, Kutschman 2019a, Kutschman 2019b, Tajti 2019, Turner & Tucker 2020, Cameron 2020, Briguori 2020, Amoroso 2020, Zimin 2020, Rao 2019, Bunney 2019, Unpublished Osprey Market Acceptance Evaluation Summary Report 2020, Unpublished Manuscript 2020	Clinically meaningful contrast minimization of 40% on average (See Section 7). [redacted]
More likely to experience contrast administration at or below the maximum contrast media dose	Gurm 2019a, Briguori 2020, Turner &Tucker 2020, Cameron 2020, Zimin 2020, Kutschman 2019a, Kutschman 2019b, Rao 2019, Gurm 2019b, Unpublished Manuscript 2020	Clinically meaningful contrast minimization results in more patients receiving contrast media volumes at or below the maximum contrast dose (See Section 7). [redacted]

		[redacted] The ability to ensure consistent and safer contrast media doses supports enablement of angiography access to at-risk patients, particularly those with moderate or severe pre-existing kidney disease. In addition, lower contrast volumes are associated with lower CI-AKI risk (Gurm 2019b).
Maintenance of image quality	Corcione 2017, Sapontis 2017, Desch 2018, Gurm 2019a, Locklear 2018, Bruno 2019, Rao 2019, Zimin 2020, Briguori 2020, Amoroso 2020, Unpublished Osprey Market Acceptance Evaluation Summary Report 2020	Multiple clinical trials demonstrate clinically meaningful contrast media volume reduction while maintaining image quality. Two studies involved independent image review.
Reduction in CI-AKI incidence	Gurm 2019a, Castro 2018, Sattar 2018, Bunney 2019, Kutschman 2019a, Kutschman 2019b, Turner & Tucker 2020, Cameron 2020, Briguori 2020, Rao 2019, Unpublished Manuscript 2020	Use of DyeVert in population healthcare management CI-AKI reduction quality improvement projects and controlled studies reduces the relative risk of CI-AKI (See Section 7). [redacted]
Reduction in overall length of stay	James 2013, Kerr 2014, Amin 2020, Prasad 2020, Briguori 2020	CI-AKI is associated with an increased length of stay of at least 2 days. Use of DyeVert resulted in a lower overall length of stay compared to Controls in

		which the DyeVert was not used.
Reduction in CI-AKI associated morbidity	James 2013, Valle 2017, See 2018	AKI is associated with an increased risk of worsening chronic kidney disease, developing major adverse kidney events, end stage renal disease, and major cardiovascular events. Of 14 studies (70 031 participants) that reported on cardiovascular events, all reported an increased risk associated with CI-AKI after coronary angiography. The pooled RR from these studies for cardiovascular events was 2.42 (95% CI, 1.62–3.64). Three studies (18 457 participants) reported on the risk of progression to end stage renal disease, which ranged from 0% to 0.2% in those without CI-AKI, and from 0.2% to 4.5% in those with CI-AKI (James 2013). Development of acute kidney injury is associated with increased rates of myocardial infarction, bleeding, and recurrent renal injury after discharge, with the hazard of adverse events increasing with the severity of the acute kidney injury. These events occur most frequently in the first 30 days, but increased rates for adverse events persist to 1 year after hospital discharge. (Valle 2017). AKI was associated with an additional 10.17 chronic kidney disease cases per 100 person-years and an additional 0.39 end-stage renal disease cases per 100 person-years (See 2018).

Reduction in CI-AKI associated in-hospital mortality	James 2013, Kerr 2014, Sawhney 2015, Valle 2017, See 2018, Prasad 2020	Based on 11 studies (with 27,190 participants) that reported unadjusted results, the pooled crude RR of death was 8.19 (95% CI, 4.30–15.60; Q statistic P=0.008; I2=77.3%), whereas the pooled adjusted RR from 23 studies (with 112 413 participants) with adjusted results was 2.39 (95% CI, 1.98–2.90; Q statistic P<0.001; I2=88.3%) (James 2013). The odds ratio for death in hospital for patients with AKI relative to those without AKI was 10.52 (95% confidence interval 9.93–11.16). The relative risk of death in hospital for patients with AKI was 4.69 (4.59–4.80) (Kerr 2014). Across 16 mortality studies, follow-up ranged from 1 to 7 years and mortality up to 83% for patients with AKI at 5 years. AKI was associated with increased mortality in all but one study regardless of pre-AKI baseline (HR 1.08 to 4.59) or recovery of renal function (HR 1.08 to 5.75) (Sawhney 2015). Development of acute kidney injury is associated with increased rates of death. Hazard of events also increased with severity of in-hospital AKI (AKIN stage 2/3: HR, 2.52; 95% CI, 2.36–2.70; AKIN stage 1: HR, 1.65; 95% CI, 1.60–1.69). (Valle 2017) Risk of death increased from AKI Stage 1 (pooled adjusted HR,1.35;95% CI,1.27–1.44) to AKI Stage 2 (pooled adjusted HR,

		1.64;95% CI,1.50–1.80) and AKI Stage 3 (pooled adjusted HR, 2.76; 95% CI, 2.28–3.35). This pattern was demonstrated across all subgroups of clinical setting and the gradient of risk across AKI severities was highly significant (P < 0.001) (See 2018). AKI was associated with higher 30-day in-hospital mortality (OR adjusted = 2.55; 95% CI: 2.40, 2.70) Prasad 2020).
Reduction in CI-AKI associated post-procedure nursing care	Prasad 2020	Patients experiencing CI-AKI are more likely to be discharged to hospice, transferred to another acute care hospital or to nursing/rehabilitation facility (Prasad 2020).
Reduction in CI-AKI associated post-procedure readmissions	Kerr 2014, Valle 2017, Prasad 2020	Lifetime cost of post-discharge care for patients with AKI is estimated to be £179 million (Kerr 2014). Development of in-hospital AKI was associated with higher rates of post-discharge rehospitalization for AKI (AKIN stage 2/3: HR, 2.22; 95% CI, 2.04–2.41; AKIN stage 1: HR, 1.70; 95% CI, 1.64–1.76) and AKI requiring dialysis (AKIN stage 2/3: HR, 4.73; 95% CI, 3.73–5.99; AKIN stage 1: HR, 2.59; 95% CI, 2.29–2.92). After adjustment, hazard of death, myocardial infarction, or rehospitalization for bleeding at 1 year remained higher with increasing severity of renal injury. Rehospitalization for AKI was most common among patients having AKIN stage 2/3 AKI (AKIN 2/3: 16.7% versus AKIN 1: 12.9% versus no AKI: 4.4%;

		P<0.001), as was AKI requiring dialysis (2.2% versus 1.1% versus 0.2%; P<0.001 (Valle 2017). AKI was associated with higher 30-day readmission risk (OR adjusted = 1.52; 95% CI: 1.50, 1.55) Prasad 2020).
System benefits		
Accurate, real-time contrast media dose monitoring relative to the maximum dose target and recording	Corcione 2017, Gurm 2019a, Desch 2018, Tajti 2019, Briguori 2020, Zimin 2020, Turner & Tucker 2020, Kutschman 2019, Cameron 2020	During the case, the Display actively monitors contrast use during each injection and cumulatively relative to a dose target. The Display notifies the user periodically as the actual contrast used approaches the dose target. These features bring regular awareness to contrast use and contrast use relative to the pre-determined maximum dose, which supports clinical decision making to limit contrast use and compliance to clinical guidelines.
Contrast-media related population risk factor reduction	Gurm 2019a, Turner & Tucker 2020, Cameron 2020, Briguori 2020, Amoroso 2020, Bunney 2019, Kutschman 2019a, Kutschman 2019b, Tajti 2019, Sapontis 2017, Corcione 2017, Desch 2018, Bruno 2019, Bath 2019, Rao 2019, Gurm 2011, Gurm 2019b, Unpublished Manuscript 2020	Contrast minimization provided by DyeVert reduces two important risk factors for CI-AKI: total contrast dose, and total contrast dose relative to baseline kidney function. As a result, greater proportions of the population receive contrast doses below the established maximum contrast dose. Conversely, fewer patients exceed a contrast media dose greater than three times their baseline kidney function, which has been shown to be a marker of increasing CI-AKI risk (Gurm 2011 & Gurm 2019b).
Improved adherence to recommended guidelines for contrast minimization as part of an initiative to reduce CI-AKI	Stewart 2009, Amin 2017, Prasad 2017, Castro 2018, Product Instructions for Use, Turner &Tucker 2020, Kutschman 2019a,	Gaps exist between clinical guidelines and clinical practice as it relates to the care of at-risk patients. Technology-supported

	Kutschman 2019b, Cameron 2020, Unpublished Manuscript 2020	patient-centered care programs have the potential to improve consistency of delivering on CI-AKI prevention strategies. During case set-up, the Display prompts the user to enter renal function status. This prompts the staff to ensure an eGFR value is available, thereby enabling this value to be used as recommended by clinical guidelines for pre-procedural patient risk screening, patient informed consent, and calculating a maximum contrast dose. Without this information in advance of the procedure, staff may miss identification of at-risk patients, fail to appropriately consent patients, and fail to establish a pre-procedure maximum contrast dose for the patient. During case set-up, the Display prompts the user to specify and record the maximum contrast media dose threshold for the case. Maximum contrast dose thresholds are often not set pre-procedurally, documented in the medical record, and/or are used to guide clinical decision making during the procedure.
Reduced number of bed stays/length of stay and related services	Amin 2020, Prasad 2020, Briguori 2020	As noted above, CI-AKI is associated with extended length-of-stay. Therefore, CI-AKI prevention has the potential to reduce overall length of stay for the index procedure as well as costs associated with extending a stay due to CI-AKI such as room and board, pharmacy costs, renal ultrasounds, lab tests, additional cardiology consultation, and additional nephrology consultation.

Cost benefits		
Reduced healthcare burden due to CI-AKI prevention	Amin 2020, Kerr 2014, Kerr, 2017, Prasad 2020, Javanbakht 2020, Turner & Tucker 2020, Cameron 2020, Kutschman 2019a, Briguori 2020, Unpublished Manuscript 2020	CI-AKI prevention has the potential to reduce costs associated with extended length of stay, post-procedure nursing care and readmissions. Those with AKI had higher hospitalization cost than those without ($38,869, SD 42,583 vs $17,167 SD 13,994, p <0.001). Room and board costs were the largest driver of AKI costs ($4,841). After adjustment, the incremental cost associated with an AKI was $9,448 (95% confidence interval $9,338 to $9,558, p <0.001). Extrapolated to the United States, our findings imply an annual AKI cost burden of 411.3 million US$ (Amin 2020). A Markov model estimates the lifetime cost of post-discharge care for people who have had AKI as inpatients in 2010–11 at £179 million. These costs arise through higher incidence of CKD and RRT, relative to a matched population without AKI. The lifetime QALY loss is estimated at 1.4 per inpatient with AKI. Total inpatient expenditure associated with AKI admissions recorded in HES (excluding critical care use) is estimated at £380 million, which equates to approximately £1.02 billion for inpatient expenditures related to AKI in England (Kerr 2014). In particular, reducing insult to the kidneys may reduce CKD progression to high-

		burden, advanced levels of care, such as renal replacement therapy, which costs exceed £25,000 per patient per year (Kerr 2017). The AKI-related incremental cost during index visit and 30-day readmissions were estimated to be $8,416 and $580 per inpatient procedure and $927 and $6,145 per outpatient procedure. Overall excess healthcare burden associated with AKI was $1.67 billion (Prasad 2020). Economic modelling based on the clinical effectiveness of DyeVert indicate that the intervention leads to cost savings (- £435) and improved effectiveness (+ 0.028 QALYs) over the patient's lifetime, compared with current practice. The overall long-term cost saving for the NHS associated with introduction of the DyeVert is over £175 million (Javanbakht 2020). A hospital budget impact analysis found a net cost saving of $650/case with the implementation of DyeVert based on a number-needed-to-treat to avoid 1 AKI event of 10 (Turner & Tucker 2020). Another hospital reported a number-needed-to-treat to avoid 1 AKI event of 16 and indicated based on an initial analysis that the implementation of DyeVert was producing cost savings (Cameron 2020). A third hospital reported an incremental cost offset associated with AKI prevention to be at least

		$2,000/case (Kutschman 2019a). Length of in-hospital stay was longer in the Control group than in the DyeVert group (8 ± 4 vs. 6 ± 2 days; p =.003) Briguori 2020. [redacted]
Sustainability benefits		
Re-allocation of CI-AKI-related bed days	Amin 2020, Prasad 2020, Briguori 2020, Kerr 2014	59.89% of critical care bed days were for people with AKI. In multivariate regression analysis, AKI was associated with critical care bed day usage 4.32 (3.63–5.14) times the level of patients without AKI. It is estimated that, in 2010–11, there were 977,116 excess bed days associated with AKI (Kerr 2014) CI-AKI prevention has the potential to reduce overall length of stay enabling bed days saved to be allocated to the treatment of other patients.
Re-allocation of CI-AKI-related staff time	Kerr 2014, Valle 2017, Prasad 2020, Briguori 2020	CI-AKI prevention has the potential to reduce staff care time enabling time saved to be allocated to the treatment of other patients.
Facilitating earlier patient discharge	Amin 2020, Prasad 2020, Briguori 2020	CI-AKI prevention has the potential to enable more efficient discharge of at-risk patients undergoing angiography.

Briefly describe the technology (no more than 1,000 words). Include details on how the technology works, any innovative features, and if the technology must be used alongside another treatment or technology.

DyeVert Contrast Reduction Systems (DyeVert Systems) are intended to reduce the amount of contrast media administered during coronary and peripheral angiographic procedures that are performed in the Cardiac Catheter Laboratory and require manual or automated contrast media injections.

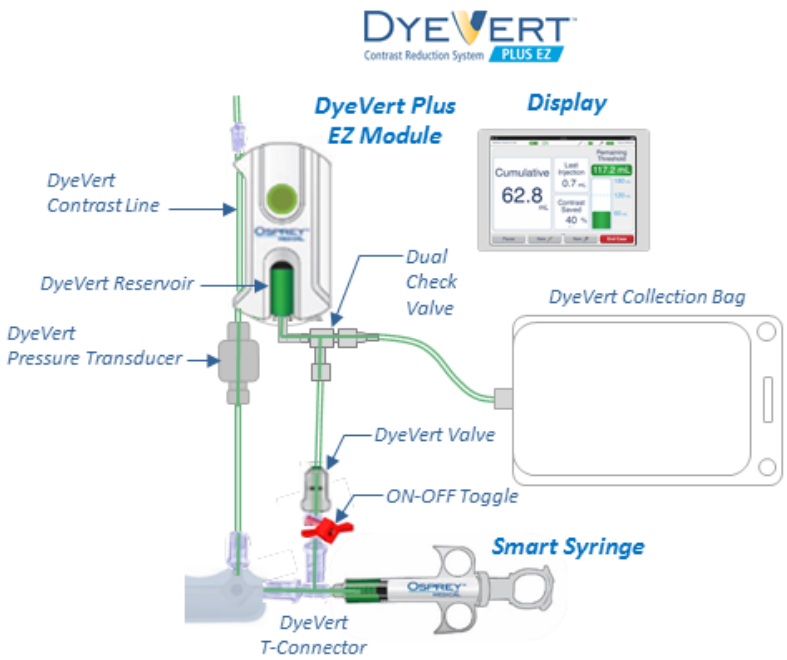


FIGURE 1: DYEVERT PLUS EZ SYSTEM

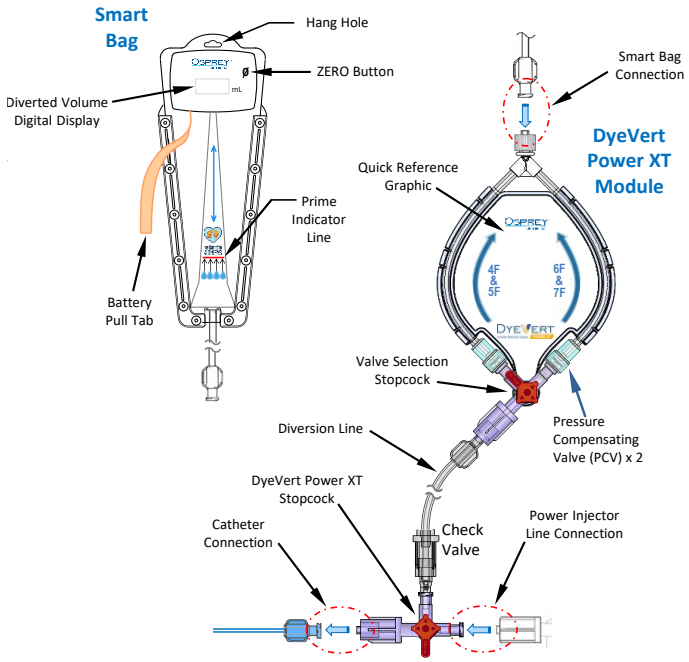


FIGURE 2: DYEVERT POWER XT SYSTEM

During procedure set-up, staff connect the DyeVert System to the contrast injection source administering contrast media (Smart Syringe or Power Injector) and the angiographic catheter placed within the patient's vasculature. Therefore, DyeVert Systems are considered non-invasive and indirect patient contacting.

The Osprey Medical DyeVert™ Plus EZ Contrast Reduction System is compatible to manual contrast injections. The Osprey Medical DyeVert Power XT System is compatible with power injectors. The systems provide fluid pathway resistance modulation and monitoring such that excess contrast volume (i.e., contrast that is not needed for diagnostic or therapeutic purposes also referred to as 'refluxed contrast') is minimized in the patient's vasculature and total contrast agent volume reduction occurs, while maintaining adequate image quality. This allows for a reduction in total contrast agent volume during coronary or peripheral imaging, while maintaining adequate image quality.

The DyeVert Plus EZ System utilizes a wireless (Bluetooth® Low Energy) communications and Hall Effect sensors to accurately monitor saline and contrast movement through the manual contrast injection Smart Syringe and DyeVert Module allowing the monitoring and display of total administered volume to the patient and total diverted volume. The total diverted volume is also referred to as contrast volume saved and contrast volume reduction to the patient. The DyeVert Power XT System uses a digital display with LED to display volume diverted as measured on the smart contrast collection bag through sensors.

The DyeVert System disposable components are single-use, EO sterile, which utilize a proprietary diversion valve. The diversion valve provides a secondary fluid path with a resistance to ensure a minimum patient contrast flow rate specification for maintaining good image quality. During injection of contrast, a portion of contrast flows through the system to the diversion valve. The fluid pressure/flow pushes a diffuser and o-ring against the molded housing of the diversion valve which has small channels which are progressively obstructed by the O-ring as it compresses under pressure from the injection. With lower injection pressures, the compression valve O-ring compresses less, creating less obstruction in channels of the insert and allowing contrast to freely pass and travel through the tubing into the waste bag of the system. During higher injection pressures, the compression valve O-ring compresses more (i.e., flattens and obstructs flow in the channels of the housing and allows less contrast to pass into the waste bag of the system (thus less contrast is diverted).

DyeVert Systems have been tested for use with a variety of catheter sizes and configurations, as well as contrast media types as noted in the corresponding product Instructions for Use.

Because the DyeVert System has no direct-patient contact and is used with components that are already part of the typical angiographic procedure, potential patient risks are similar to those associated with routine procedures not using the DyeVert System, which include air emboli and infection based on the use of sterile components, fluid administration, and intravascular techniques. The DyeVert System does not have the capability nor is it designed to independently administer contrast to the patient. Contrast media volume use and injection techniques are determined by the physician per standard of care. The system is not capable of nor is it designed to independently modify the physician injection to increase the total contrast media volume administered above what the physician would have already administered within context of baseline injections (i.e. injections without the DyeVert System).

Briefly describe the environmental impact of the technology and any sustainability considerations (no more than 1,000 words).

Incidence and prevalence of CI-AKI is increasing (Hsu, 2017, Sawhney 2018, Prasad 2020) due to a perfect storm of multifactorial causes, such as: increasing demand for angiography services (Garg 2015), increasing age of the patient population undergoing angiography (Rajani 2011) and increasing prevalence of comorbidities that increase patient risk for CI-AKI, such as chronic kidney disease (Kerr 2017, Sawhney 2018, Elbadawi 2019). Incidence and consequence of CI-AKI is disproportionately born by the most vulnerable patients including the elderly (Allen 2017, Valle 2017, Sawhney 2018). In fact, incidence is growing in the elderly at more than twice the rate of the general population in the UK (Sawhney 2018), which has implications for healthcare planning and management in an aging demographic. As a result, the CI-AKI-related healthcare burden that exceeded 1% of the NHS budget for England in 2011 is projected to increase (Kerr 2014, NICE AKI Quality Standard QS76 2014). However, data suggests up to 30% of AKI cases may be preventable (Stewart 2009); therefore, risk assessment and prevention are key factors in mitigating CI-AKI morbidity and mortality.

CI-AKI prevention measures that would have even a small reduction in CI-AKI incidence would have the potential to substantially reduce the lifetime health care burden associated with CI-AKI (Gurm 2016), thereby facilitating re-allocation of CI-AKI-related resources to other patients and disease states. CI-AKI prevention has the potential to also improve care quality for existing patients, thereby improving efficiency of current care potentially resulting in earlier patient discharge.

The COVID-19 pandemic has resulted in nearly 1 million positive cases in the UK (European Centre for Disease Prevention and Control, October 30, 2020) with case counts continuing to rise. Symptoms associated with severe COVID-19 infection may mimic acute coronary syndromes (Mahmud 2020) and myocardial injury is common in infected patients (Kang 2020), which increases patient presentation complexity, making screening for risk challenging in the cardiac cath lab. In addition, COVID-19 survivors experience short and long-term adverse outcomes including cardiovascular and renal impairment, increasing the population at-risk for CI-AKI in need of cardiac cath lab services (Leung 2020). Therefore, CI-AKI prevention strategies are particularly important as it relates to the ability to deliver high quality, patient-centered care to this growing vulnerable population.

The DyeVert System contains features that support identification and management of at-risk patients undergoing angiography procedures, which directly aligns with NICE AKI clinical guidance and the NHS initiative for delivery of high value intervention in patients with chronic kidney disease.

Ease of use and user acceptance of the DyeVert System have been demonstrated (Corcione 2017, Sapontis 2017, Gurm 2019a, Zimin 2020, Briguori 2020, Amoroso 2020, DyeVert Contrast Reduction System Unpublished Market Acceptance Evaluation Summary Report 2020). The DyeVert System was designed to be compatible for use with contemporary cardiac cath lab equipment. DyeVert System use will involve the use of disposable components.

3 Clinical context

Describe the clinical care pathway(s) that includes the proposed use of the technology, ideally using a diagram or flowchart. Provide source(s) for any relevant pathways.

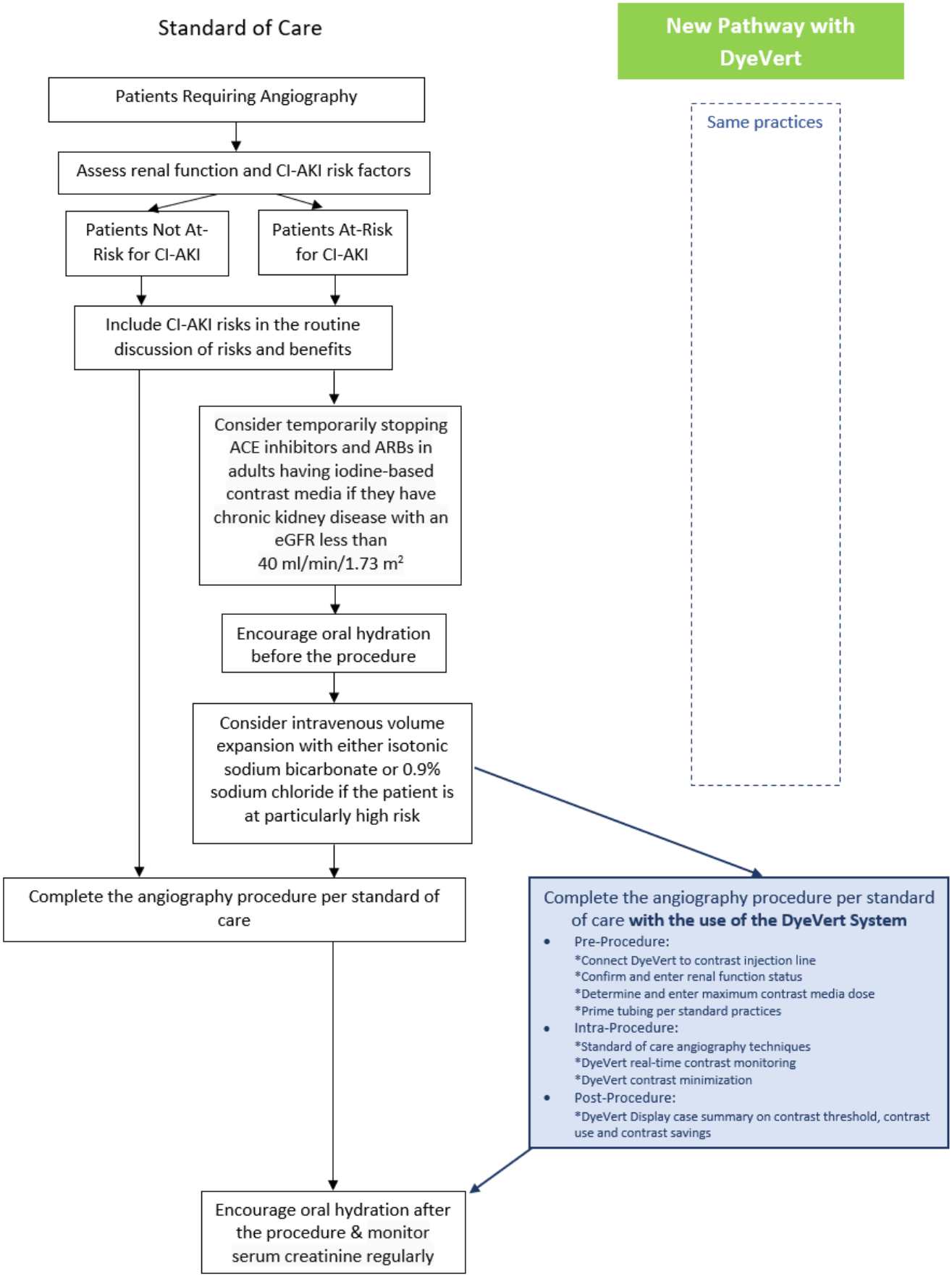
Clinical evidence has demonstrated that intra-arterial injection of contrast media during angiography can be toxic to the kidneys, leading to CI-AKI due to first-pass renal exposure when contrast media reaches the renal arteries in a relatively undiluted form. CI-AKI is a leading cause of hospital-acquired renal injury. Currently, there is no available treatment for CI-AKI; therefore, prevention measures are critical, especially in at-risk patients.

Contrast minimization is a key part of CI-AKI prevention strategies. Standard of care for minimization of contrast agent volume in coronary and peripheral angiographic procedures really lies with the clinician administering contrast media to use a volume as low as reasonably possible which is dependent upon clinician skill, attention, and awareness. Even with skilled operators, case complexity can drive the need for larger volumes of contrast media. As a result, contrast media volumes vary widely within and across clinicians administering contrast media.

NICE's guideline on acute kidney injury: prevention, detection, and management (NG148, 2019) states that increasing volume of contrast media is a risk factor for CI-AKI. This means that patients who are going to have contrast agents should be assessed for their risk of AKI. The NICE AKI Quality Standard discusses the need to identify those at risk of CI-AKI and discussing with the patient the potential causes and steps that will be taken for prevention. The European Society of Cardiology (ESC) Council for Cardiology practice noted in their 2009 guidelines for the prevention of CI-AKI that higher contrast volumes are associated with higher rates of CI-AKI and recommends in patients with chronic kidney disease, diagnostic catheterization contrast volume be < 30 mL and <100 mL for percutaneous coronary interventions (Arribas 2009). The ESC 2019 guideline for the diagnosis and management of chronic coronary syndromes stresses the need for minimization of iodinated contrast volume to prevent kidney function deterioration (Knuuti 2019).

The ESC 2019 guideline for the diagnosis and management of chronic coronary syndromes states CKD patients are less likely to receive invasive management for treatment of coronary artery disease compared to those without CKD (Knuuti 2019); therefore, procedure-based strategies to reduce CI-AKI risk factors such as contrast media volume have the potential to improve access of coronary and peripheral angiography to patients who are at a higher risk for CI-AKI.

Guideline-based prevention strategies for at risk patients are depicted in the following clinical care diagram.



*Describe any training (for healthcare professionals and patients) and system changes that would be needed if the NHS were to adopt the technology.

DyeVert Contrast Reduction Systems (DyeVert Systems) are used in the Cardiac Catheter Laboratory in addition to standard of care angiography equipment.

During equipment preparation before the procedure, Cath Lab staff connect the DyeVert System to the existing contrast injection line between the clinician administering contrast and system components that are placed within the patient; therefore, the DyeVert System is simply added to the current equipment set-up for each procedure. Cath lab staff set up and prime the DyeVert System along with all of the other procedure tubing using standard priming techniques. DyeVert System preparation is estimated to add no more than a few minutes to routine set-up activities.

During the procedure, clinicians (Consultant Cardiologist, Interventional Cardiologist, or Cath Lab staff member) complete contrast injections per usual practices and have the option to turn the DyeVert System on or off for contrast agent counting and/or contrast reduction at any time throughout the procedure. Overall procedure time is not impacted by the use of the DyeVert System.

Human factors testing demonstrates the intuitive design of the DyeVert System user interface and product Instructions for Use enable staff to use the product without formal training. However, staff introduction to product use is made available upon request.

4 Published and unpublished clinical evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used, and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		50, prior to removal of duplicate articles and removal of articles following full-text screening
Number of studies identified as being relevant to the decision problem.		21
Of the relevant studies identified:	Number of published studies (included in table 1).	8
	Number of abstracts (included in table 2).	9
	Number of ongoing studies (included in table 3).	2 ongoing studies and 2 unpublished studies

Full detail of the literature search criteria and methodology is provided in Appendix A of this document.

List of relevant studies

In the following tables, give brief details of all studies identified as being relevant to the decision problem.

- Summarise details of published studies in table 1.
- Summarise details of abstracts in table 2.
- Summarise details of ongoing and unpublished studies in table 3.
- List the results of all studies (from tables 1, 2 and 3) in table 4.

For any unpublished studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix C.

Table 1 Summary of all relevant published studies

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
A First in Human Evaluation of a Novel Contrast Media Saving Device	Sapontis et al, 2017 Location: Germany & Australia	Prospective, multicenter, single-arm, clinical pilot study	Sample size (n=44): >18 years of age, indicated for a coronary angiogram (n=34) or PCI procedure (n=10). Patients were excluded if they were undergoing a PCI for ST-segment elevation myocardial infarction, were pregnant, or were not considered appropriate candidates in the investigator's opinion. Enrolled: n=44 Completed study: n=44 (The project involved just the day of procedure) Baseline characteristics: Age (years), Mean ± SD: 69.3 ± 10.6 Median (interquartile range): 73 (63, 78) 95% CI: 61.2-67.5 Male gender, n=30 (68.2%) Procedure type, Diagnostic only: n=34 (77.3%) Diagnostic + PCI: n=7 (15.9%) PCI only: n=3 (6.8%) Baseline comorbidities: - Known coronary artery disease, n (%): 23 (52.3%) - History of unstable angina, n (%):10 (22.7%) - History of myocardial infarction, n (%):13 (29.6%) - Previous CABG, n (%): 4 (9.1%) - Previous PCI, n (%): 16 (36.4%)	Manual manifold injection and the DyeVert System	Manual manifold injection	Main outcomes: - Cumulative contrast volume attempted to be injected - Actual contrast volume injected - Contrast Volume saved, Absolute - Percent of attempted contrast volume saved - Cumulative contrast volume attempted to be injected - Actual contrast volume injected - Contrast Volume saved, Absolute - Percent of attempted contrast volume saved - Cumulative contrast volume attempted to be injected - Actual contrast volume injected - Contrast Volume saved, Absolute - Percent of attempted contrast volume saved - Image quality - Total procedure time - Fluoroscopy time - Adverse events - Physician-rated usability The DyeVert System

			- Congestive Heart Failure, n (%): 8 (18.2%) - Hypertension, n (%): 33 (75.0%) - Peripheral artery disease, n (%): 4 (9.1%) - Diabetes, n (%): 15 (34.1%) - Chronic kidney disease, n (%): 19 (43.2%)			reduces over-injection and minimizes total contrast volumes by optimizing the contrast flow rate to the patient while diverting excess contrast away from the patient, along with decreasing reflux of CM into the aorta, while achieving image quality adequate to successfully perform coronary diagnostic and interventional procedures. DyeVert System has an acceptable intraprocedural use time and acceptable size for use with a standard manifold. It does not interfere with procedural objectives or alter the conduct of the procedure indicating it can be used effectively for almost all cases.
Contrast minimization with the new generation DyeVert Plus System for contrast reduction and real-time monitoring during coronary and peripheral	Corcione et al, 2017 Location: Italy	Retrospective, observational, single-arm, single-center study	Sample size (n=10): Patients with coronary diagnostic procedures (n=5), percutaneous coronary intervention (n=3), and peripheral interventions (n=2). Enrolled: n=10 Completed study: n=10 Baseline characteristics: Age (years), Mean ± SD: 66.0 ± 12.04 Baseline Serum Creatinine (mg/dL), Mean ± SD: 1.0 ± 0.2	Manual manifold injection and the DyeVert System	None	Main outcomes: - Cumulative contrast volume attempted to be injected - Actual contrast volume injected - Contrast volume saved, Absolute - Percent of attempted contrast volume saved - Volume estimate from manual measurement - Volume estimate from DyeVert Plus system

procedures: first experience						- Absolute difference in volume estimates - Absolute difference in volume estimates - Actual CMV/eGFR ratios - Actual CMV/eGFR ratios (% of cases in each ratio grouping) - Attempted CMV/eGFR ratios - Attempted CMV/eGFR ratios (% of cases in each ratio grouping) - Attempted vs actual CMV/eGFR ratio difference - Adverse events - Physician-rated usability The results show that DyeVert Plus can substantially reduce total contrast volume in coronary and endovascular procedures, with an average contrast saving of 56 mL in absolute terms and 42% in relative terms. Notably, in all cases, the DyeVert Plus system was capable of achieving clinically relevant reductions in contrast. All procedures were uneventful and hospital stays were devoid of complications.
Impact of a novel contrast reduction system on	Desch et al, 2018	Prospective, single-center, open-label, randomised	Sample size (n=96): Patients ≥18 years of age, scheduled for a diagnostic coronary angiogram due to suspected	Manual manifold injection and the	Manual manifold injection (n=48)	Main outcomes: - Fluoroscopy time - Procedure time

contrast savings in coronary angiography – The DyeVert randomised controlled trial	Location: Germany	controlled study	coronary artery disease or progression of known coronary artery disease. Exclusion criteria included ST-elevation myocardial infarction, known anomalous coronary anatomy, previous coronary artery bypass grafting, severe peripheral artery disease at the access site, examination without specific diagnostic coronary angiogram (i.e. staged percutaneous coronary intervention), and pregnancy. Enrolled: n=96 Completed study: n=94 subjects were evaluable for the primary endpoint (One patient violated an exclusion criterion (known coronary anomaly), in another patient CM volume could not be evaluated since the CM bottle was inadvertently discarded). Baseline characteristics: Age (years), DyeVert: Mean ± SD: 68.6 ± 13.6 Control: Mean ± SD: 66.2 ± 12.8 P= 0.39 Male gender, DyeVert: n=28 (58.3%) Control: n=28 (58.3) P= 1 Baseline comorbidities: - Known coronary artery disease, n (%): DyeVert: 15 (31.3); Control: 17 (35.4); P= 0.83 - Congestive heart failure, n (%): DyeVert: 20 (41.7); Control: 19 (39.6); P= 1.00 - Known peripheral artery disease, n (%): DyeVert: 8 (16.7); Control: 8 (16.7); P= 1.00 - Arterial hypertension, n (%): DyeVert: 35 (72.9); Control: 34 (70.8); P= 1.00	DyeVert System (n=48)		- Actual contrast volume injected - Percent of attempted contrast volume saved - Image quality - Adverse events The DyeVert™ system significantly reduces the volume of CM administered during diagnostic coronary angiographies. These savings are achieved without a reduction in image quality at an excellent safety profile without device-related events. The system is designed to reduce the injection overshoot by the operator leading to decreased aortic reflux, hence optimizing intracoronary CM application. This study shows a significant 49.5% reduction of CI-AKI in a posthoc analysis of patients with a glomerular filtration rate between 40 and 60 mL/min/m2. This study confirms the effect of the DyeVert™ system on clinical outcomes in patients at high-risk for CI-AKI and/or moderate chronic kidney disease.

			- Diabetes mellitus, n (%): DyeVert: 6 (12.5); Control: 8 (16.7); P= 0.77 - Chronic kidney disease, n (%): DyeVert: 33 (68.8); Control: 37 (77.1); P= 0.49 - Anaemia, n (%): DyeVert: 5 (10.4); Control: 8 (16.7); P= 0.55 - Prior PCI, n (%): DyeVert: 11 (22.9); Control: 13 (27.1); P= 0.81			
Minimizing radiographic contrast administration during coronary angiography using a novel contrast reduction system: A multicenter observational study of the DyeVert™ plus contrast reduction system	Gurm et al, 2019a Location: USA	Prospective multicenter, single-arm, observational study	Sample size (n=114): ≥18 years old patients, scheduled to undergo CAG and/or PCI, and had a baseline estimated glomerular filtration rate (eGFR) of ≥20 and ≤60 mL/min/1.73 m^2. Subjects were excluded from participation if they had acute ST-elevation myocardial infarction or known coronary artery fistulas, had a body mass index (BMI) >40, were currently pregnant, were undergoing a chronic total occlusion procedure or optical coherence tomography analysis, were planning to undergo transcatheter aortic valve replacement within 72 hr of the index procedure, or had a condition known to require large volumes of contrast (>10 mL) for each injection. Enrolled: n=114 Completed study: n=105 subjects were evaluable for the primary endpoint. All enrolled subjects contributed to the secondary endpoint analysis. Baseline characteristics: Age (years), Mean ± SD: 72 ± 9 Male gender, n=82 (72%) eGFR (mL/min/1.73 m^2), Mean ± SD: 43 ± 11 Serum creatinine (mg/dL), Mean ± SD: 1.6 ± 0.5 Procedure type,	Manual manifold injection and the DyeVert System	None	Main outcomes: - DyeVert System Set-Up & Priming - Contrast volume threshold - Cumulative contrast volume attempted to be injected - Actual contrast volume injected - Percent of attempted contrast volume saved - Actual CMV/eGFR ratios - Attempted CMV/eGFR ratios - Image quality - CI-AKI rate - Adjusted CI-AKI rate - CI-AKI Rate Reduction, Absolute - CI-AKI Rate Reduction, Relative - Adverse events - Fluoroscopy time The overall magnitude of the CMV saved is both clinically meaningful and statistically significant. In the majority of cases, the CMV delivered is less than the predefined CMV threshold. The observed

			CAG only: n=74 (65%) CAG + PCI: n=30 (26%) PCI only: n=10 (9%) Baseline comorbidities: - Hypertension, n (%): 110 (96) - Coronary artery disease, n (%): 86 (75) - Prior PCI, n (%): 60 (53) - Diabetes, n (%): 60 (53) - Congestive heart failure, n (%): 54 (47) - Prior coronary artery bypass graft, n (%): 40 (35) - Prior myocardial infarction, n (%): 39 (34) - Anemia, n (%): 33 (29) - Angina, n (%): 30 (26) Baseline projected CI-AKI risk: - Mehran Risk Score, mean ± STD: 9.0 ± 3.9			CI-AKI rate in this study is significantly lower than predicted and adds to the large body of data suggesting that strategies to reduce CMV can result in improved patient outcomes. Concurrent with the reduction in CMV, the use of DyeVert Plus resulted in a shift in the actual versus attempted CMV/eGFR ratio. Since the association between CI-AKI and CMV/eGFR is non-linear, a left-ward shift would be expected to significantly reduce the incidence of AKI. Indeed, none of the patients in whom the CMV/eGFR ratio was less than 1, developed AKI. The DyeVert Plus System attunes the entire catheterization laboratory to the importance of CM thresholds and CMV minimization and potentially helps drive renal safety in the catheterization laboratory.
Early clinical experiences with a novel contrast volume reduction system during	Bruno et al, 2019 Location: Germany	Retrospective, observational, single-arm, single-center pilot study	Sample size (n=9): Patients who had diagnostic or interventional invasive coronary angiography over 2 consecutive days in November 2018. Enrolled: n=9	DyeVert Power XT system use with an automated contrast delivery system	None	Main outcomes: - Actual Contrast Volume Injected - Cumulative Contrast Volume Attempted to be Injected

invasive coronary angiography			Completed study: n=9 (The project involved just the day of procedure) Baseline characteristics: Age (years), Mean ± SD: 71 ± 10 Male gender, n=5 (56%) eGFR (MDRD; mL/min/1.73 m^2), Mean ± SD: 71.5 ± 9.4 eGFR (CKD-EPI; mL/min/1.73 m^2), Mean ± SD: 67.8 ± 10.3 Serum creatinine (mg/dL), Mean ± SD: 1.15 ± 0.36 Baseline comorbidities: - Hypertension (%): 7 (78) - Diabetes mellitus (%): 4(44) - Congestive heart failure (%): 6 (67) - Prior coronary artery disease (%): 7 (78) Baseline projected CI-AKI risk (Mehran Risk Score): - Moderate risk 67% - High risk 22%			- Percent of Attempted Contrast Volume saved - Attempted CMV/Creatinine Clearance (CrCl) Ratios - Actual CMV/CrCl Ratios - Image quality - Adverse events This study shows the DyeVert Power XT System reduces CM volume to the patient – without reducing image quality for the physician and increasing risk to the patient for adverse events in procedures involving automated contrast injection systems. A reduction of 61% for the ratio of total CM volume to creatinine clearance was reported.
Use of the DyeVert System in Chronic Total Occlusion Percutaneous Coronary Intervention	Tajti et al, 2019 Location: USA	Retrospective, observational, single-center study	Sample size (n=130): Patients who underwent chronic total occlusion (CTO) percutaneous coronary intervention (PCI) Enrolled: n=130 Completed study: n=130 Baseline characteristics: Age (years), Mean ± SD: DyeVert used: 67.7 ± 8.9; DyeVert not used: 66.1 ± 11.7; P= .38 Male gender, (%): DyeVert used: 82.1; DyeVert not used: 78.0; P= .60	Manual manifold injection and the DyeVert System (n=39)	Manual manifold injection (n=91)	Main outcomes: - Procedural success - Non-CTO PCI - Length of hospital stay - Procedural time - Fluoroscopy time - Actual Contrast Volume Injected - Procedural complications - In-Hospital AKI - Postprocedural AKI - Air kerma radiation - Major adverse cardiac event - Procedural complications

			eGFR (mL/min/1.73 m^2), Median (interquartile range): DyeVert used: 71.6 (54.6-82.5); DyeVert not used: 77.1 (57.0-88.9); P= .26 Serum creatinine (mg/dL), Median (interquartile range): DyeVert used: 1.1 (0.9-1.2); DyeVert not used: 1.0 (0.9-1.2); P= .50 Baseline comorbidities: - Diabetes, (%): DyeVert used: 48.7; DyeVert not used: 41.8; P= .46 - Dyslipidemia, (%): DyeVert used: 94.9; DyeVert not used: 97.8; P= .37 - Hypertension, (%): DyeVert used: 89.7; DyeVert not used: 82.6; P= .79 - Congestive heart failure, (%): DyeVert used: 20.5; DyeVert not used: 19.8; P= .92 - Prior myocardial infarction, (%): DyeVert used: 53.9; DyeVert not used: 34.1; P= .04 - Prior coronary artery bypass graft, (%): DyeVert used: 48.7; DyeVert not used: 37.4; P= .23 - Prior PCI, (%): DyeVert used: 71.8; DyeVert not used: 62.6; P= .32 - Prior cerebrovascular disease, (%): DyeVert used: 15.4; DyeVert not used: 6.7; P= .18 - Prior peripheral vascular disease, (%): DyeVert used: 20.5; DyeVert not used: 5.6; P= .01 - Chronic pulmonary disease, (%): DyeVert used: 12.8; DyeVert not used: 15.6; P= .69 - Currently on dialysis, (%): DyeVert used: 2.6; DyeVert not used: 3.3; P= .77 - Prior failed CTO-PCI, (%): DyeVert used: 15.0; DyeVert not used: 20.2; P=0.48 Technical Characteristics - CTO length, (mm): DyeVert used: 40; DyeVert not used: 30; P=0.18			- Adverse events - eGFR at discharge - Creatinine at discharge - Change in eGFR - Change in creatinine The main finding of this study is that the DyeVert System can be used during CTO-PCI and is associated with administration of less contrast volume. This study shows 20% lower contrast media volume in patients undergoing CTO-PCI.

			- Balloon undialatable lesions, (%):DyeVert used:27.3; DyeVert not used: 14.6; P=0.11			
Impact of a contrast media volume control device on acute kidney injury rate in patients with acute coronary syndrome	Briguori et al, 2020 Location: Italy	Retrospective, observational, single-center, propensity-matched controlled, investigator-driven study	Sample size (n=180): Patients with ACS who had urgent or immediate coronary angiography or angioplasty. Patients with end-stage renal failure requiring dialysis, with recent (≤7 days) CM exposure and those referred from a spoke centre for an invasive treatment but not hospitalized in our institution were excluded. Enrolled: DyeVert Group n=112; Control Group n=339 Completed study: DyeVert cases were propensity matched to Controls, n=180 Baseline characteristics: Age (years), Mean ± SD: DyeVert: 62.5 ± 13.4; Control: 63.5 ± 12.5; P= .61 Male gender, (%): DyeVert: 64 (71%); Control: 69 (76.5%); P= .39 Serum creatinine (mg/dL), Median (interquartile range): DyeVert: 0.99 (0.83-1.14); Control: 0.97 (0.82-1.22); P= .97 eGFR (mL/min/1.73 m^2), Mean ± SD: DyeVert: 74 ± 26; Control: 79 ± 28; P= 1.00 Baseline comorbidities: - Systemic hypertension, n (%): DyeVert: 55 (61); Control: 56 (62); P= .78 - Diabetes, n (%): DyeVert: 20 (22); Control: 16 (18); P= .46	Manual manifold injection and the DyeVert System (n=90)	Manual manifold injection (n=90)	Main outcomes: - Actual Contrast Volume Injected - Percent of cases where actual contrast volume injected exceeded the predefined contrast threshold - Percent of Attempted Contrast Volume saved - Contrast volume saved, Absolute - Rate of CI-AKI - Stage 1 CI-AKI - Stage 2 & 3 CI-AKI - Length of in-hospital stay - Length of in hospital stay in patients who experienced AKI -1-month MAE rate - Serum creatinine - Receiver Operating Characteric Curve Analysis - Independent Predictors of AKI - In hospital renal failure requiring RRT - Progression of kidney disease - Image quality The reduction in CM volume obtained by the

			- Peripheral chronic artery disease, n (%): DyeVert: 74 (21); Control: 71 (20); P= .78 - Left ventricular ejection fraction <40%, n (%): DyeVert: 15 (17); Control: 14 (15); P= .84 - Killip class ≥2, n (%): DyeVert: 11 (12); Control: 10 (11); P= .95 Baseline projected CI-AKI risk: - Mehran Risk Score, mean ± STD: DyeVert: 4 ± 2; Control: 4 ± 3; P=.72 - Mehran Risk Score, % high risk: DyeVert 12%; Control: 10% high risk; P=.81 - Gurm Risk Score, mean ± STD: DyeVert: 8 ± 7; Control: 7 ± 7; P=.34 - Gurm Risk Score % high risk: DyeVert: 49%; Control: 35%; P=.097			DyeVert System is associated with a significant reduction in CI-AKI rate. This study shows a significant direct correlation between CM volume and maximal absolute difference in SCr in the Control group but not in the DyeVert group. This finding suggests that the use of the DyeVert system, by limiting CM volume, may neutralize the clinical impact of CM on the occurrence of CI-AKI in ACS patients. The 63% CI-AKI relative risk reduction observed in the DyeVert group is obtained even with a high hydration regimen. Incidence of in-hospital MACE rate was low (0.77%) and similar in both groups (0% in DyeVert vs 2.2% in Control); p>.99). No device-related complications occurred.
A feasibility study of the DyeVert™ plus contrast reduction system to reduce contrast media volumes in percutaneous	Zimin et al, 2020 Location: USA	Prospective, post-market, single-arm, clinical feasibility study	Sample size (n=30). ≥18 years of age, undergoing coronary OCT for diagnostic and/or PCI procedures, and able to provide informed consent. Patients excluded from the study included those with emergent presentation and those deemed not suitable for catheterization with ad hoc coronary intervention.	Manual manifold injection with OCT imaging and the DyeVert System (N=15)	Manual manifold injection with OCT imaging (n=15)	Main outcomes: - Contrast volume threshold - Cumulative contrast volume attempted to be injected - Actual contrast volume injected - Contrast volume saved, Absolute

coronary procedures using optical coherence tomography (OCT)			Enrolled: Contrast endpoint: DyeVert Group n=15 patients undergoing 16 OCT-guided procedures; Image quality endpoint: DyeVert Group n=16 procedures, Control Group n=15 procedures Completed study: Contrast endpoint: DyeVert Group n=14 patients undergoing 15 OCT-guided procedures (1 patient excluded due to imaging protocol violation); Image quality endpoint: DyeVert Group n=15 procedures (1 patient excluded due to OCT procedural error), Control Group n=15 procedures Baseline characteristics: Age (years), Mean ± SD: 67 ± 11 Male gender, (%): 11 (78.6%) eGFR (mL/min/1.73 m^2), Mean ± SD: 71 ± 20 Serum creatinine (mg/dL), Mean ± SD: 1.04 ± 0.28 Procedure type (DyeVert Group), CAG only: n=0 (0%) CAG + PCI: n=13 (86.7%) PCI only: n=2 (13.3%) Baseline comorbidities (DyeVert Group): - Hyperlipidemia, n (%): 13 (92.9) - Hypertension, n (%): 12 (85.7) - Prior PCI, n (%): 8 (57.1) - Diabetes, n (%): 7 (50) - Chronic lung disease, n (%): 3 (21.4) - Congestive heart failure, n (%): 2 (14.2) - Chronic kidney disease, n (%): 1 (7) - Currently on dialysis, n (%): 1 (7) - Peripheral artery disease, n (%): 1 (7)			- Percent of Attempted Contrast Volume saved - Total procedural time - Adverse events - Image quality The reported data demonstrate a 37.5% mean savings in CMV delivered to patients during these procedures, which were performed by manual injection. Independent comparative analyses of images acquired during PCI procedures performed using the DyeVert System among the study participants versus images from a control group of patients who underwent OCT-guided PCI without the use of the DyeVert System indicated that the clear region of interest in the DyeVert Group was non-inferior to that in the Control Group. The device directly reduces CMV delivered to the patient by minimizing wasted reflux into the aortic root and the wireless display component indirectly increases clinicians' awareness of CMV by providing real-time feedback on total CMV delivered to the patient compared to the clinician's

						predefined CM usage threshold.

Table 2 Summary of all relevant abstracts [THIS PAGE LEFT BLANK]

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
Real-world impact of a quality improvement program for acute kidney injury prevention in the cardiac cath lab	Turner & Tucker 2020 Location: USA	Retrospective, observational, single-center, real-world data analysis from the National Cardiovascular Data Registry (NCDR) Cath PCI Registry	Sample size (n=703). PCIs, all comers, DyeVert use in n=536 patients with CKD or STEMI Approximately 30% of the cath lab population is at risk for CI-AKI	Manual manifold injection and the DyeVert System	None	Main outcomes: - Contrast volume injected - Contrast volume saved, Absolute - CMV/eGFR ratio - Attempted vs actual CMV/eGFR ratio difference - Actual CMV/eGFR ratios - Attempted CMV/eGFR ratios - Absolute reduction in CI-AKI - Relative reduction in CI-AKI - Number-Need-to-Treat to Avoid 1 CI-AKI event - Cost neutrality boundary Preliminary results of this ongoing quality improvement program highlight the clinical and economic effectiveness of a real-world initiative for improving outcomes for at-risk patients undergoing angiography.
Use of DyeVert Plus to reduce contrast exposure in high-	Bath et al, 2019	Prospective, single-center, randomised controlled trial	Sample size (n=108).	Manual manifold injection and the DyeVert System (n=49)	Manual manifold injection (n=59)	Main outcomes: - Actual Contrast Volume Injected

risk patients undergoing coronary angiography	Location: the USA		Diagnostic coronary angiography, all patients had CKD			- Percent of Attempted Contrast Volume saved There is statistically and a clinically significant reduction in the total CMV with DyeVert Plus as compared to manual injection in coronary angiography. Thus, leading to decreased CM exposure to the kidneys in high-risk patients which have been found to reduce the incidence of CIN.
Clinical and economic outcomes of a comprehensive clinical quality initiative for reducing acute kidney injury in chronic kidney disease patients undergoing coronary angiography	Kutschman et al, 2019a Location: USA	Retrospective, observational, single-center, real-world data analysis	Sample size (n=206). Chronic kidney disease patients who underwent diagnostic coronary angiography and/or PCI. Patients on dialysis were excluded. Baseline characteristics: Age (years), Mean ± SD: 69 ± 11 Male gender, (%): 57% eGFR (mL/min/1.73 m^2), Mean ± SD: 43 ± 13 Procedure type, PCI: 63% Diagnostic angiography: 37%	Manual manifold injection and the DyeVert System (n=128)	Manual manifold injection (n=78)	Main outcomes: - Percent of Attempted Contrast Volume saved - Actual Contrast Volume Injected - CMV/eGFR ratio - Attempted vs actual CMV/eGFR ratio difference - CI-AKI rate - Absolute reduction in CI-AKI - Relative reduction in CI-AKI - Number-Need-to-Treat to Avoid 1 AKI event - Hospital budget impact Implementation of the CI-AKI reduction protocol has already resulted in positive

						clinical and economic outcomes.
Comprehensive clinical quality initiative for reducing acute kidney injury in at-risk patients undergoing diagnostic coronary angiogram and/or percutaneous coronary interventions	Kutschman et al., 2019b Location: USA	Retrospective, observational, single-center, real-world data analysis	Sample size (n=501). All comer patients who underwent a diagnostic coronary angiography and/or percutaneous coronary interventions. Patients on dialysis were excluded. DyeVert System use in all inpatients and high-risk outpatients Baseline characteristics: Age (years), Mean ± SD: 66 ± 12 Male gender, (%): 63% eGFR (mL/min/1.73 m^2), Mean ± SD: 64 ± 32 Serum creatinine (mg/dL), Mean ± SD: 1.6 ± 1.6 Procedure type, Diagnostic only: 31% PCI only: 69% (Chronic total occlusions: 9%) Baseline comorbidities: - Hyperlipidemia, (%): 57% - Hypertension, (%): 82% - 4 or more comorbidities, (%): 74% - Cardiovascular disease, (%): 55% - Prior PCI, (%): 27% - Prior CABG, (%): 23% - Diabetes, (%): 55% - Chronic lung disease, (%): 13% - Heart failure, (%): 23% - Obesity, (%): 14%	Manual manifold injection and the DyeVert System (n=258)	Manual manifold injection (n=243)	Main outcomes: - Contrast volume threshold - Actual Contrast Volume Injected - Percent of Attempted Contrast Volume saved - Contrast volume saved, Absolute - Actual CMV/eGFR ratio - % Under contrast threshold - CI-AKI rate - Absolute reduction in CI-AKI - Relative reduction in CI-AKI This targeted, ongoing CI-AKI prevention quality improvement effort thus far resulted in a statistically significant and clinically meaningful reduction in CI-AKI events.

			- Cerebrovascular disease, (%): 8% - Anemia, (%): 7% - Chronic kidney disease, (%): 33% - Dialysis, (%): 9% - Peripheral artery disease, (%): 5% - Hypotension, (%): 1%			
Impact of using DyeVert PLUS on the incidence of acute kidney injury after cardiac catheterization with coronary interventions in high-risk patients	Sattar et al, 2018 Location: USA	Retrospective, observational, single-center, real-world data analysis	Sample size (n=109). Percutaneous coronary interventions, all patients had CKDBaseline characteristics: Age (years), DyeVert: Mean: 68.5 Control: Mean: 71.3 Male gender, DyeVert: 41% Control: 65% eGFR (mL/min/1.73 m^2), Mean: DyeVert: 43.6 Control: 47.7 Serum creatinine (mg/dL), Mean: DyeVert: 1.56 Control: 1.51 Procedure type, PCI using DyeVert: n=41 (38%) PCI using Control: n=68 (62%) Baseline comorbidities: - Hypertension, (%): Dyevert: 90% Control: 92.6% - Diabetes, (%): Dyevert: 53.6% Control: 51.2%	Manual manifold injection and the DyeVert System (n=41)	Manual manifold injection (n=68)	Main outcomes: - Pre and post procedure serum Cr - Change in SCr - Incidence of AKI - Absolute reduction in CI-AKI - Relative reduction in CI-AKI - Average contrast usage Utilization of the DyeVert Plus resulted in lower average contrast use during procedures. The pre and post-procedure Cr did not have a significant difference in either group. The DyeVert group showed a lower absolute incidence of CI-AKI but this difference was not statistically significant. The true clinical impact of DyeVert may not have been observed due to the small sample size and bias

						due to general awareness of contrast levels and CI-AKI.
DyeVert Plus contrast reduction system use in patients undergoing highly complex peripheral vascular interventions	Rao, 2019 Location: USA	Retrospective, observational, single arm, case series	Sample size (n=7). Highly complex peripheral vascular interventions. Baseline characteristics: Age (years), Mean ± SD: 66 ± 13 Male gender, (%): 43% eGFR (mL/min/1.73 m^2), Mean ± SD: 45.7 ± 29.2 Serum creatinine (mg/dL), Mean ± SD: 1.6 ± 0.6 Baseline comorbidities: - Hypertension, (%): 71% - Congestive heart failure, (%): 57% - Atrial fibrillation, (%): 29% - Myocardial infarction, (%) 29% - Coronary artery disease, (%) 43% - Ulcers, (%): 100% - Cellulitis, (%): 43% - Rutherford class V, (%): 43% - Rutherford class IV, (%): 43% - Wound infection, (%): 29% - Deep vein thrombosis, (%): 14% - Rutherford class III, (%): 14% - Diabetes, (%): 86% - Chronic kidney disease, (%): 86%	Manual manifold injection and the DyeVert System	None	Main outcomes: - Mean CMV per case - CMV/eGFR ratios - Renal function post-procedure -Maintenance of image quality -Contrast-media related population risk factor reduction The DyeVert plus use in Peripheral vascular interventions to reduce CMV was feasible and resulted in clinically meaningful contrast reduction such that CMVs and CMV/eGFR ratios were reduced in all patients.

Contemporary use of contrast dye reduction technology in a tertiary academic hospital: patient characteristics and acute kidney injury outcomes following percutaneous coronary interventions	Bunney et al, 2019 Location: USA	Retrospective, observational, single-center, real-world data analysis from the National Cardiovascular Data Registry (NCDR) Cath PCI Registry	Sample size (n=799). Percutaneous coronary interventions, all comers Baseline characteristics: Age (years), Mean: DyeVert: 63 No DyeVert: 61 eGFR (<30 mL/min/1.73 m^2), (%): DyeVert: 10.3 No DyeVert: 3.2 eGFR (30-44 mL/min/1.73 m2), (%): DyeVert: 20.7 No DyeVert: 6 eGFR (45-60 mL/min/1.73 m2), (%): DyeVert: 24.2 No DyeVert: 14.3 eGFR (>60 mL/min/1.73 m2), (%): DyeVert: 44.8 No DyeVert: 76.5 Baseline comorbidities: - Diabetes, (%): DyeVert: 72.4; No DyeVert: 48.4 - Prior heart failure, (%): DyeVert: 27.6; No DyeVert: 15.3 Procedure characteristic: - Multivessel interventions, (%): DyeVert: 31; No DyeVert: 25 - Hemodynamic support, (%): DyeVert: 20; No DyeVert: 3.7	Manual manifold injection and the DyeVert System (n=29)	Manual manifold injection (n=770)	Main outcomes: - CI-AKI rate - Absolute reduction in CI-AKI - Relative reduction in CI-AKI - Mean contrast used There is a lower non risk adjusted CI-AKI rate in these patients when compared to the patients without DyeVert use despite the higher risk for CI-AKI. While the mean contrast use was comparable among the two groups, the patients in the DyeVert Group underwent more complex PCIs.

			- Complex lesions, (%): DyeVert: 72; No DyeVert: 58			
First European experience using a novel contrast reduction system during coronary angiography with automated contrast injection	Amoroso et al, 2020 Location: the Netherlands, Germany, UK	Retrospective, observational, mutlicenter, single arm study	Sample size (n=26). Patients who underwent a diagnostic coronary angiography (54%) and/or percutaneous coronary interventions (46%).	DyeVert Power XT system use with an automated contrast delivery system	None	Main outcomes: - Actual contrast volume injected - Percent of attempted contrast volume saved - Image quality - Physician-rated usability Data collected in this project suggest DyeVert Power XT System use with automated contrast injectors during coronary angiography enables meaningful contrast media volume savings without diminishing image quality or disrupting clinical practices thereby providing a feasible procedure-based strategy to reduce CI-AKI risk through reduction of a known risk factor, contrast media volume.
Reduction of contrast-induced acute kidney injury in a cardiac catheterization laboratory: A quality improvement initiative	Cameron et al, 2020 Location: USA	Retrospective, observational, single-center, real-world data analysis from the National Cardiovascular Data Registry (NCDR) Cath PCI Registry	Sample size (n=1956). PCIs, all comers, DyeVert use in n=423 patients with CKD 1123 (57%) diagnostic cases and 833 (43%) percutaneous coronary intervention cases.	Manual manifold injection and the DyeVert System (n=423)	None	Main outcomes: - Contrast volume injected - Contrast volume saved, Absolute - Percent of attempted contrast volume saved - CMV/eGFR ratio

			Quality improvement protocol for CI-AKI prevention followed in 1,789 (91%) cases.			- Attempted vs actual CMV/eGFR ratio difference -% Under contrast threshold - Dyevert attempted CMV/eGFR ratio - Dyevert actual CMV/eGFR ratio - Absolute reduction in CI-AKI (PCI Procedures) - Relative reduction in CI-AKI (PCI Procedures) - Relative reduction in CI-AKI, Diagnostic Procedures - Number-Need-to-Treat to Avoid 1 CI-AKI event - Hospital budget impact Patient-centred care delivery was augmented by focused contrast reduction strategies including a novel CMV monitoring and minimization system (DyeVert) in high-risk patients, which reduced known CI-AKI risk factors associated with total contrast volume delivered (CMV, CMV/eGFR ratio).

Table 3 Summary of all relevant ongoing or unpublished studies

Data source	Author, year (expected completion) and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Outcomes
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

			[redacted]			[redacted]
Single-Center Prospective Study to Investigate the Difference in the Incidence of Contrast-Induced Nephropathy in High-Risk Patients with the Use of the Dye-Vert Plus System https://clinicaltrials.gov/ct2/show/record/NCT04279457	Estimated Primary Completion Date: February 3, 2022	Prospective, single-center randomized controlled trial	Sample size: (n=1802) Inclusion Criteria: • 18 years of age or older • Scheduled to undergo CAG and/or PCI • Baseline estimated glomerular filtration rate (eGFR) of ≥20 and ≤60 mL/ min/1.73 m2 • Serum creatinine > 1.5mg/dl • Obtaining a Cardiac catheterization. • HTN/Diabetes • Inpatient and outpatient Exclusion criteria: • 91 years of age or older	Manual manifold injection and the DyeVert System with a standardized hydration protocol	Manual manifold injection and a standardized hydration protocol	Main outcomes: - CI-AKI rates - Contrast volume delivered to the patient -Contrast-related complications -Healthcare economics Not available. (Outcomes are being collected)

			• Serum creatinine < 1.5mg/dl • eGFR > 60ml/min • Pregnancy • Dialysis • Dye Allergy			
DyeVert™ System Use for Contrast Monitoring and Minimization in At-Risk Patients Undergoing Angiography Procedures: A Real-World Registry (DyeMINISH) https://clinicaltrials.gov/ct2/show/NCT03825094	Estimated Study Completion Date: December 2023	Retrospective, multi-center, observational study	Sample size: up to 10,000 participants at up to 50 centers Patients who underwent a diagnostic and/or interventional angiography procedure who are at risk for CI-AKI Comparative health outcomes substudy included **Inclusion Criteria:** DyeVert Group Patients: Patient underwent a diagnostic and/or interventional angiography procedure in which the DyeVert System was used in a majority of the case Control Group Patients: Patient underwent a diagnostic and/or interventional angiography procedure in which the DyeVert System was not used **Exclusion Criteria:** Required data was not collected or is not available	Manual manifold injection and the DyeVert System	Manual manifold injection	Main outcomes: - Contrast Volume Threshold target - % Cases Contrast Volume Threshold was Exceeded - Contrast Volume Delivered to the Patient- Contrast Volume/eGFR Ratio - DyeVert System Contrast Volume Saved (mL and %) - Major adverse renal and cardiac events through 120 days post-index procedure - CI-AKI rate Not available. (Outcomes are being collected)

Table 4 Results of all relevant studies (from tables 1, 2, and 3)

Study	Results	Company comments
Sapontis et al, 2017 Evaluation of a Novel Contrast Media Saving Device	**Cumulative contrast volume attempted to be injected (mL) (All Procedures)** Mean ± SD: 172.9 ± 116.8 (Min, Max): (70, 533) **Actual contrast volume injected (mL) (All Procedures)** Mean ± SD: 88.7 ± 56.9 (Min, Max): (37, 263) **Contrast Volume saved, absolute (mL) (All Procedures)** Mean ± SD: 84.1 ± 66.1 (Min, Max): (33, 317) **Percent of attempted contrast volume saved (All Procedures)** Mean ± SD: 47.4% ± 8.7% (P <0.0001) (Min, Max): (31.9%, 66.1%) **Cumulative contrast volume attempted to be injected (mL) (Diagnostic Only)** Mean ± SD: 122.6 ± 43.6 (Min, Max): (70, 250) **Actual contrast volume injected (mL) (Diagnostic Only)** Mean ± SD: 65.3 ± 26.6 (Min, Max): (37, 154) **Contrast Volume saved, absolute (mL) (Diagnostic Only)** Mean ± SD: 57.3 ± 24.8	Supports claimed benefits of the technology: • Total contrast media volume reduction (on average 40% reduction in contrast media dose delivered to the patient) • Contrast-media related population risk factor reduction • Maintenance of image quality • No device-related adverse events

	(Min, Max): (33, 126) **Percent of attempted contrast volume saved (Diagnostic Only)** Mean ± SD: 46.6% ± 68.6% (Min, Max): (31.9%, 66.1%) **Cumulative contrast volume attempted to be injected (mL) (PCI)** Mean ± SD: 343.8 ± 127.4 (Min, Max): (112, 533) **Actual contrast volume injected (mL) (PCI)** Mean ± SD: 168.3 ± 61.5 (Min, Max): (56, 263) **Contrast Volume saved, Absolute (mL) (PCI)** Mean ± SD: 175.5 ± 81.5 (Min, Max): (56, 317) **Percent of attempted contrast volume saved (PCI)** Mean ± SD: 50.3% ± 8.8% (Min, Max): (36.6%, 63.4%) **Procedure type did not significantly impact percentage of attempted contrast volume saved** **Acceptable image quality** N= 43/44 (98%) Acceptable DyeVert System Set-Up and Priming 95% Diagnostic and/or Interventional Procedure Objectives Could Be Accomplished 96%	

	Diagnostic and/or Interventional Technique Did Not Need to be Altered 98% Authors report: “The DyeVert System is easy to use with current cath lab standard manual set-up. “Further, it requires very minimal training for use." **Total procedure time (min)** Mean ± SD: 20.2 ± 22.9 (Min, Max): (3, 87) **Fluoroscopy time (min)** Mean ± SD: 8.6 ± 7.2 (Min, Max): (1.6, 31.1) **Adverse events** No device-related adverse events were reported	
Corcione et al, 2017 Contrast minimization with the new generation DyeVert Plus System for contrast reduction and real-time monitoring during coronary and peripheral procedures: first experience	**Cumulative contrast volume attempted to be injected (Theoretical total contrast volume) (mL)** Mean (95% CI): 135.7 (95.2-186.7) Median (95% CI): 107.8 (83.1-187.5) **Actual contrast volume injected (mL)** Mean (95% CI): 79.9 (54.4-111.0) Median (95% CI): 62.6 (43.3-121.3) **Contrast volume saved, Absolute (mL)** Mean (95% CI): 55.8 (39.5-77.4), P<.05 Median (95% CI): 47.2 (35.2-81.5) **Percent of attempted contrast volume saved (%)** Mean (95% CI): 41.8 (37.7-46.0), P<.05	Supports claimed benefits of the technology: • Accurate, real-time, contrast media dose monitoring (DyeVert System data compared to manual measurements) • Total contrast media volume reduction (on average 40% reduction in contrast media dose delivered to the patient) • Contrast-media related population risk factor reduction • Maintenance of image quality • No device-related adverse events

	Median (95% CI): 40.7 (37.6-47.1) **Volume estimate from manual measurement (mL)** Mean (95% CI): 77.0 (49.8 to 110.7) Median (95% CI): 58.0 (35.5 to 110.3) **Volume estimate from DyeVert Plus system (mL)** Mean (95% CI): 75.3 (47.7 to 111.3) Median (95% CI): 55.6 (41.2 to 106.1) **Absolute difference in volume estimates (mL)** Mean (95% CI): -1.6 (-2.9 to -0.4), P<.05 Median (95% CI): -1.8 (-3.8 to -0.4) **Absolute difference in volume estimates (mL)** Mean (95% CI): -1.9 (-3.5 to 0.2), P>.05 Median (95% CI): -1.3 (-4.8 to 0.6) **Actual CMV/eGFR ratios** Mean ± SD: 1.0 ± 0.6 **Actual CMV/eGFR ratios (% of cases in each ratio grouping)** ≤1 in 60% of cases ≤2 in 90% of cases ≤3 in 90% of cases >3 in 10% of cases **Attempted CMV/eGFR ratios** Mean ± SD: 1.8 ± 0.9 **Attempted CMV/eGFR ratios (% of cases in each ratio grouping)** ≤1 in 40% of cases ≤2 in 60% of cases ≤3 in 90% of cases	

	>3 in 10% of cases **Attempted vs actual CMV/eGFR ratio difference** Mean: 0.7 **Adverse events** No device-related adverse events were reported. A single case of asymptomatic CIN in an 82-year-old gentleman with baseline moderate renal failure. This patient underwent carotid angiography and angioplasty, and despite the transient increase in serum creatinine after the procedure, could be discharged uneventfully 3 days after the procedure, with serum creatinine levels returning to the baseline values. **Acceptable image quality based on physician feedback:** 100% Authors report: "…the device was user friendly, requiring minimal preparation and training… "…it is easy to implement into the standard cath lab routine"	
Desch et al, 2018 Impact of a novel contrast reduction system on contrast savings in coronary angiography – The DyeVert randomised controlled trial	**Fluoroscopy time (min)** Mean ± SD: 3.9 ± 3.9 min in DyeVert System Group versus 3.7 ± 3.5 min in Control Group, P = 0.76 **Procedure time (min)** Mean ± SD: 11.1 ± 8.4 min in DyeVert System Group versus 9.1 ± 5.5 min in Control Group, P = 0.169 **Actual contrast volume injected (mL)** Mean ± SD: 36.9 ± 10.9 mL in DyeVert System Group versus 62.5 ± 12.7 mL in Control Group, P<0.001 **Percent of attempted contrast volume saved (%)** 41% decrease in the amount of CM used based on Log-transformed CM volume (P<0.001) and a non-parametric Wilcoxon test (P<0.001) The contrast reduction was consistent across all subgroups including 5 different physicians	Supports claimed benefits of the technology: • Total contrast media volume reduction • Contrast-media related population risk factor reduction • Maintenance of image quality • Accurate, real-time contrast media dose monitoring relative to the maximum dose target and recording • No device-related adverse events

	Percentage of images graded as adequate based on the physicians' feedback 95.5% versus 95.0% in DyeVert System and Control Groups respectively (P=0.74) Image quality was also evaluated based on physician feedback regarding the turning “OFF” of the DyeVert System at any time during the procedure. There were zero (0) instances where the system was turned off due to inadequate image quality or other device-related reasons. **Percentage of images graded as adequate based on the reviewers' feedback** Images deemed adequate, n [%]: DyeVert™ 320 [90.7] versus control 364 [97.3] Images deemed inadequate n [%]: DyeVert™ 33 [9.3] versus control 10 [2.7] Differences in rates [DyeVert™– control] -6.7, 95% lower confidence bound−9.6, P=0.03 for non-inferiority The predominant reason for inadequate image quality was inadequate catheter position (76.3%). **Adverse events** No adverse events were reported related to the DyeVert™ system.	
Gurm et al, 2019a Minimizing radiographic contrast administration during coronary angiography using a novel contrast reduction system: A multicenter observational study of the DyeVert™ plus contrast reduction system	**DyeVert system set-up & priming (min)** Mean ± SD: 3.3 ± 2.9 **Contrast volume threshold (mL)** Mean ± SD: 119 ± 48 mL (Min, Max): (40, 236) **Cumulative contrast volume attempted to be injected (mL)** Mean ± SD: 112 ± 85 mL	Supports claimed benefits of the technology: • Accurate, real-time, contrast media dose monitoring relative to the maximum dose target and recording • Total contrast media volume reduction (on average 40% reduction in contrast media dose delivered to the patient) • More likely to experience contrast administration at or below the maximum contrast media dose • Maintenance of image quality • No device-related adverse events • Reduction in CI-AKI incidence • Contrast-media related population risk factor reduction

	(Min, Max): (22, 681) **Actual contrast volume injected (mL)** Mean ± SD: 67 ± 51 mL (Min, Max): (12, 403) **Percent of attempted contrast volume saved (%)** Mean ± SD: 40.1 ± 8.8% (95% CI 38.4, 41.8; P < 0.0001) **Percent of cases where actual contrast volume injected was less than the predefined contrast threshold (%)** 91 cases (87%) **Actual CMV/eGFR ratios:** ≤1 in 33% of cases ≤2 in 75% of cases ≤3 in 92% of cases >3 in 8% of cases **Attempted CMV/eGFR ratios:** ≤1 in 7% of cases ≤2 in 42% of cases ≤3 in 74% of cases >3 in 26% of cases At lower CMV/eGFR ratios, the use of DyeVert Plus increased the percentage of subjects with ratios <1 from 7% (attempted) to 33% (actual) and with ratios <2 from 42% (attempted) to 75% (actual). Conversely, at higher CMV/eGFR ratios, the use of DyeVert Plus reduced the percentage of subjects with ratios >2 from 58% (attempted) to 25% (actual). **Image quality** Image quality was maintained in all but one diagnostic + PCI case where the DyeVert System was turned off for 1 injection only and	

	then resumed using the DyeVert System for the remainder of the case. **CI-AKI rate (Observed Rate, Full Safety Cohort)** N=11/114 (9.6%) 7 of these occurring in subjects with baseline eGFR <30. Investigators attributed the CI-AKI events to the following causes: 5 (4.4%) were fluid management related (over- or under-diuresis, diuretic use/congestive heart failure), 3 (2.6%) were contrast-related, 1 was related to a diabetic complication, 1 was due to a recent prior surgery, and in 1 case, the cause was unknown. **Adjusted CI-AKI rate (Observed rate, only subjects with pre and post-procedure serum creatinine)** N=11/54 (20.4%) **CI-AKI rate** For CMV/eGFR ≤1: 0% For CMV/eGFR >1-2: 12.5% For CMV/eGFR >2-3: 15.8% For CMV/eGFR >3: 22.2% Observed AKI rates increased with increasing CMV/eGFR ratios. **CI-AKI rate (Adjusted rate, using Mehran definition)** 6/54 (11.1%) **Predicted risk of CI-AKI**: 14% (Based on an imputed Mehran risk score) **CI-AKI rate reduction, absolute (%)** 2.9% **CI-AKI rate reduction, relative (%)** 20.7% **Adverse events** No DyeVert Plus System-related AEs or cases of contrast-related anaphylaxis were reported.	

	Fluoroscopy time (min) Mean ± SD: 12.8 ± 14.4 min Author's report: "The DyeVert Plus System probably impacts contrast dose via two related yet equally important mechanisms. Firstly, by minimizing wasted reflux into the aortic root, the system directly reduces the CMV administered to the patient. Secondly, by providing direct monitoring of the total CMV delivered to the patient, the system provides direct feedback to the operator and permits modifying the procedure to ensure that the predetermined CM threshold is not exceeded. Finally, the DyeVert Plus System attunes the entire catheterization laboratory to the importance of CM thresholds and CMV minimization and potentially helps drive renal safety in the catheterization laboratory. "	
Bruno et al, 2019 Early clinical experiences with a novel contrast volume reduction system during invasive coronary angiography	**Actual contrast volume injected (mL)** Mean: 80.6 mL (range 45.5 mL to 211.9 mL) **Cumulative contrast volume attempted to be injected (mL)** Mean: 127.8 mL (range 71.6 mL to 304.9 mL) **Percent of attempted contrast volume saved** Mean: 38.9% (range 31.0% to 47.0%) **Attempted CMV/Creatinine Clearance (CrCl) ratios:** Mean: 1.84 (array: 1.03–4.41) **Actual CMV/CrCl ratios:** Mean: 1.12 (array: 0.73–3.04) **Image quality** Image quality maintained in all cases. **Adverse events** No device-related complications occurred.	Supports claimed benefits of the technology. • Total contrast media volume reduction (on average 40% reduction in contrast media dose delivered to the patient) • Maintenance of image quality • No device-related adverse events • Contrast-media related population risk factor reduction
Tajti et al, 2019	**Actual contrast volume injected (mL, median [interquartile range])**	Supports claimed benefits of the technology. • Accurate, real-time, contrast media dose

Use of the DyeVert System in chronic total occlusion percutaneous coronary intervention	DyeVert used: 200(153-256) DyeVert not used: 250(170-303) P-value= 0.04 **Procedural success** DyeVert used (%): 82.1 DyeVert not used (%): 87.9 P-value= 0.38 **Non-CTO PCI** DyeVert used (%): 30.0 DyeVert not used (%): 18.5 P-value= 0.14 **Length of hospital stay (days, median [interquartile range])** DyeVert used: 1(1-1) DyeVert not used: 1(1-2) P-value= 0.06 **Procedural time (min, median [interquartile range])** DyeVert used: 220(128-294) DyeVert not used: 152(100-225) P-value= 0.03 **Fluoroscopy time (min, median [interquartile range])** DyeVert used: 59.6(27.0-90.4) DyeVert not used: 41.6(28.0-73.5) P-value= 0.20 **Air kerma radiation (gray, median [interquartile range])**	• Total contrast media volume reduction • Contrast-media related population risk factor reduction

	DyeVert used: 1.64(1.00-2.8) DyeVert not used: 2.45(1.4-3.7) P-value= 0.13 **Procedural complications** DyeVert used (%): 15.4 DyeVert not used (%): 15.4 P-value>0.99 **In-Hospital AKI** DyeVert used: 0.90% DyeVert not used: 2.2% P-value>0.99 **Postprocedural AKI** DyeVert used: 1/39 (2.6%) DyeVert not used: 2/91 (2.2%) **Major adverse cardiac event** DyeVert used (%): 0.00 DyeVert not used (%): 1.10 P-value>0.99 **Procedural complications** DyeVert used (%): 15.4% DyeVert not used (%): 15.4% P-value>0.99 **Adverse events** No device-related complications occurred.	

	eGFR at discharge (ml/min/1.73m^2, median [interquartile range]) DyeVert used: 73.2(60.4-85.0) DyeVert not used: 78.3(55.4-93.0) P-value= 0.42 **Creatinine at discharge (mg/dL, median [interquartile range])** DyeVert used: 1.0(0.8-1.2) DyeVert not used: 1.0(0.8-1.2) P-value= 0.70 **Change in eGFR (ml/min/1.73m^2, median [interquartile range])** DyeVert used: -2.9(-10.7-0.7) DyeVert not used: -1.6(-11.1-4.2) P-value= 0.90 **Change in creatinine (mg/dL, median [interquartile range]))** DyeVert used: 0.1(0.0-0.1) DyeVert not used: 0.0(-0.1-0.1) P-value= 0.77	
Briguori, 2020 Impact of a contrast media volume control device on acute kidney injury rate in patients with acute coronary syndrome	**Actual contrast volume injected (mL, median [interquartile range])** DyeVert: 99 (69–136) mL Control: 130 (120–188) mL P-value <.001 **Percent of cases where actual contrast volume injected exceeded the predefined contrast threshold (%)** DyeVert: n/N (%): 43/90 (47%)	Supports claimed benefits of the technology. • Accurate, real-time, contrast media dose monitoring relative to the maximum dose target and recording • Total contrast media volume reduction • More likely to experience contrast administration at or below the maximum contrast media dose • Maintenance of image quality • No device-related adverse events • Reduction in CI-AKI incidence • Reduction in overall length of stay • Contrast-media related population risk factor reduction

	Control: n/N (%): 54/90 (60%) OR = 0.60; 95% CI: 0.33–1.08 **Percent of attempted contrast volume saved** Mean ± SD: 38 ± 13% **Contrast volume saved, absolute (mL)** DyeVert: Mean ± SD: 99 ± 49.6 Control: Mean ± SD: 130 ± 50.4 **Rate of AKI** DyeVert: n/N (%): 7/90 (8%) Control: n/N (%): 17/90 (19%) OR = 0.37; 95% CI: 0.14–0.95; P <.047 **Stage 1 AKI** DyeVert: n/N (%): 6/7 (85.7%) Control: n/N (%): 13/17 (76.5%) **Stage 2 & 3 AKI** DyeVert: n/N (%): 1/7 (14.3%) Control: n/N (%): 4/17 (23.5%) P =.15 **Length of in-hospital stay (days)** DyeVert: 6 ± 2 days Control: 8 ± 4 days P =.003 **Length of in hospital stay in patients who experienced AKI** Patients with AKI: 7 ± 3 days	• Reduced number of bed stays/length of stay and related services • Reduced healthcare burden due to CI-AKI prevention

	Patients without AKI: 9 ± 6 days P =.074 **1-month MAE rate** (This is a composite of all-cause death, new myocardial infarction, stroke, renal failure requiring replacement therapy, and sustained kidney injury) DyeVert: n/N (%): 4/90 (4.4%) Control: n/N (%): 8/90 (8.8%) OR = 1.78; 95% CI: 0.51–5.26; P=0.37 Mean serum creatinine was significantly lower at 48 hours and 72 hours post procedure in the DyeVert Group (P=.005) **Receiver operating characteristic curve analysis (Area under curve) – Discriminatory power of actual contrast volume injected and AKI** DyeVert: 0.51; 95% CI: 0.26–0.761; P =.93 Control: 0.70; 95% CI: 0.59–0.81; P=.010 Authors Report: “We observed a significant direct correlation between CM volume and maximal absolute difference in SCr in the Control group but not in the DyeVert group. This finding suggests that the use of the DyeVert system, by limiting CM volume, may neutralize the clinical impact of CM on the occurrence of AKI in ACS patients.” **Multivariate logistic regression, Independent predictors of AKI** LVEF (left ventricular ejection fraction): odds ratio: 0.94; 95% confidence interval: 0.88–0.98; P=.010; DyeVert group: odds ratio: 0.28; 95% confidence interval: 0.08–0.96; P=.015; Age: odds ratio: 1.01; 95% confidence interval: 1.01–1.12; P=.025 **In hospital renal failure requiring RRT**	

	DyeVert: n/N (%): 0/90 (0%) Control: n/N (%): 2/90 (2.2%) P =.49 **Progression of kidney disease** (Including dialysis and sustained kidney damage) DyeVert: n/N (%): 0/90 (0%) Control: n/N (%): 3/90 (3.3%) P =.26 **Image quality** The DyeVert system was not turned off under any circumstances due to inadequate/poor image quality or other device-related reasons.	
Zimin et al, 2020 A feasibility study of the DyeVert™ plus contrast reduction system to reduce contrast media volumes in percutaneous coronary procedures using optical coherence tomography	**Contrast volume threshold (mL)** Mean ± SD: 264.47 ± 79.33 mL (97.5% CI: 213.06–315.87) **Cumulative contrast volume attempted to be injected (mL)** Mean ± SD: 342.01 ± 129.8 mL (97.5% CI: 257.92–426.11) **Actual contrast volume injected (mL)** Mean ± SD: 216.21 ± 88.87 mL (97.5% CI: 158.62–273.79) In 14 (93.3%) of 15 procedures, the CMV delivered to the patient was less than the predetermined CMV threshold. **Contrast volume saved, absolute (mL)** Mean ± SD: 125.81 ± 47.10 mL	Supports claimed benefits of the technology. • Accurate, real-time, contrast media dose monitoring relative to the maximum dose target and recording • Total contrast media volume reduction • More likely to experience contrast administration at or below the maximum contrast media dose • Maintenance of image quality • No device-related adverse events

	(97.5% CI: 95.29–156.33) **Percent of attempted contrast volume saved** Mean ± SD:: 37.5 ± 5.3% **Total procedural time (min)** DyeVert: Mean ± SD: 63 ± 26.6 Control: Mean ± SD: 47.98 ± 20.1 P-value= 0.09 **Adverse events** No device-related complications or adverse events were documented in the DyeVert group. **Acceptable image quality based on physician feedback:** 100% **Image quality based on independent imaging core lab analysis:** Clear image length %: DyeVert 86.6 ± 15.6%, Control 90.9 ± 10.4% (p<0.0001) Clear stent length %: DyeVert 92.1 ± 14.8%, Control 95.3 ± 11.3% (p<0.0001) Clear region of interest %: DyeVert 95.7 ± 9.9%, Control 97.7 ± 7.6% (p<0.0001)	
Turner & Tucker, 2020 Real world impact of a quality improvement program for acute kidney injury prevention in the cardiac Cath Lab	**Contrast volume injected (mL, mean ± STD):** Actual= 95 ± 61, Attempted = 137 ± 82 **Contrast volume saved, absolute (mL, mean ± STD):** 42 ± 28 **CMV/eGFR ratio (mean ± STD):** Actual =2.1 ± 1.5, Attempted =3.1 ± 2.0 **Attempted vs actual CMV/eGFR ratio difference** Mean: 1.0	Supports claimed benefits of the technology. • Accurate, real-time, contrast media dose monitoring relative to the maximum dose target and recording • Total contrast media volume reduction • More likely to experience contrast administration at or below the maximum contrast media dose • Reduction in CI-AKI incidence • Contrast-media related population risk factor reduction • Improved adherence to recommended guidelines for contrast minimization as part of an initiative to reduce CI-AKI

	Actual CMV/eGFR ratios ≤1 in 18% cases ≤2 in 60% cases ≤3 in 82% cases >3 in 18% cases **Attempted CMV/eGFR ratios** ≤1 in 6% cases ≤2 in 33% cases ≤3 in 62% cases >3 in 38% cases **82% stayed under 3x baseline eGFR** **Absolute reduction in CI-AKI:**10.46% **Relative reduction in CI-AKI:** 83.7% Number-Need-to-Treat to Avoid 1 CI-AKI event = 10 Hospital budget impact estimated to be $650 cost saving per case Cost neutrality boundary: absolute reduction of CI-AKI down to 3.6%, NNT up to 28, CI-AKI event costs down to $3,500	• Display data entry of renal function status supports pre-procedural risk screening and the ability to calculate a maximum contrast media dose • Display data entry of contrast media maximum dose threshold supports establishment and recording of a pre-procedural contrast dose • Reduced healthcare burden due to CI-AKI prevention
Bath et al, 2019 Use of DyeVertPlus to reduce contrast exposure in high-risk patients undergoing coronary angiography	**Actual contrast volume injected (mL)** **DyeVert Plus:** Mean: 62.7+/-9.5 ml (95% C.I.) **Manual injection:** Mean:87.6+/-11.0 ml (95% C.I.) P=0.0004 Contrast media volume delivered via DyeVert Plus was 43.8% below the threshold volume (eGFRx3) for the cohort as compared to 31.4% in the manual injection cohort (p=0.05). **Percent of attempted contrast volume saved**	Supports claimed benefits of the technology. • Total contrast media volume reduction • Contrast-media related population risk factor reduction

	Mean ± SD: 34.9% +/-3.0 (95% C.I.)	

Kutschman et al, 2019a
 	
Clinical and economic outcomes of a comprehensive clinical quality initiative for reducing acute kidney injury in chronic kidney disease patients undergoing coronary angiography
	Percent of attempted contrast volume saved
	
	Mean ± SD: 40.5 ± 8.2%
	
	Actual contrast volume injected, overall (mL)
	
	Mean ± SD: 103 ± 61 mL
	
	CMV/eGFR ratio (mean ± STD):
	
	DyeVert Group = 2.5 ± 1.8, Control Group = 3.7 ± 5.3
	
	P<0.05
	
	Attempted vs actual CMV/eGFR ratio difference
	
	Mean: 1.1
	
	CI-AKI rate (%):
	
	DyeVert Group: 9.4%
	
	Control Group: 21.8%
	
	P<0.05
	
	Absolute reduction in CI-AKI:12.4%
	
	Relative reduction in CI-AKI: 57%
	
	Number-Need-to-Treat to Avoid 1 CI-AKI event = 8
	
	Hospital budget impact estimated to be at least $2,000 in cost savings per case
		Supports claimed benefits of the technology.
		• Accurate, real-time, contrast media dose monitoring relative to the maximum dose target and recording
		• Total contrast media volume reduction
		• More likely to experience contrast administration at or below the maximum contrast media dose
		• Reduction in CI-AKI incidence
		• Contrast-media related population risk factor reduction
		• Improved adherence to recommended guidelines for contrast minimization as part of an initiative to reduce CI-AKI
		  • Display data entry of renal function status supports pre-procedural risk screening and the ability to calculate a maximum contrast media dose
		  • Display data entry of contrast media maximum dose threshold supports establishment and recording of a pre-procedural contrast dose
		• Reduced healthcare burden due to CI-AKI prevention

Kutschman et al, 2019b Comprehensive clinical quality initiative for reducing acute kidney injury in at-risk patients undergoing diagnostic coronary angiogram and/or percutaneous coronary interventions	**Contrast volume threshold (mL, mean ± STD):** DyeVert used: 189.7 ± 77.9 DyeVert not used: 194.1 ± 102.5 P-value=0.57 **Actual contrast volume injected (mL, mean ± STD):**	Supports claimed benefits of the technology. • Accurate, real-time, contrast media dose monitoring relative to the maximum dose target and recording • Total contrast media volume reduction • More likely to experience contrast administration at or below the maximum contrast media dose • Reduction in CI-AKI incidence • Contrast-media related population risk factor reduction

	DyeVert used: 103.8 ± 60.0
	
	DyeVert not used: 125.9 ± 80.7
	
	P-value=0.0003
	
	Percent of attempted contrast volume saved
	
	Mean: 40%
	
	Contrast volume saved, absolute (mL)
	
	Mean: 58 mL
	
	Actual CMV/eGFR ratio (mL, mean ± STD):
	
	DyeVert used: 2.1 ± 2.2
	
	DyeVert not used: 3.2 ± 5.6
	
	P-value=0.003
	
	% Under contrast threshold:
	
	DyeVert used: 86%
	
	DyeVert not used:75%
	
	P-value=0.0015
	
	CI-AKI rate (%):
	
	DyeVert used: 6.9%
	
	DyeVert not used:10.3%
	
	Absolute reduction in CI-AKI: 3.4%
	
	Relative reduction in CI-AKI: 33%
	
	As contrast volumes relative to the patient's baseline renal function increased, CI-AKI rates also increased.
		• Improved adherence to recommended guidelines for contrast minimization as part of an initiative to reduce CI-AKI
		  • Display data entry of renal function status supports pre-procedural risk screening and the ability to calculate a maximum contrast media dose
		  • Display data entry of contrast media maximum dose threshold supports establishment and recording of a pre-procedural contrast dose

Sattar et al, 2018 Impact of using DyeVert PLUS on incidence of acute kidney injury after cardiac catheterization with coronary interventions in high-risk patients	Mean pre and post procedure serum Cr in DyeVert group was 1.56 and 1.56 with a mean decrease of 0.002 (p=0.97). Mean pre and post procedure Cr without DyeVert was 1.51 and 1.54 respectively with a mean increase of 0.35 (p=0.44, SD 0.37, 95% CI [-0.06,0.12]). Change in SCr was not significant between the two groups but numerically lower in DyeVert vs higher in the control (-0.002 vs +0.35) The incidence of CI-AKI in the DyeVert vs non-DyeVert group was 12.2% vs 16.2% (p=0.56 pearson Chi Sq, OR 0.71, 95% CI [0.23, 2.24]). **Absolute reduction in CI-AKI:** 4.0% **Relative reduction in CI-AKI:** 25% Average contrast usage in DyeVert vs non-DyeVert group was 128 ml vs.155 ml.	Supports claimed benefits of the technology. • Total contrast media volume reduction • Reduction in CI-AKI incidence
Rao et al, 2019 DyeVert Plus contrast reduction system use in patients undergoing highly complex peripheral vascular interventions	Mean CMV per case was 50 ± 23 mL (range 25-100 mL) CMV of ~70-80 mL is typical for the diagnostic component of the procedure alone and significantly more for procedures also including an intervention CMV/eGFR ratios ranged from 0.4 to 3.7. Actual CMV/eGFR ratios were <2 in 86% of cases and <1 in 43% with DyeVert Plus use. No patients had worsening of renal function post-procedure.	Supports claimed benefits of the technology. • Total contrast media volume reduction • More likely to experience contrast administration at or below the maximum contrast media dose • Reduction in CI-AKI incidence • Contrast-media related population risk factor reduction •
Bunney et al, 2020 Contemporary use of contrast Dye reduction technology in a tertiary academic hospital: Patient characteristics and acute kidney injury outcomes following percutaneous coronary interventions	CI-**AKI rate:** DyeVert used: 3.45% DyeVert not used: 9.35% **Absolute reduction in CI-AKI:** 5.9% **Relative reduction in CI-AKI:** 63% DyeVert is most often used in patients with CKD and those who are at highest risk for AKI. There is a lower non-risk adjusted CI-AKI	Supports claimed benefits of the technology. • Total contrast media volume reduction • Reduction in CI-AKI incidence • Contrast-media related population risk factor reduction

	rate in DyeVert patients despite their higher risk compared to those in which DyeVert was not used. **Mean contrast used (mL):** DyeVert used: 194 DyeVert not used: 192 DyeVert is most often used in procedures involving multivessel interventions, requiring hemodynamic support and complex lesions. Despite this, contrast volumes were similar between procedures in which DyeVert was used vs not used.	
Amoroso et al, 2020 First European experience using a novel contrast reduction system during coronary angiography with automated contrast injection	**Actual contrast volume injected (mL, mean ± STD):** 87.9 ± 51.5 mL (range 30.6 – 211.9 mL) **Percent of attempted contrast volume saved** 34.4 ± 6.2% (range 24.1– 47.0%) **Image quality:** N=25/26 (96%) (In one case, the physician noted while placing a stent in the obtuse margin of the circumflex one image was not as opacified as desired around the stent pre-dilation) Physicians described DyeVert System set-up, priming, and intraprocedural usability (including overall satisfaction) as acceptable in all (100%) cases.	Supports claimed benefits of the technology. • Total contrast media volume reduction • Contrast-media related population risk factor reduction
Cameron et al, 2020 Reduction of contrast-induced acute kidney injury in a cardiac catheterization laboratory: A quality improvement initiative	**Contrast volume injected (mL, mean ± STD):** 91 ± 55 mL (range 17 –296) actual 144 ± 79 mL (range 26 – 446) attempted (actual mL + saved mL) **Contrast volume saved, absolute (mL, mean ± STD):** 53 ± 28 mL **Percent of attempted contrast volume saved:** 38 ± 8% **CMV/eGFR ratio:** 2.1 actual, 3.4 attempted	Supports claimed benefits of the technology. • Accurate, real-time, contrast media dose monitoring relative to the maximum dose target and recording • Total contrast media volume reduction • More likely to experience contrast administration at or below the maximum contrast media dose • Reduction in CI-AKI incidence • Contrast-media related population risk factor reduction • Improved adherence to recommended guidelines for contrast minimization as part of an initiative to reduce CI-AKI

	Attempted vs actual CMV/eGFR ratio difference Mean: 1.3 **% Under contrast threshold:** 84% of cases based on actual contrast volume injected vs 58% based on attempted contrast volume injected **Dyevert attempted CMV/eGFR ratio** % CM/eGFR ≤ 1.0: 3% % CM/eGFR ≤ 2.0: 36% % CM/eGFR ≤ 3.0: 58% % CM/eGFR >3.0: 42% **Dyevert actual CMV/eGFR ratio** % CM/eGFR ≤ 1.0: 27% % CM/eGFR ≤ 2.0: 61% % CM/eGFR ≤ 3.0: 84% % CM/eGFR >3.0: 16% **82% stayed under 3x baseline eGFR** **Absolute reduction in CI-AKI (PCI Procedures):** 6.5% **Relative reduction in CI-AKI (PCI Procedures):** 57% **Relative reduction in CI-AKI, Diagnostic Procedures: 30**% Number-Need-to-Treat to Avoid 1 CI-AKI event = 16 Hospital budget impact estimates the program is producing cost savings	• Display data entry of renal function status supports pre-procedural risk screening and the ability to calculate a maximum contrast media dose • Display data entry of contrast media maximum dose threshold supports establishment and recording of a pre-procedural contrast dose • Reduced healthcare burden due to CI-AKI prevention
[redacted]	[redacted]	[redacted]

	[redacted]	
[redacted]	[redacted]	[redacted]

5 Details of relevant studies

Please give details of all relevant studies (all studies in table 4). Copy and paste a new table into the document for each study. Please use 1 table per study.

Sapontis et al, 2017 A first in human evaluation of a novel contrast media saving device	
How are the findings relevant to the decision problem?	Study evaluated the usability and contrast volume savings of the novel DyeVert system.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Total contrast media volume reduction (on average 40% reduction in contrast media dose delivered to the patient) • Contrast-media related population risk factor reduction • Maintenance of image quality • No device-related adverse events .
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Limitations of the study include the modest sample size, single-arm design, and lack of use of an independent, blinded reviewer for image assessment.
How was the study funded?	Contract grant sponsor: Osprey Medical, Inc. Minneapolis, MN.

Corcione et al, 2017 Contrast minimization with the new generation DyeVert Plus system for contrast reduction and real-time monitoring during coronary and peripheral procedures: First experience	
How are the findings relevant to the decision problem?	Study appraised the role of the DyeVert Plus system inclusive of contrast reduction and real-time monitoring in a consecutive series of patients undergoing coronary or invasive peripheral procedures.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Accurate, real-time, contrast media dose monitoring (DyeVert System data compared to manual measurements) • Total contrast media volume reduction (on average 40% reduction in contrast media dose delivered to the patient) • Contrast-media related population risk factor reduction • Maintenance of image quality • No device-related adverse events

Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Study acknowledges that despite the favourable results, they have only included a small number of patients and dedicated trials are required to further confirm or disprove the results.
How was the study funded?	Not specified.

Desch et al, 2017 Impact of a novel contrast reduction system on contrast savings in coronary angiography – The DyeVert randomised controlled trial	
How are the findings relevant to the decision problem?	Study involved a randomised controlled trial to examine whether the novel DyeVert contrast reduction system leads to a reduction in CM volume in patients undergoing diagnostic coronary angiography.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. Study shows a significant reduction in CM volume in patients undergoing diagnostic coronary angiography using the DyeVert system. Additionally, no adverse events related to the device were identified and image quality was non-inferior compared to the control. • Total contrast media volume reduction • Contrast-media related population risk factor reduction • Maintenance of image quality • No device-related adverse events
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Limitations of the study include a lack of blinding of operators to treatment allocation which might have introduced bias (due to the nature of how the technology is used, operator blinding is not possible), the use of a single clinical site (rather than multiple) to perform coronary angiographies.
How was the study funded?	Grant support: The study was fully sponsored by Osprey Medical, Inc. Minneapolis, MN.

Gurm et al, 2019a Minimizing radiographic contrast administration during coronary angiography using a novel contrast reduction system: A multicenter observational study of the DyeVert™ plus contrast reduction system	
How are the findings relevant to the decision problem?	Study evaluated the contrast media volume savings using the DyeVert Plus Contrast Reduction System in patients undergoing diagnostic coronary angiogram and/or percutaneous coronary interventional procedures performed with manual injections.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. Study shows overall contrast media volume savings per procedure associated with the DyeVert system. Additionally, image quality was maintained, and no adverse events related to the DyeVert system were reported. • Accurate, real-time, contrast media dose monitoring relative to the maximum dose target and recording • Total contrast media volume reduction (on average 40% reduction in contrast media dose delivered to the patient) • More likely to experience contrast administration at or below the maximum contrast media dose • Maintenance of image quality • No device-related adverse events • Reduction in CI-AKI incidence • Contrast-media related population risk factor reduction • Improved access of coronary and peripheral angiography to patients with CI-AKI risk factors
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Study used an objective performance criterion based on published literature instead of a concurrent control group. Additionally, data on CI-AKI was based only on available subject data based on standard of care practices rather than coming from protocol-required post-procedure laboratory data.
How was the study funded?	Study was sponsored and funded by Osprey Medical, Inc.

Bruno et al, 2019

Early clinical experiences with a novel contrast volume reduction system during invasive coronary angiography	
How are the findings relevant to the decision problem?	Study focussed on use of the DyeVert Power XT system and its impact on contrast media volume savings amongst patients undergoing diagnostic or interventional coronary angiography.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Total contrast media volume reduction (on average 40% reduction in contrast media dose delivered to the patient) • Maintenance of image quality • No device-related adverse events • Contrast-media related population risk factor reduction
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Limitations include lack of randomization, no control group, small sample size and an estimation of reduction in CM dose based on contrast collection bag demarcations.
How was the study funded?	Funding provided by Osprey Medical, Inc.

Tajti et al, 2019 Use of the DyeVert system in chronic total occlusion percutaneous coronary intervention	
How are the findings relevant to the decision problem?	Study looked at procedural outcomes associated with the DyeVert system compared to outcomes in those who did not use the system, in a population of patients undergoing chronic total occlusion percutaneous coronary intervention.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. Study shows significant savings in median contrast volume used in DyeVert patients (50ml lower per procedure). Additionally, there were no in-hospital complications associated with the DyeVert system and no device-related procedural complication.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Limitations include lack of long-term follow-up, and the fact that the guide size was slightly smaller in the DyeVert group, which could have contributed to the lower contrast volume administered. In this study, DyeVert was selected based on the procedure type of

	chronic total occlusion percutaneous coronary interventions (PCI), which is a complex segment of the PCI population and differs from the other studies that selected DyeVert based on pre-procedure patient CI-AKI risk factors. Also underpowered for assessing differences in CI-AKI rates and didn't provide any risk adjustment for CI-AKI rates based on the wide-ranging technical complexity of CTO procedures.
How was the study funded?	Abbott Northwestern Hospital Foundation, Minneapolis, Minnesota

Briguori, 2020 Impact of a contrast media volume control device on acute kidney injury rate in patients with acute coronary syndrome	
How are the findings relevant to the decision problem?	Study looked at difference in contrast media volume used in patients using the DyeVert system compared with patients receiving manual methods, difference in acute kidney injury rates, and difference in length of hospital stay in those patients experiencing an acute kidney injury, amongst a group of patients with acute coronary syndrome undergoing invasive coronary procedures.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Accurate, real-time, contrast media dose monitoring relative to the maximum dose target and recording • Total contrast media volume reduction • More likely to experience contrast administration at or below the maximum contrast media dose • Maintenance of image quality • No device-related adverse events • Reduction in CI-AKI incidence • Reduction in overall length of stay • Contrast-media related population risk factor reduction • Reduced number of bed stays/length of stay and related services • Reduced healthcare burden due to CI-AKI prevention
Will any information from this study be used in the economic model?	Yes. Informs the economic model parameters related to CI-AKI rate and relative risk of CI-AKI rate in the intervention arm of the model.

What are the limitations of this evidence?	Limitations include the small sample size and the fact that the study was a single-centre, observational, non-randomized design. Additionally, it is noted that there was a lack of a Clinical Event Committee.
How was the study funded?	Not specified.

Zimin et al, 2020 A feasibility study of the DyeVert™ plus contrast reduction system to reduce contrast media volumes in percutaneous coronary procedures using optical coherence tomography	
How are the findings relevant to the decision problem?	Study looked at impact of the DyeVert system on the volume of contrast media delivered, as well as its impact on image quality in patients undergoing optical coherence tomography-guided percutaneous coronary intervention procedures.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Accurate, real-time, contrast media dose monitoring relative to the maximum dose target and recording • Total contrast media volume reduction • More likely to experience contrast administration at or below the maximum contrast media dose • Maintenance of image quality • No device-related adverse events
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Limitations include the small sample size and the fact that the study did not collect post-procedure laboratory data on patients to facilitate the identification of CI-AKI, which was not a clinical outcome for this study.
How was the study funded?	Study partially funded by Osprey Medical Inc.

Turner & Tucker, 2020 Real world impact of a quality improvement program for acute kidney injury prevention in the cardiac Cath Lab	
How are the findings relevant to the decision problem?	Study looked at impact of an ongoing quality improvement program (including the DyeVert system) at preventing contrast-induced acute kidney injury.

Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes.
	• Accurate, real-time, contrast media dose monitoring relative to the maximum dose target and recording
	• Total contrast media volume reduction
	• More likely to experience contrast administration at or below the maximum contrast media dose
	• Reduction in CI-AKI incidence
	• Contrast-media related population risk factor reduction
	• Improved adherence to recommended guidelines for contrast minimization as part of an initiative to reduce CI-AKI
	  • Display data entry of renal function status supports pre-procedural risk screening and the ability to calculate a maximum contrast media dose
	  • Display data entry of contrast media maximum dose threshold supports establishment and recording of a pre-procedural contrast dose
	• Improved access of coronary and peripheral angiography to patients with CI-AKI risk factors
	• Reduced healthcare burden due to CI-AKI prevention

Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	None reported.
How was the study funded?	Not specified.

Bath et al, 2019 Use of DyeVert Plus to reduce contrast exposure in high-risk patients undergoing coronary angiography	
How are the findings relevant to the decision problem?	Study looked at impact of the DyeVert Plus system on contrast reduction during a diagnostic coronary angiogram.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Total contrast media volume reduction • Contrast-media related population risk factor reduction
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	None reported.

How was the study funded?	Not specified.

Kutschman et al, 2019a Clinical and Economic Outcomes of a Comprehensive Clinical Quality Initiative for Reducing Acute Kidney Injury in Chronic Kidney Disease Patients Undergoing Coronary Angiography	
How are the findings relevant to the decision problem?	Study looked at impact of the DyeVert system on contrast media volume savings and acute kidney injury rates amongst patients with chronic kidney disease undergoing cardiac catheterization.

Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes.
	• Accurate, real-time, contrast media dose monitoring relative to the maximum dose target and recording
	• Total contrast media volume reduction
	• More likely to experience contrast administration at or below the maximum contrast media dose
	• Reduction in CI-AKI incidence
	• Contrast-media related population risk factor reduction
	• Improved adherence to recommended guidelines for contrast minimization as part of an initiative to reduce CI-AKI
	  • Display data entry of renal function status supports pre-procedural risk screening and the ability to calculate a maximum contrast media dose
	  • Display data entry of contrast media maximum dose threshold supports establishment and recording of a pre-procedural contrast dose
	• Improved access of coronary and peripheral angiography to patients with CI-AKI risk factors
	• Reduced healthcare burden due to CI-AKI prevention

Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	None reported.
How was the study funded?	Not specified.

Kutschman et al, 2019b Comprehensive clinical quality initiative for reducing acute kidney injury in at-risk patients undergoing diagnostic coronary angiogram and/or percutaneous coronary interventions

How are the findings relevant to the decision problem?	Study looked at impact of a protocol involving use of the DyeVert system on contrast media volume savings and acute kidney injury rates amongst patients undergoing diagnostic coronary angiograms and percutaneous coronary interventions.

Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes.
	• Accurate, real-time, contrast media dose monitoring relative to the maximum dose target and recording
	• Total contrast media volume reduction
	• More likely to experience contrast administration at or below the maximum contrast media dose
	• Reduction in CI-AKI incidence
	• Contrast-media related population risk factor reduction
	• Improved adherence to recommended guidelines for contrast minimization as part of an initiative to reduce CI-AKI
	  • Display data entry of renal function status supports pre-procedural risk screening and the ability to calculate a maximum contrast media dose
	  • Display data entry of contrast media maximum dose threshold supports establishment and recording of a pre-procedural contrast dose
	Improved access of coronary and peripheral angiography to patients with CI-AKI risk factors

Will any information from this study be used in the economic model?	Yes. Informs the economic model parameters related to CI-AKI rate and relative risk of CI-AKI rate in the intervention arm of the model.
What are the limitations of this evidence?	None reported.
How was the study funded?	Osprey Medical provided research support services

Sattar et al, 2018 Impact of using DyeVert PLUS on incidence of acute kidney injury after cardiac catheterization with coronary interventions in high-risk patients	
How are the findings relevant to the decision problem?	Study looked at impact of the DyeVert Plus system on contrast media volume savings amongst a group of patients undergoing percutaneous coronary interventions.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Total contrast media volume reduction • Reduction in CI-AKI incidence

Will any information from this study be used in the economic model?	Yes. Informs the economic model parameters related to CI-AKI rate and relative risk of CI-AKI rate in the intervention arm of the model.
What are the limitations of this evidence?	Low overall incidence of acute kidney injury during the study period rendered the sample size too small to elucidate a significant difference between groups. Additionally, an un-blinded observational study has inherent bias, most noticeably, the awareness during the study period for concerted efforts to reduce contrast usage in the control group.
How was the study funded?	Not specified.

Rao et al, 2019 DyeVert Plus contrast reduction system use in patients undergoing highly complex peripheral vascular interventions	
How are the findings relevant to the decision problem?	Study reported on a systematic review of recent cases which involved use of the DyeVert system to reduce contrast media use in peripheral vascular interventions.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Total contrast media volume reduction • More likely to experience contrast administration at or below the maximum contrast media dose • Reduction in CI-AKI incidence • Contrast-media related population risk factor reduction • Improved access of coronary and peripheral angiography to patients with CI-AKI risk factors
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	None reported.
How was the study funded?	Not specified.

Bunney et al, 2020 Contemporary use of contrast Dye reduction technology in a tertiary academic hospital: Patient characteristics and acute kidney injury outcomes following percutaneous coronary interventions	
How are the findings relevant to the decision problem?	Study involved providing a description of the clinical characteristics and acute kidney injury rates of chronic kidney disease

	patients undergoing use of the DyeVert system in a local hospital in the USA.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Total contrast media volume reduction • Reduction in CI-AKI incidence • Contrast-media related population risk factor reduction • Improved access of coronary and peripheral angiography to patients with CI-AKI risk factors
Will any information from this study be used in the economic model?	Yes. Informs the economic model parameters related to CI-AKI rate and relative risk of CI-AKI rate in the intervention arm of the model.
What are the limitations of this evidence?	None reported.
How was the study funded?	Not specified.

Amoroso et al, 2020 First European experience using a novel contrast reduction system during coronary angiography with automated contrast injection	
How are the findings relevant to the decision problem?	Study reported the first European experience using a novel contrast reduction device (the DyeVert system) during coronary angiography with automated contrast injection.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. • Total contrast media volume reduction Contrast-media related population risk factor reduction
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	None reported.
How was the study funded?	Not specified.

Cameron et al, 2020 Reduction of contrast-induced acute kidney injury in a cardiac catheterization laboratory: A quality improvement initiative	
How are the findings relevant to the decision problem?	Study reported on the development and results from an ongoing quality improvement initiative (involving use of the DyeVert system) implemented at a hospital cardiac catheterization laboratory.

Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes
	• Accurate, real-time, contrast media dose monitoring relative to the maximum dose target and recording
	• Total contrast media volume reduction
	• More likely to experience contrast administration at or below the maximum contrast media dose
	• Reduction in CI-AKI incidence
	• Contrast-media related population risk factor reduction
	• Improved adherence to recommended guidelines for contrast minimization as part of an initiative to reduce CI-AKI
	  • Display data entry of renal function status supports pre-procedural risk screening and the ability to calculate a maximum contrast media dose
	  • Display data entry of contrast media maximum dose threshold supports establishment and recording of a pre-procedural contrast dose
	• Improved access of coronary and peripheral angiography to patients with CI-AKI risk factors
	• Reduced healthcare burden due to CI-AKI prevention

Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	None reported.
How was the study funded?	Not specified.

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6 Adverse events

Describe any adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude). Please provide links and references.

A search of the Medicine and Healthcare Products Regulatory Agency (MHRA) website (20th November 2020) showed no manufacturer field safety notices or medical device alerts have been issued for DyeVert (https://www.gov.uk/drug-device-alerts).

Osprey Medical has received US FDA 510(k) clearance for the DyeVert™ Plus Contrast Reduction System, DyeVert™ Plus EZ Contrast Reduction System with a classification product code "DXT" (Injector And Syringe, Angiographic) (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm). DyeVert™ Power XT System pre-market notification submission (510(k)) is pending.

Search of the FDA recall database (20th November 2020) with the term "DyeVert" returned no result. (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm).

A search of the FDA adverse databases (MAUDE, MDR and MedSun) with search dates from 1976 to 20th November 2020 using the product code "DXT" and, or "DyeVert" identified 2 records and both of them were user's fault, and patients did not experience an adverse event. Therefore, we can conclude that the device is safe when used as intended.

Since the search period, there have been no vigilance reports or recalls. There have been two FDA MDR reports due to reported air present in device during use due to an identified isolated manufacturing issue with no patient adverse event(s). These were reported as required under FDA reporting requirements.

Describe any adverse events and outcomes associated with the technology in the clinical evidence.

Adverse events reported in published clinical studies identified:

From the published clinical studies by Sapontis et al, 2017 and Bruno et al, 2019, no device related adverse events were reported. In the studies by Desch et al, 2018, Gurm et al, 2019a, and Zimin et al, 2020, it was highlighted that no adverse events related to the DyeVert System (or DyeVert Plus System in the case of Gurm et al, 2019a) or cases of contrast-related anaphylaxis were reported. In Corcione et al, 2017, one case of contrast-induced nephropathy was identified however it was not device related. In the study by Tajti et al, 2019, adverse events were reported for patients in the intervention and comparator groups. Adverse events that occurred, and percentage of the sample experiencing these events in each group, were as follows: Acute Myocardial Infarction = Intervention (0%), Comparator

(1.1%); Stroke = Intervention (0%), Comparator (1.1%); Procedural complications (overall) = Intervention (15.4%), Comparator (15.4%); Perforation = Intervention (5.13%), Comparator (4.4%); Vascular access complication = Intervention (2.56%), Comparator (2.8%); Bleeding = Intervention (0%), Comparator (2.2%); Acute kidney injury = Intervention (0.9%), Comparator (2.2%); Aortocoronary dissection = Intervention (2.56%), Comparator (1.1%); Other = Intervention (7.69%), Comparator (3.3%). Adverse events reported were broadly similar in the intervention and comparator arms of the study, with no adverse events reported related to use of the DyeVert system specifically. In the study by Briguori et al, 2020, adverse events were reported for patients in the intervention and comparator groups. Adverse events that occurred, and percentage of the sample experiencing these events in each group, were as follows: Death = Intervention (3.3%), Comparator (3.3%); Dialysis = Intervention (0%), Comparator (1.1%); Sustained kidney damage = Intervention (0%), Comparator (2.2%); New myocardial infarction = Intervention (1.1%), Comparator (2.2%). As in the previous study, adverse events were again broadly similar in the intervention and comparator groups, with no adverse events reported related to the DyeVert system.

Adverse events reported in abstracts identified:

Details related to adverse events and their occurrence were not reported in the abstracts from Bath et al, 2019, Cameron et al, 2020, Amoroso et al, 2020, Kutschman et al, 2019a, Kutschman et al, 2019b, Bunney et al, 2019, Sattar et al, 2018, Castro et al, 2018, Turner & Tucker, 2020. In the abstract by Rao et al, 2019 it was highlighted that there were no immediate complications nor evidence of contrast-induced nephropathy related to the system or the procedure.

Adverse events reported in unpublished studies identified:

[redacted]

7 Evidence synthesis and meta-analysis

Although evidence synthesis and meta-analyses are not necessary for a submission, they are encouraged if data are available to support such an approach.

If an evidence synthesis is not considered appropriate, please instead complete the section on qualitative review.

If a quantitative evidence synthesis is appropriate, describe the methods used. Include a rationale for the studies selected.

In order to quantitatively synthesise data identified from included published studies, unpublished studies and abstracts, six separate fixed and random effects meta-analyses were conducted, each looking at a different outcome reported in individual studies. The following meta-analyses were carried out:

1) Pooled estimate of relative risk of CI-AKI in DyeVert group compared to control group,
2) Pooled estimate of CI-AKI rate in DyeVert group,
3) Pooled estimate of CI-AKI rate in control group,
4) Pooled estimate of absolute contrast volume in DyeVert group compared to control group (5 double-arm studies),
5) Pooled estimate of absolute contrast volume in DyeVert group compared to control group (4 published double-arm studies),
6) Pooled estimate of relative contrast volume saved in DyeVert group (8 single-arm studies),
7) Pooled estimate of relative contrast volume saved in DyeVert group (8 published single-arm studies),
8) Pooled estimate of the image quality (%) among in DyeVert group (8 studies),
9) Pooled estimate of the image quality (%) among in DyeVert group (7 published studies),
10) Pooled estimate of actual versus attempted CV/eGFR ratio
11) Pooled estimate of actual versus attempted CV/eGFR ratios by CV/eGFR group
12) Pooled estimate of contrast threshold management

The number of studies included in each analysis varied depending on the type of outcomes reported in each analysis, study design, homogeneity of patients' populations as well as the way in which they were presented. For instance, in the meta-analysis focussing on the relative risk of acute kidney injury in the DyeVert group compared to the control group, only studies with two arms (i.e., intervention vs control) were included as the output of the meta-analysis was the overall relative risk of experiencing acute kidney injury in the intervention arm.

Results of each analysis, as well as the associated forest plot and overall treatment effect, are presented in the section below. In addition, statistics to indicate whether heterogeneity and publication bias are present in each analysis are also presented. The I^2 statistic, used to test for the presence of heterogeneity, tells us how much of the total variation in effects is due to variation in true effects between studies. The I^2 statistic can be interpreted as follows:

$I^2 = \left(\frac{tau^2}{tau^2 + SE_Y^2}\right) \times 100\%$, Y is summary effect

$I^2 = 25\%$ Low evidence of heterogeneity

$I^2 = 50\%$ Moderate evidence of heterogeneity

$I^2 = 75\%$ Strong evidence of heterogeneity

The p-value of the Q statistic can also be examined to explore the presence of heterogeneity. The p-value is the probability of finding heterogeneity of degree Q assuming that there is no heterogeneity:

$p < 0.01$: strong evidence of heterogeneity

$p < 0.10$: some evidence of heterogeneity

$p > 0.10$: insufficient evidence to identify heterogeneity

Report all relevant results, including diagrams if appropriate.

1) Pooled estimate of the relative risk of CI-AKI in the intervention (DyeVert) versus control group among 4 double-arm studies, calculated as **0.59 (CI%95: 0.38-0.89)**

Meta-analysis: relative risk

Variable for studies	Studies
1. Intervention groups	
Variable for total number of cases	DyeVert_n
Variable for number of positive cases	DyeVert_AKI
2. Control groups	
Variable for total number of cases	Control_n
Variable for number of positive cases	Control_AKI

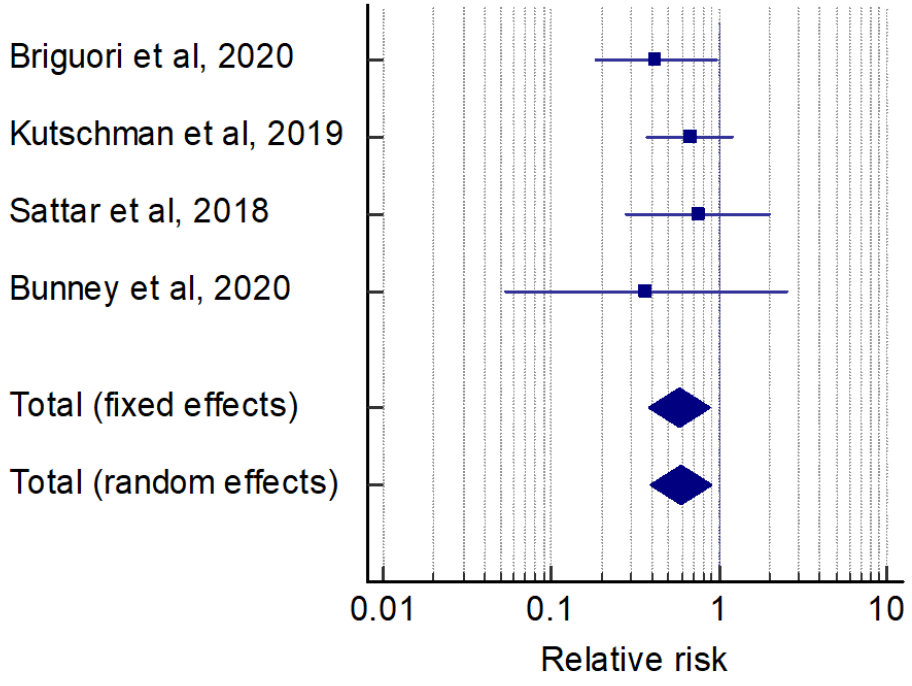
Study	Intervention	Controls	Relative risk	95% CI	z	P	Weight (%)	
							Fixed	Random
Briguori et al, 2020	7/90	17/90	0.421	0.185 to 0.956			25.89	25.89
Kutschman et al, 2019	17/258	25/243	0.670	0.374 to 1.199			51.45	51.45
Sattar et al, 2018	5/41	11/68	0.753	0.282 to 2.013			18.02	18.02
Bunney et al, 2020	1/29	71/770	0.369	0.0531 to 2.562			4.64	4.64
Total (fixed effects)	30/418	124/1171	0.579	0.381 to 0.879	-2.565	0.010	100.00	100.00
Total (random effects)	30/418	124/1171	0.590	0.389 to 0.896	-2.477	0.013	100.00	100.00

Test for heterogeneity

Q	1.3033
DF	3
Significance level	P = 0.7284
I^2 (inconsistency)	0.00%
95% CI for I^2	0.00 to 70.28

Publication bias

Egger's test	
Intercept	-0.7111
95% CI	-5.0074 to 3.5853
Significance level	P = 0.5503
Begg's test	
Kendall's Tau	-0.3333
Significance level	P = 0.4969



2) Pooled estimate of the rate of CI-AKI in the intervention group (DyeVert) among 4 double-arm studies, calculated as **7.71% (CI%95: 5.36%-10.44%)**

Meta-analysis: proportion

Variable for studies	Studies
Variable for total number of cases	DyeVert_n
Variable for number of positive cases	DyeVert_AKI

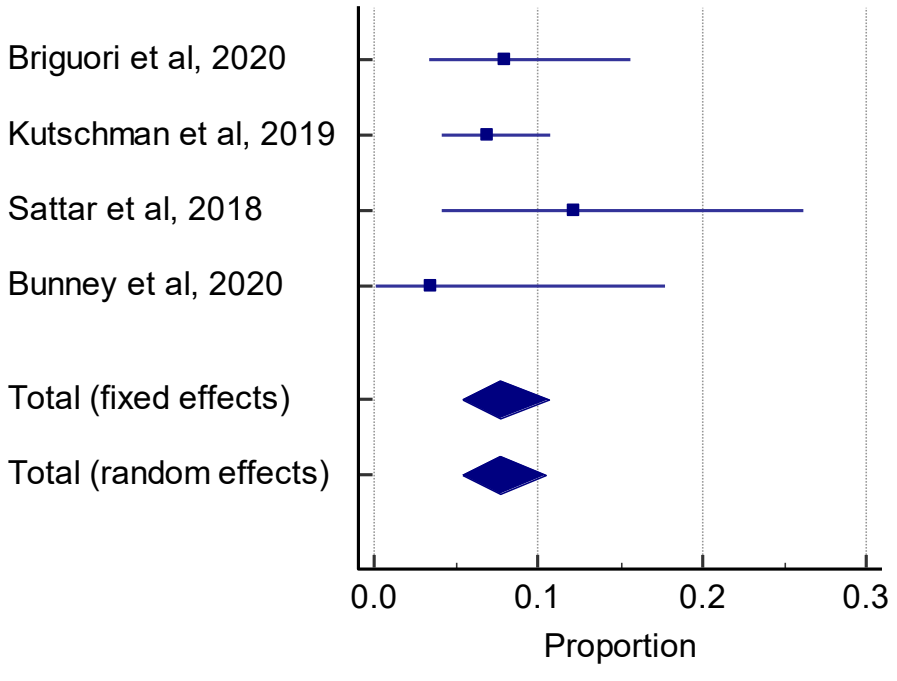
Study	Sample size	Proportion (%)	95% CI	Weight (%)	
				Fixed	Random
Briguori et al, 2020	90	8.000	3.328 to 15.652	21.56	21.56
Kutschman et al, 2019	258	6.900	4.127 to 10.711	61.37	61.37
Sattar et al, 2018	41	12.200	4.084 to 26.211	9.95	9.95
Bunney et al, 2020	29	3.450	0.0874 to 17.767	7.11	7.11
Total (fixed effects)	418	7.710	5.351 to 10.682	100.00	100.00
Total (random effects)	418	7.710	5.361 to 10.444	100.00	100.00

Test for heterogeneity

Q	1.9621
DF	3
Significance level	P = 0.5803
I^2 (inconsistency)	0.00%
95% CI for I^2	0.00 to 80.26

Publication bias

Egger's test	
Intercept	0.5620
95% CI	-4.4335 to 5.5574
Significance level	P = 0.6762
Begg's test	
Kendall's Tau	0.0000
Significance level	P = 1.0000



3) Pooled estimate of the rate of CI-AKI in the control group among 4 double-arm studies, calculated as **12.55% (CI%95: 8.74%-16.93%)**

Meta-analysis: proportion

Variable for studies	Studies
Variable for total number of cases	Control_n
Variable for number of positive cases	Control_AKI

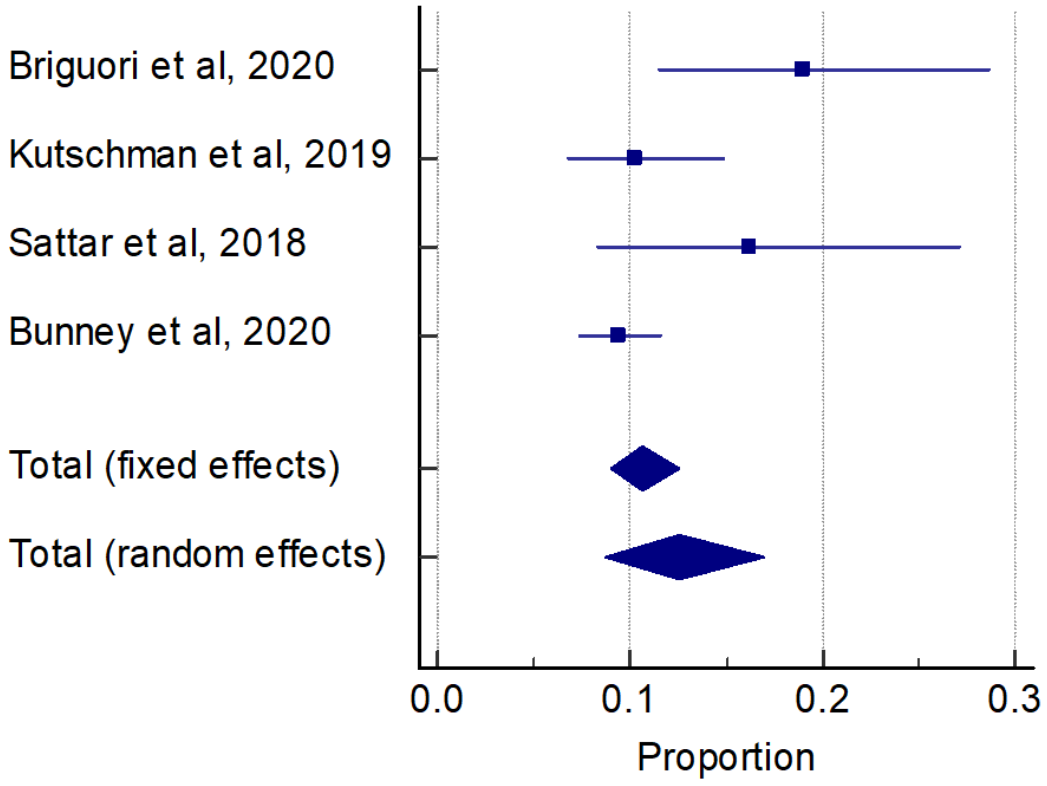
Study	Sample size	Proportion (%)	95% CI	Weight (%)	
				Fixed	Random
Briguori et al, 2020	90	19.000	11.495 to 28.636	7.74	19.16
Kutschman et al, 2019	243	10.300	6.779 to 14.826	20.77	28.62
Sattar et al, 2018	68	16.200	8.379 to 27.131	5.87	16.41
Bunney et al, 2020	770	9.350	7.388 to 11.630	65.62	35.81
Total (fixed effects)	1171	10.677	8.969 to 12.585	100.00	100.00
Total (random effects)	1171	12.552	8.745 to 16.934	100.00	100.00

Test for heterogeneity

Q	8.9892
DF	3
Significance level	P = 0.0294
I^2 (inconsistency)	66.63%
95% CI for I^2	2.38 to 88.59

Publication bias

Egger's test	
Intercept	3.1018
95% CI	-0.6136 to 6.8172
Significance level	P = 0.0695
Begg's test	
Kendall's Tau	0.6667
Significance level	P = 0.1742



4) [redacted]

Meta-analysis: continuous measure

Variable for studies	Study
1. Intervention groups	
Variable for number of cases	DyeVert_n
Variable for mean	DyeVert_m
Variable for SD	DyeVert_sd
2. Control groups	
Variable for number of cases	Control_n
Variable for mean	Control_m
Variable for SD	Control_sd

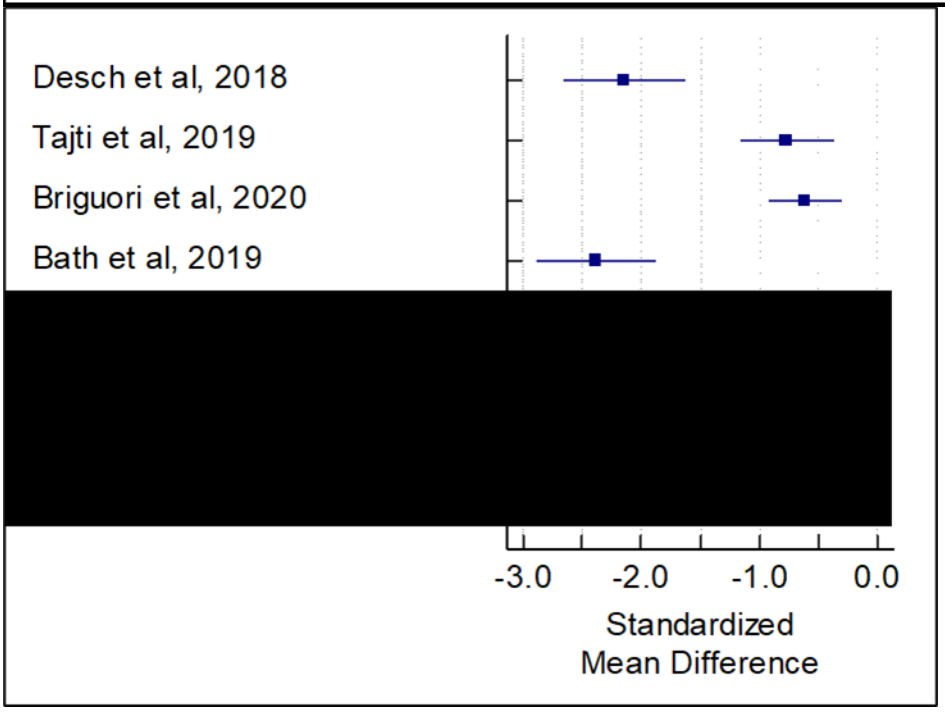
Study	N1	N2	Total	SMD	SE	95% CI	t	P	Weight (%)	
									Fixed	Random
Desch et al, 2018	48	48	96	-2.146	0.255	-2.652 to -1.640			9.16	19.31
Tajti et al, 2019	39	91	130	-0.769	0.196	-1.157 to -0.381			15.48	20.05
Briguori et al, 2020	90	90	180	-0.617	0.152	-0.917 to -0.317			25.79	20.51
Bath et al, 2019	49	59	108	-2.389	0.252	-2.888 to -1.891			9.41	19.36
[redacted]										

Test for heterogeneity

Q	84.2520
DF	4
Significance level	P < 0.0001
I^2 (inconsistency)	95.25%
95% CI for I^2	91.54 to 97.34

Publication bias

Egger's test	
Intercept	-13.6890
95% CI	-22.4299 to -4.9481
Significance level	P = 0.0155
Begg's test	
Kendall's Tau	-0.8000
Significance level	P = 0.0500



5) Pooled estimate of the standardized mean difference in absolute contrast volume (mL) in the intervention and control group calculated as **-1.463 (CI%95: -2.339: -0.588)** among 4 **published** double-arm studies. Two double-arm studies (Bunney et al, 2020 and Sattar et al, 2018 excluded from the meta-analysis because they did not report the standard deviation of mean in the abstract)

Meta-analysis: continuous measure

Variable for studies	Study
1. Intervention groups	
Variable for number of cases	DyeVert_n
Variable for mean	DyeVert_m
Variable for SD	DyeVert_sd
2. Control groups	
Variable for number of cases	Control_n
Variable for mean	Control_m
Variable for SD	Control_sd

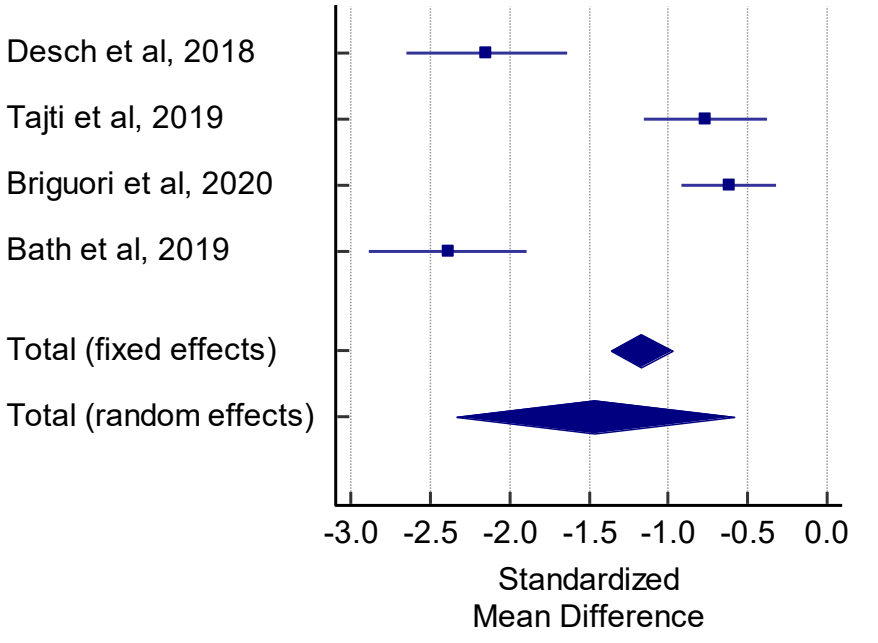
Study	N1	N2	Total	SMD	SE	95% CI	t	P	Weight (%)	
									Fixed	Random
Desch et al, 2018	48	48	96	-2.146	0.255	-2.652 to -1.640			15.31	24.45
Tajti et al, 2019	39	91	130	-0.769	0.196	-1.157 to -0.381			25.87	25.27
Briguori et al, 2020	90	90	180	-0.617	0.152	-0.917 to -0.317			43.09	25.78
Bath et al, 2019	49	59	108	-2.389	0.252	-2.888 to -1.891			15.73	24.50
Total (fixed effects)	226	288	514	-1.169	0.0998	-1.365 to -0.973	-11.722	<0.001	100.00	100.00
Total (random effects)	226	288	514	-1.463	0.446	-2.339 to -0.588	-3.282	0.001	100.00	100.00

Test for heterogeneity

Q	55.5661
DF	3
Significance level	P < 0.0001
I^2 (inconsistency)	94.60%
95% CI for I^2	89.25 to 97.29

Publication bias

Egger's test	
Intercept	-16.1696
95% CI	-34.7635 to 2.4242
Significance level	P = 0.0646
Begg's test	
Kendall's Tau	-0.6667
Significance level	P = 0.1742



6) [redacted]

Variable for studies	Studies
Variable for total number of cases	n
Variable for number of positive cases	CMV

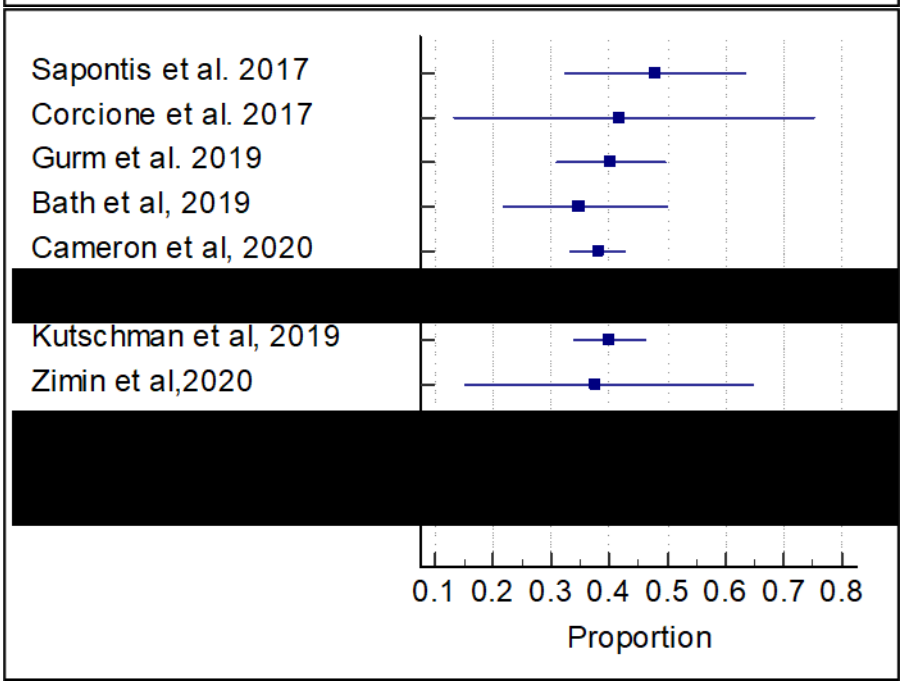
Study	Proportion (%)	95% CI
Sapontis et al. 2017	47.700	32.436 to 63.285
Corcione et al. 2017	41.800	13.260 to 75.189
Gurm et al. 2019	40.100	31.032 to 49.695
Bath et al, 2019	34.900	21.848 to 49.849
Cameron et al, 2020	38.000	33.354 to 42.815
[redacted]		
Kutschman et al, 2019	40.000	33.974 to 46.258
Zimin et al,2020	37.500	15.198 to 64.565
[redacted]		

Test for heterogeneity

Q	3.2965
DF	7
Significance level	P = 0.8563
I^2 (inconsistency)	0.00%
95% CI for I^2	0.00 to 31.87

Publication bias

Egger's test	
Intercept	0.4048
95% CI	-0.8492 to 1.6588
Significance level	P = 0.4597
Begg's test	
Kendall's Tau	0.2143
Significance level	P = 0.4579



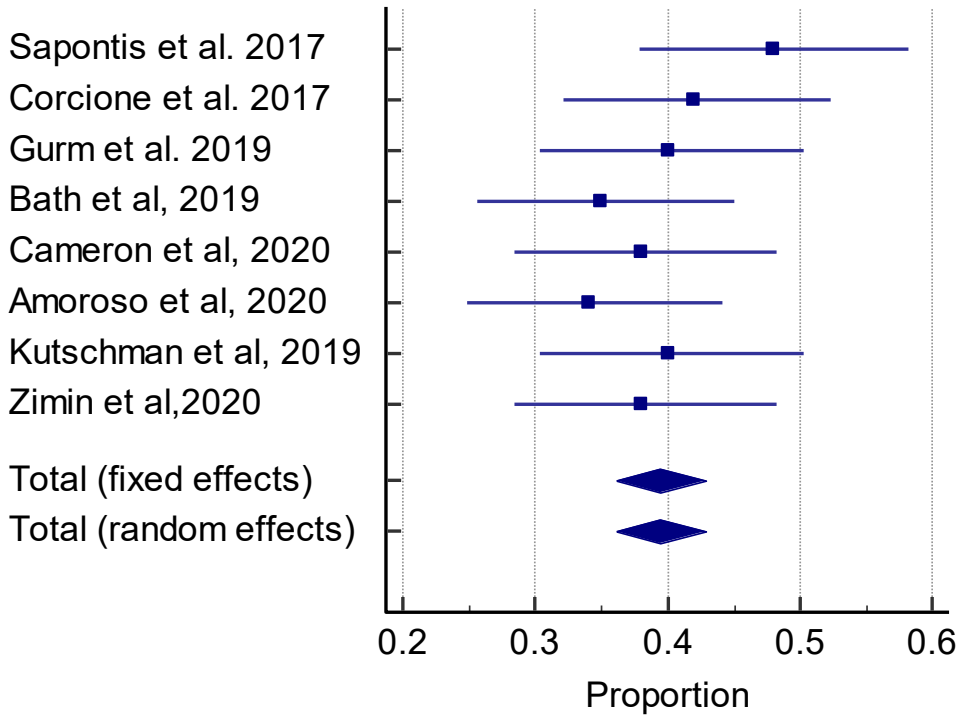
7) Pooled estimate of the contrast volume saving (%) in the intervention group among 8 **published** single-arm studies calculated as **39.43% (CI%95: 36.09%-42.82%)**

Variable for studies	Study
Variable for total number of cases	n
Variable for number of positive cases	contrast_volume_saving

Study	Proportion (%)	95% CI
Sapontis et al. 2017	48.000	37.901 to 58.221
Corcione et al. 2017	42.000	32.199 to 52.288
Gurm et al. 2019	40.000	30.329 to 50.279
Bath et al, 2019	34.900	25.638 to 45.082
Cameron et al, 2020	38.000	28.477 to 48.254
Amoroso et al, 2020	34.000	24.822 to 44.153
Kutschman et al, 2019	40.000	30.329 to 50.279
Zimin et al,2020	38.000	28.477 to 48.254
Total (fixed effects)	39.434	36.047 to 42.899
Total (random effects)	39.434	36.092 to 42.827

Test for heterogeneity

Q	5.5532
DF	7
Significance level	P = 0.5928
I^2 (inconsistency)	0.00%
95% CI for I^2	0.00 to 59.56



8) [redacted]

Meta-analysis: proportion

Variable for studies	Author
Variable for total number of cases	n
Variable for number of positive cases	Image_quality

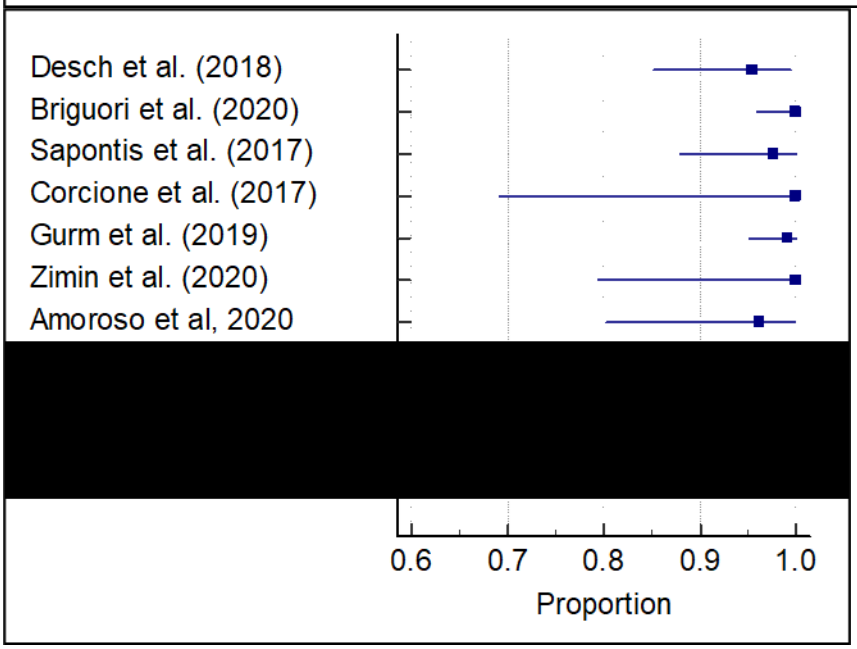
Study	Sample size	Proportion (%)	95% CI	Weight (%)	
				Fixed	Random
Desch et al. (2018)	48	95.500	85.262 to 99.382	9.78	9.78
Briguori et al. (2020)	90	100.000	95.984 to 100.000	18.16	18.16
Sapontis et al. (2017)	44	97.727	87.976 to 99.942	8.98	8.98
Corcione et al. (2017)	10	100.000	69.150 to 100.000	2.20	2.20
Gurm et al. (2019)	114	99.123	95.209 to 99.978	22.95	22.95
Zimin et al. (2020)	16	100.000	79.409 to 100.000	3.39	3.39
Amoroso et al, 2020	26	96.154	80.363 to 99.903	5.39	5.39

Test for heterogeneity

Q	6.7842
DF	7
Significance level	P = 0.4517
I^2 (inconsistency)	0.00%
95% CI for I^2	0.00 to 66.90

Publication bias

Egger's test	
Intercept	-0.6408
95% CI	-3.0093 to 1.7277
Significance level	P = 0.5326
Begg's test	
Kendall's Tau	0.0000
Significance level	P = 1.0000



9) Pooled estimate of the image quality (%) among 7 **published** clinical studies calculated as 98.20% (CI%95: 96.54%-99.33%)

Variable for studies	Author
Variable for total number of cases	n
Variable for number of positive cases	Image_quality

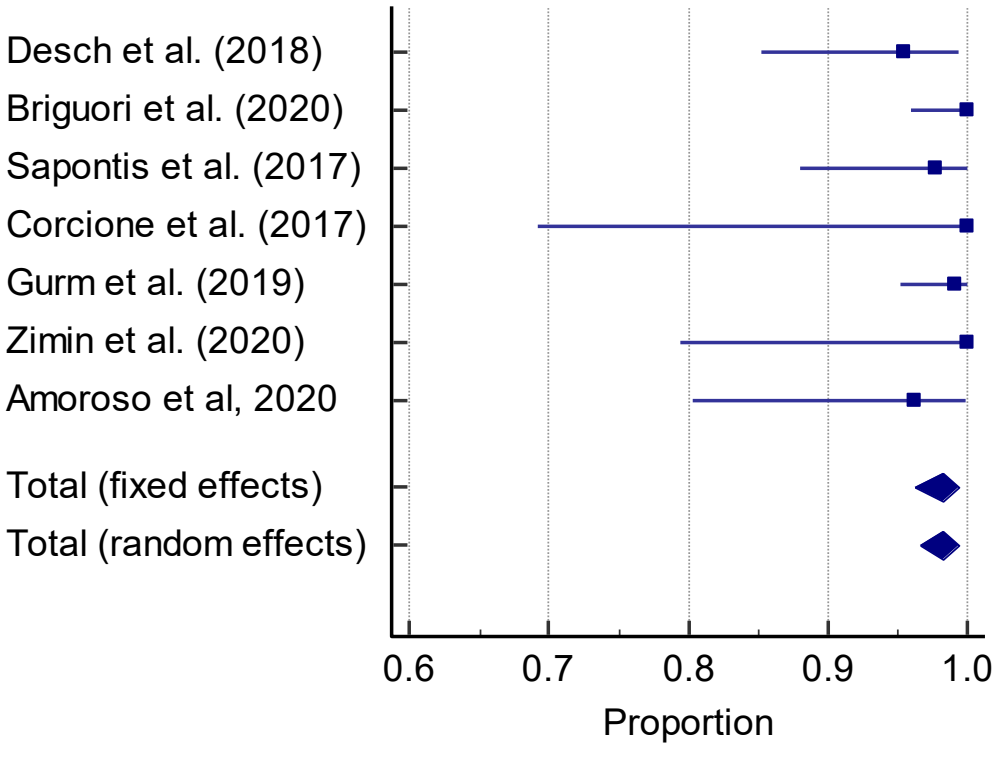
Study	Sample size	Proportion (%)	95% CI	Weight (%)	
				Fixed	Random
Desch et al. (2018)	48	95.500	85.262 to 99.382	13.80	13.94
Briguori et al. (2020)	90	100.000	95.984 to 100.000	25.63	25.49
Sapontis et al. (2017)	44	97.727	87.976 to 99.942	12.68	12.82
Corcione et al. (2017)	10	100.000	69.150 to 100.000	3.10	3.17
Gurm et al. (2019)	114	99.123	95.209 to 99.978	32.39	31.93
Zimin et al. (2020)	16	100.000	79.409 to 100.000	4.79	4.90
Amoroso et al, 2020	26	96.154	80.363 to 99.903	7.61	7.75
Total (fixed effects)	348	98.222	96.239 to 99.324	100.00	100.00
Total (random effects)	348	98.207	96.542 to 99.337	100.00	100.00

Test for heterogeneity

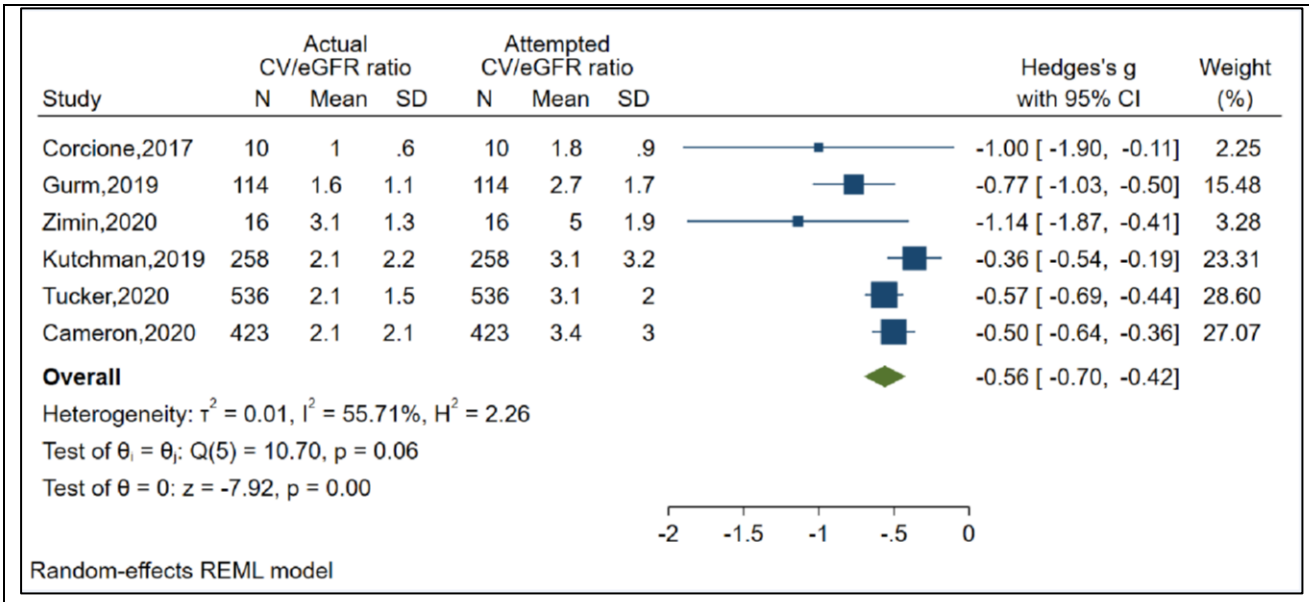
Q	6.1062
DF	6
Significance level	P = 0.4114
I^2 (inconsistency)	1.74%
95% CI for I^2	0.00 to 71.79

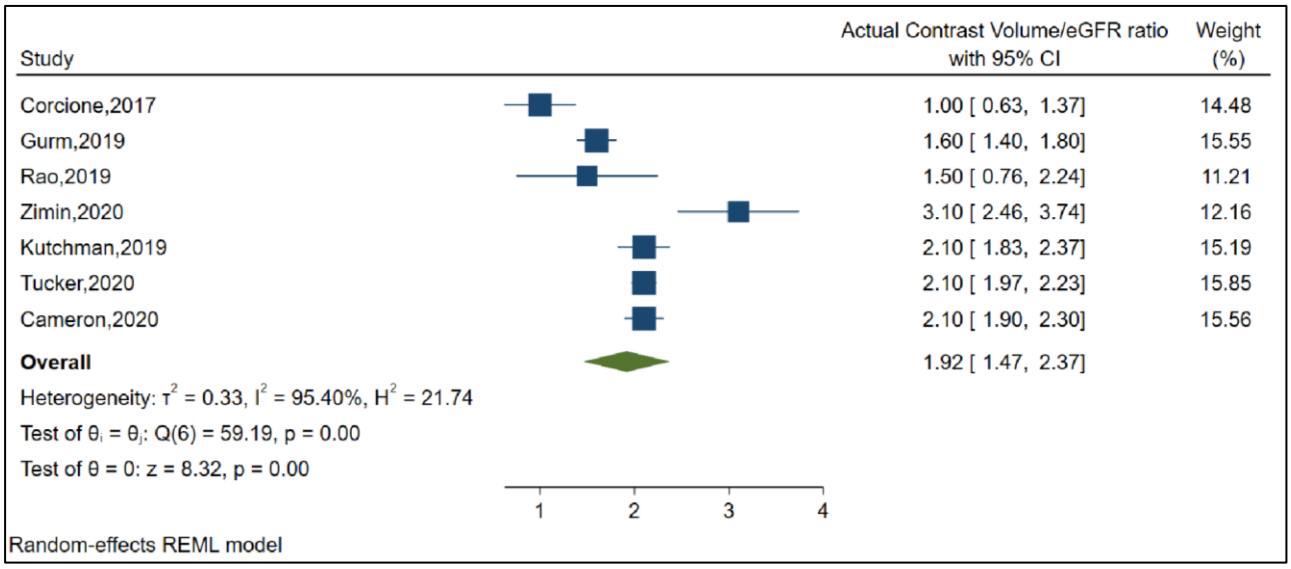
Publication bias

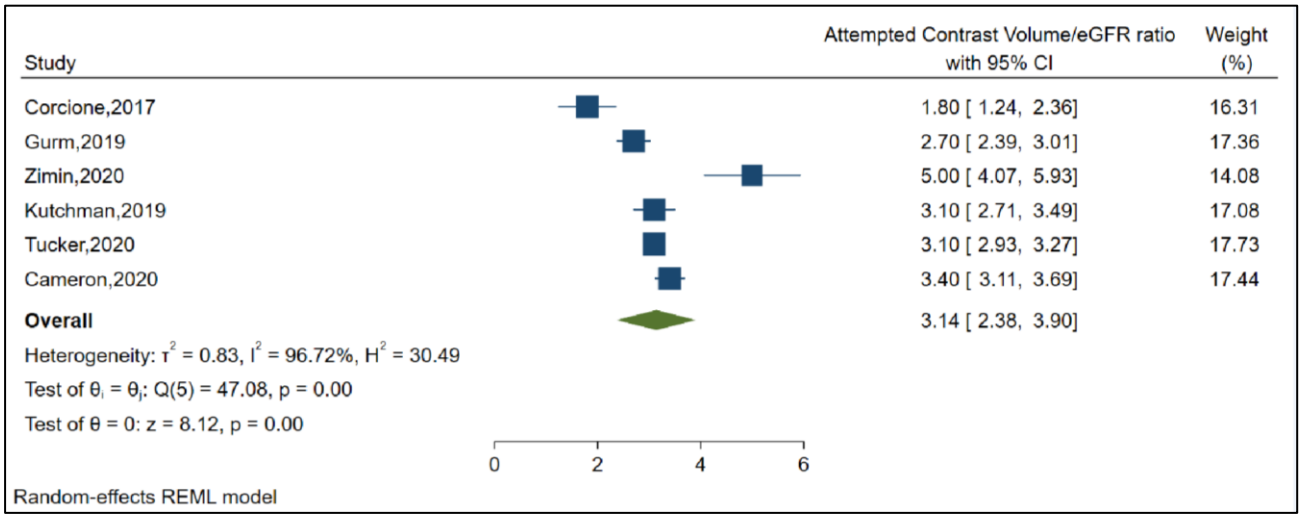
Egger's test	
Intercept	-1.2793
95% CI	-3.9244 to 1.3659
Significance level	P = 0.2689
Begg's test	
Kendall's Tau	-0.1429
Significance level	P = 0.6523



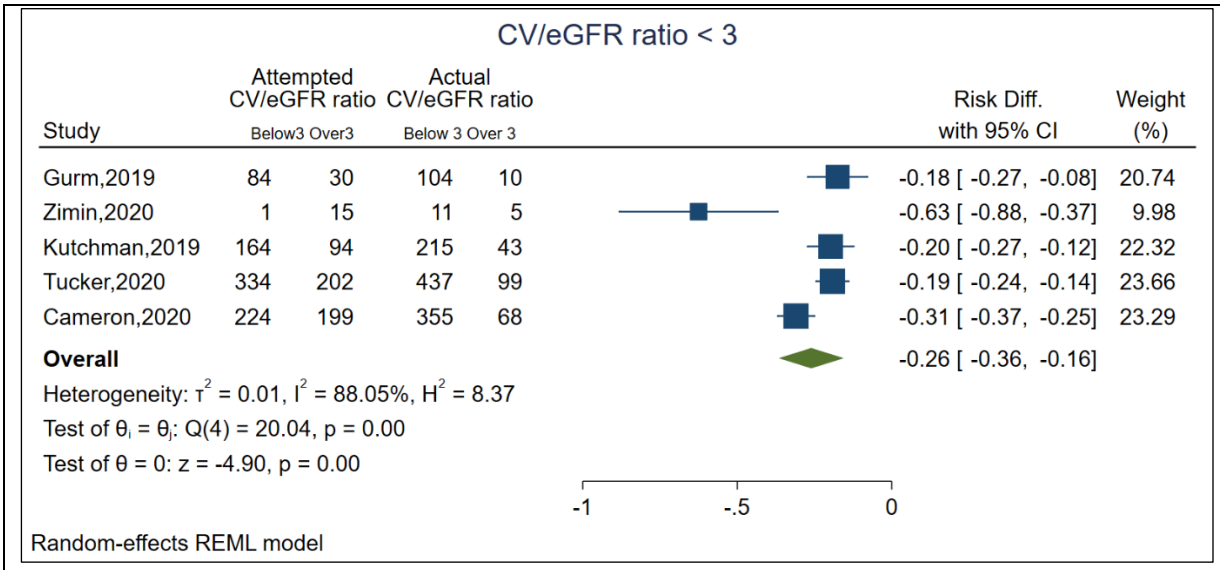
10) Pooled estimate of actual versus attempted CV/eGFR ratio

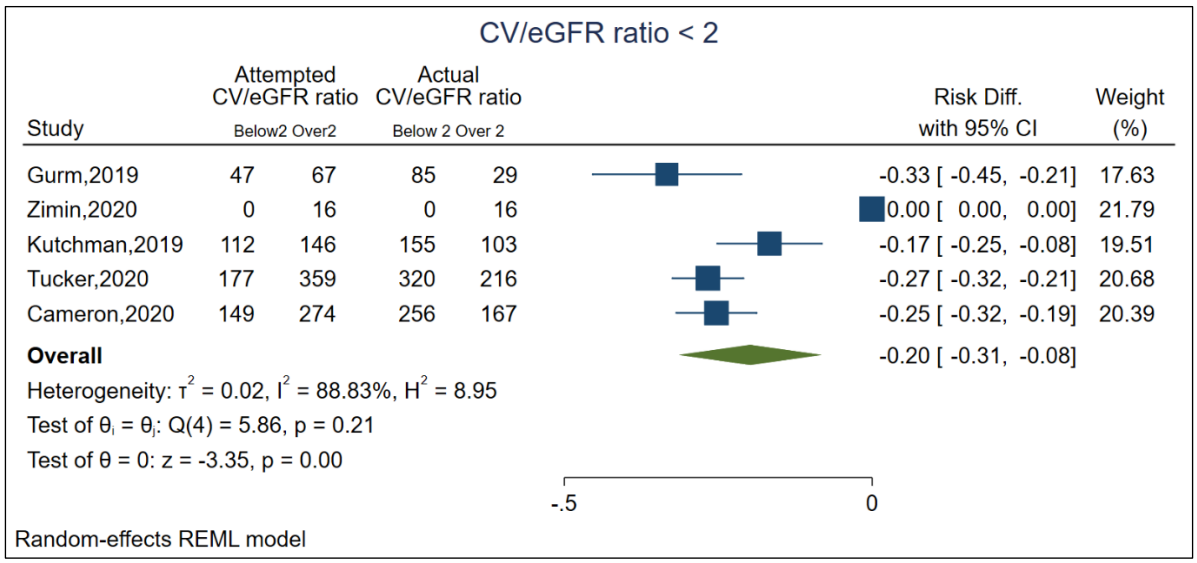


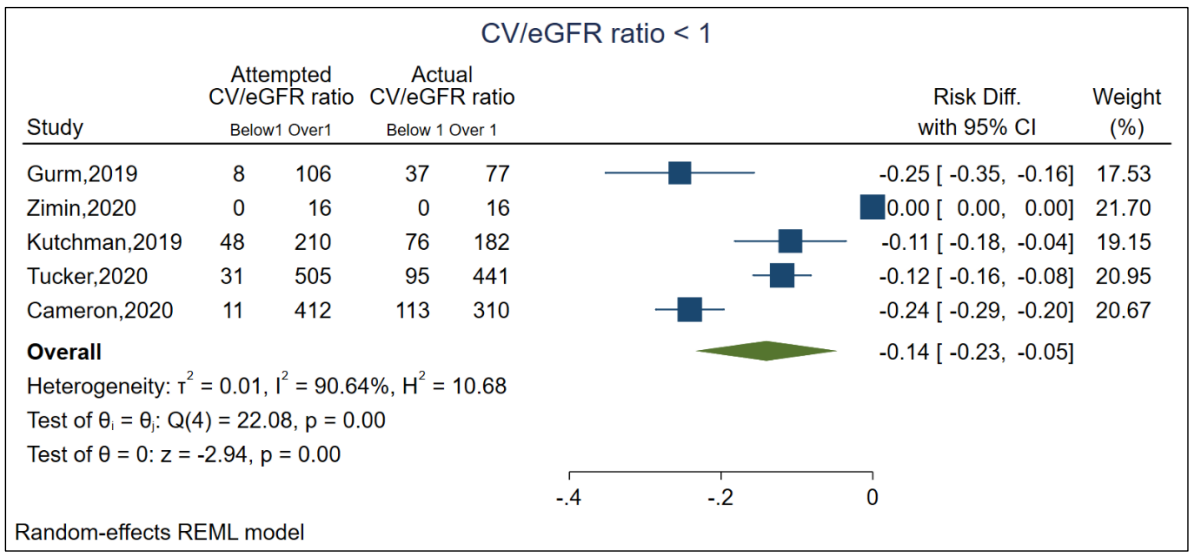




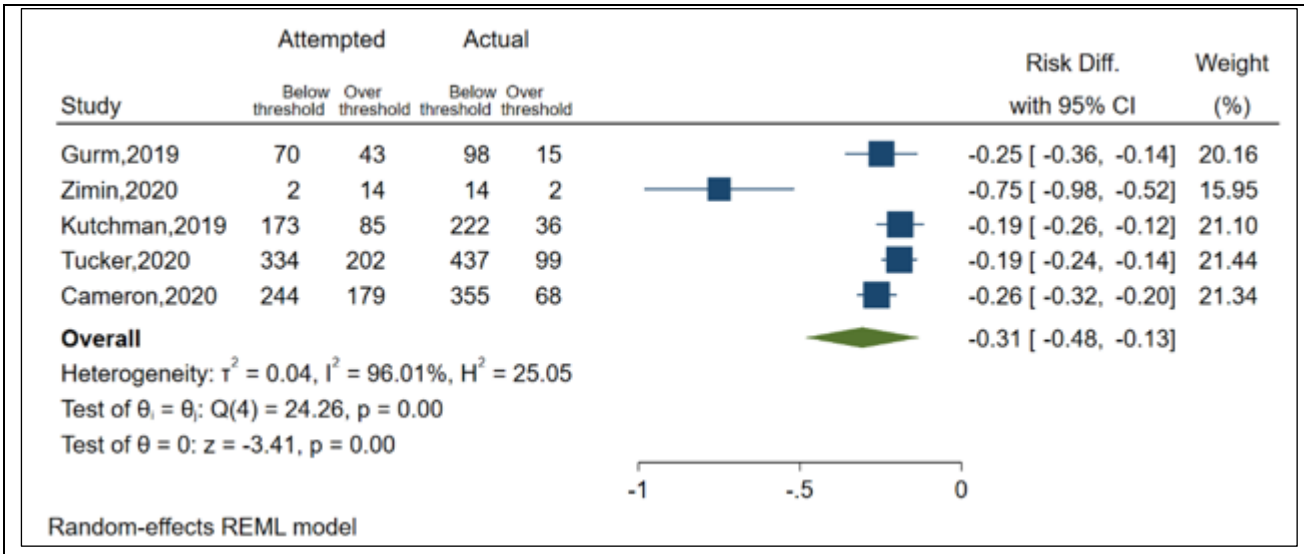
11) Pooled estimate of actual versus attempted CV/eGFR ratios by CV/eGFR group







12) Pooled estimate of contrast threshold management



Explain the main findings and conclusions drawn from the evidence synthesis.

Results from each meta-analysis are explained below:

1) Four double-armed studies were included in this analysis, exploring the risk of experiencing CI-AKI among patients receiving the DyeVert system compared to patients not receiving the DyeVert system. Results of this analysis indicated an overall relative risk of 0.59 (CI%95: 0.38-0.89). Therefore, those patients who received the DyeVert system had 0.59 times the risk of experiencing CI-AKI compared to those who did not receive the DyeVert system. Results were statistically significant with a p-value < 0.01. The I^2 statistic was 0.00%, which suggests very low evidence of heterogeneity.

2) This analysis included the same four studies as the previous analysis and estimated the pooled likelihood of patients in the DyeVert group experiencing CI-AKI. The estimated value was 7.71% (CI%95: 5.36%-10.44%) across studies.

3) This analysis included the same four studies as the previous analysis and estimated the pooled likelihood of patients in the control group experiencing CI-AKI. The estimated value was 12.55% (CI%95: 8.74%-16.93%) across studies. In the test for heterogeneity, the p-value of the Q statistic was 0.0009, indicating strong evidence of heterogeneity.

4) This analysis looked at the standardized mean difference in absolute contrast volume saved in the DyeVert group compared to the control group. Results of the analysis showed a difference [redacted] Results were statistically significant with a p-value < 0.001, although statistics on heterogeneity suggest that there is strong evidence of heterogeneity.

5) This analysis looked at the standardized mean difference in absolute contrast volume saved in the DyeVert group compared to the control group in four published studies. Results of the analysis showed a difference of -1.463 (CI%95: -2.339: -0.588). Results were statistically significant with a p-value < 0.001, although statistics on heterogeneity suggest that there is strong evidence of heterogeneity.

6) This analysis explored the pooled estimate of contrast volume savings (%) in the DyeVert group in eight single-arm studies. Results of the analysis indicated a pooled volume saving of [redacted] across studies.

7) This analysis explored the pooled estimate of contrast volume savings (%) in the DyeVert group in 8 single-arm published studies. Results of the analysis indicated a pooled volume saving of 39.43% (CI%95: 36.09%-42.82%) across studies.

8) This analysis explored the image quality (%) based on the physicians' feedback in the DyeVert group in eight clinical studies. Results indicated that the overall image quality was adequate in [redacted] of the patients.

9) This analysis explored the image quality (%) based on the physicians' feedback in the DyeVert group in seven published clinical studies. Results indicated that the overall image quality was adequate in 98.20% (CI%95: 96.54%-99.33%) of the patients.

10) This analysis explored the actual versus attempted CV/eGFR ratio in the DyeVert group. Results indicate use of the DyeVert System reduces the actual CV/eGFR ratio compared to the attempted CV/eGFR ratio (Hedges's g -0.56 (-0.7, -0.42)).

11) This analysis explored the actual versus attempted CV/eGFR ratio by CV/eGFR ratio group among in the DyeVert group. Results indicate use of the DyeVert System has reduced the risk of receiving contrast volumes that exceed each CV/eGFR ratio grouping based on actual contrast volume delivered to the patient compared to the attempted contrast volume (CV/eGFR ratio <3 group RD -0.26 (CI%95: -0.36, -0.16); CV/eGFR ratio <2 group RD -0.20 (CI%95: -0.31, -0.08); CV/eGFR ratio <1 group RD -0.14 (CI%95: -0.23, -0.05)).

12) This analysis explored contrast threshold management based on actual contrast volume delivered versus attempted contrast volume in the DyeVert group. Results indicate use of the DyeVert System has reduced risk of receiving contrast volumes that exceed the pre-defined maximum contrast threshold based on actual contrast volume delivered to the patient compared to the attempted contrast volume (RD -0.31 (CI%95: -0.48, -0.13)).

Conclusions based on the results of meta-analyses:

The DyeVert System reduces the risk of experiencing CI-AKI when at-risk patients in the DyeVert Group are compared with patients who undergo angiography without DyeVert System use (Control Group). Overall, a lower percentage of patients using the DyeVert System experience CI-AKI compared to the Control Group. Results of the analyses also show that the DyeVert System reduces the absolute volume of contrast media used, as well as the percentage of volume used by 40%. DyeVert System use also reduces CV/eGFR ratios and the risk of receiving contrast volumes that exceed each CV/eGFR ratio groupings down to <1 times the patients baseline eGFR. DyeVert System use also reduces the risk of receiving contrast volumes that exceed the physician's pre-defined maximum contrast dose threshold. In addition, contrast reduction is achieved without having negative impact on image quality.

Critical appraisal of published studies:

All identified published studies included in the meta-analyses were also critically appraised using appropriate and validated quality assessment instruments. In the majority of studies where the following details were reported (in some cases it was unclear, or not required due to the nature of the analysis), it was found: that the cohort was recruited in an appropriate way, the exposure was accurately measured to minimize bias, the outcome was measured accurately to minimize bias, all-important confounding factors were considered, the follow-up of patients was appropriate and complete, and the results were presented in a precise manner (i.e. with confidence intervals around effect estimates, and p-values). Overall, the studies were found to be of good quality which allows one to consider the presented results as robust and to be an accurate reflection of the outcomes and potential benefits associated with the DyeVert System. If required, a detailed quality assessment of all included published studies is available and can be provided.

Qualitative review

Please only complete this section if a quantitative evidence synthesis is not appropriate.

Explain why a quantitative review is not appropriate and instead provide a qualitative review. This review should summarise the overall results of the individual studies with reference to their critical appraisal.

Not applicable

8 Summary and interpretation of clinical evidence

Summarise the main clinical evidence, highlighting the clinical benefit and any risks relating to adverse events from the technology.

Use of the DyeVert System has been shown to reduce two significant risk factors of CI-AKI: contrast volume and contrast volume/eGFR ratio. Evidence supporting contrast-related risk factor reduction includes 8 published manuscripts and 9 published abstracts/posters, which were included in the critical literature appraisal. In addition, 2 unpublished studies and 1 published case report also confirm DyeVert System performance. A meta-analysis involving a total of 10 publications demonstrated a significant reduction of -1.226 in standardized mean difference in absolute contrast volume delivered to the patient in cases involving use of the DyeVert System versus Control Group cases (DyeVert System not used) and a pooled estimate of contrast volume savings as a percentage of the total contrast volume attempted (contrast volume delivered + contrast volume saved) of 39.88%. In DyeVert cases, there was an absolute contrast volume savings per case ranged from 34 mL to 84 mL (mean ± STD: 65 ± 27). A pooled estimate of DyeVert Cases compared the attempted contrast volume/eGFR ratio to the actual contrast volume/eGFR and the results indicate the actual contrast volume/eGFR ratio was significantly reduced (Hedges's g -0.56). [redacted]

A pooled estimate involving five studies of DyeVert Cases demonstrate the shift in population to lower CV/eGFR ratios based on actual contrast delivered versus the attempted contrast volume. Results indicate use of the DyeVert System reduced the risk of receiving contrast volumes that exceed successively lower CV/eGFR ratio groupings based on actual contrast volume delivered to the patient compared to the attempted contrast volume down to <1 time the patients baseline eGFR (CV/eGFR ratio <3 group RD -0.26 (CI%95: -0.36, -0.16); CV/eGFR ratio <2 group RD -0.20 (CI%95: -0.31, -0.08); CV/eGFR ratio <1 group RD -0.14 (CI%95: -0.23, -0.05)).

A pooled estimate involving five studies of DyeVert cases explored contrast threshold management based on actual contrast volume delivered versus attempted contrast volume. Results indicate use of the DyeVert System reduced the risk of receiving contrast volumes that exceed the physician's pre-defined maximum contrast dose threshold based on actual contrast volume delivered to the patient compared to the attempted contrast volume (RD -0.31 (CI%95: -0.48, -0.13)). Additionally, two studies explored the proportion of patients that exceeded the pre-defined contrast dose threshold based on actual contrast volume delivered between a DyeVert group and a Control group in which the DyeVert System was not used resulting in a mean 36% versus 59% of patients exceeding the contrast dose threshold in each group, respectively. [redacted]

Additionally, the DyeVert System reduces the absolute volume of contrast media used without having negative impact on the image quality as demonstrated in 11 studies. All studies involved real-time image quality assessment by the DyeVert System user and two studies additionally involved image analysis by a blinded reviewer. A meta-analysis involving a total of 8 publications demonstrated a pooled estimate of 97.89% of cases reported image quality was maintained.

No DyeVert System-related adverse events were found in searches of the MHRA and FDA databases or reported in any of the clinical studies identified.

Contrast-related risk factor reduction has been shown to be associated with a reduction in CI-AKI. Evidence supporting CI-AKI reduction includes 2 published manuscripts, 1 unpublished manuscript, and 8 published abstracts. This evidence aligns with current clinical guideline recommendations for the reduction of CI-AKI. Three studies involve DyeVert System use in CI-AKI prevention quality improvement programs and 6 studies involve a control group that did not have DyeVert System use during the case. Additionally, 2 single-arm studies reported CI-AKI rates. Of these, one study compared the actual CI-AKI rate with the projected CI-AKI using a published risk prediction model. A meta-analysis involving a total of 4 publications demonstrated a pooled estimate of CI-AKI in the DyeVert group of 7.71% versus 12.55% in the Control group, reflecting an absolute difference of 4.84% or a pooled relative risk estimate of 0.59. Overall, a lower percentage of patients undergoing procedures involving use of the DyeVert System experience CI-AKI compared with patients not using the system.

Given the significant morbidity and mortality associated with CI-AKI, prevention measures have the potential to positively impact CI-AKI-related healthcare burden. Economic modelling based on the clinical effectiveness of DyeVert indicate that the intervention leads to cost savings (-£435) and improved effectiveness (+ 0.028 QALYs) over the patient's lifetime, compared with current practice, a projected overall long-term cost saving for the NHS of £175 million. Modelling translates to real-world experience as several hospitals report budget impact analysis that demonstrate a net cost savings/case ranging from $650 to $2,000/case.

Literature supports CI-AKI prevention has the potential to reduce costs associated with short-term and long-term morbidity, mortality, extended length-of-stay, increased post-procedure nursing care and increased readmissions. A prospective study of DyeVert System use compared to standard of care without DyeVert System use reported reduced length-of-stay.

Clinically meaningful contrast minimization results in more patients receiving contrast media volumes at or below the maximum contrast dose. The ability to ensure consistent and safer contrast media doses supports enablement of angiography access to at-risk patients, particularly those with moderate or severe pre-existing kidney disease.

Gaps exist between clinical guidelines and clinical practice as it relates to the care of at-risk patients. Technology-supported patient-centered care programs have the potential to improve consistency of delivering on CI-AKI prevention strategies. In addition, DyeVert System use provides real-time clinical decision support and improved adherence to recommended guidelines for CI-AKI prevention:

- During case set-up, the Display prompts the user to enter renal function status. This prompts the staff to ensure an eGFR value is available, thereby enabling this value to be used as recommended by clinical guidelines for pre-procedural patient risk screening, patient informed consent, and calculating a maximum contrast dose. Without this information in advance of the procedure, staff may miss identification of at-risk patients, fail to appropriately consent patients, and fail to establish a pre-procedure maximum contrast dose for the patient.
- During case set-up, the Display prompts the user to specify and record the maximum contrast media dose threshold for the case. Maximum contrast dose thresholds are often not set pre-procedurally, documented in the medical record, and/or are used to guide clinical decision making during the procedure.
- During the case, the Display actively monitors contrast use during each injection and cumulatively relative to a dose target, and the Display notifies the user periodically as the actual contrast used approaches the dose target. These features bring regular awareness to contrast use and contrast use relative to the pre-determined maximum dose, which supports clinical decision making to limit contrast use for each patient.
- The DyeVert System also records critical case information often missing in the medical record such as the maximum contrast dose target for the case and total contrast delivered to the patient.

Briefly discuss the relevance of the evidence base to the scope. This should focus on the claimed benefits described in the scope and the quality and quantity of the included studies.

The collective evidence base includes studies of the DyeVert System, supporting published literature related to CI-AKI, and clinical practice guidelines involving CI-AKI. The relevance of this evidence to the scope is provided below.

- DyeVert Evidence: 8 published manuscripts, 10 published abstracts/posters, 2 unpublished studies and 1 published case report
    - These studies were conducted in the UK as well as major markets with similar population characteristics and standards of care such as the USA, Australia, Germany, the Netherlands, and Italy
    - Patients included in the studies were those at-risk for CI-AKI
    - A majority of the evidence was collected in real-world use settings, which demonstrates DyeVert System performance as an adjunct to routine standard of care.
    - Comparative trials involved control groups that involved conventional manual or automated injection of contrast media as noted
    - Outcomes included in the scope are represented in the evidence collected
    - All identified published studies included in the meta-analyses were also critically appraised using appropriate and validated quality assessment instruments. Overall, the studies were found to be of good quality which allows one to consider the presented results as robust and to be an accurate reflection of the outcomes and potential benefits associated with the DyeVert system.

- Supporting Evidence: 24 published manuscripts
    - These studies describe CI-AKI incidence and the associated short- and long-term morbidity, mortality, and health care burden.
    - UK data sources were used wherever possible
    - Data from markets with similar population characteristics and standards of care such as the USA are also included

- Guidelines: 4 published clinical guidelines
    - Two guidelines published by NICE related to acute kidney injury
    - Two guidelines published by ESC related to prevention of acute kidney injury
        - These guidelines specifically address the target patient population and provide at-risk criteria and procedure-based recommendations for CI-AKI prevention and the minimization of iodinated contrast media

Identify any factors which might be different between the patients in the submitted studies and patients having routine care in the UK NHS.

None known.

Describe any criteria that would be used in clinical practice to select patients for whom the technology would be most appropriate.

The DyeVert System is intended for patients undergoing coronary and/or peripheral angiography involving the use of iodinated contrast media who are at risk of contrast induced kidney injury, such as those with chronic kidney disease, heart failure, diabetes, renal transplant, aged 75 years and over, or hypovolaemia.

Briefly summarise the strengths and limitations of the clinical evidence for the technology.

Strengths:

- A large number of studies focusing on the clinical effectiveness of the DyeVert System have been identified (8 published, 2 unpublished and 2 ongoing, and 9 abstracts).
- A majority of the evidence is collected in real-world use settings.
- The countries in which studies have been conducted are varied (UK, USA, Germany, the Netherlands, Italy, Australia), allowing for an understanding of potential clinical impact in a wide range of settings.
- All studies which have focussed on CM volume savings as an outcome have reported favourable results for the DyeVert System. In many cases, results were significant and clinically meaningful.
- Impact of the DyeVert System on CI-AKI rates has been favourable across studies (in those studies which reported acute kidney injury rates as an outcome).
- In those studies that reported on impact of the DyeVert System on image quality, there was rare decline in quality identified.
- Potential economic benefits of introduction of the DyeVert System have been reported in a published economic model that has been further validated by clinical studies.

Limitations:

- Certain studies highlighted a small sample size included as being a drawback of the study (Briguori et al, 2020, Bruno et al, 2019, Corcione et al, 2017, Desch et al, 2018, Sapontis et al, 2017, Zimin et al, 2020, Sattar et al, 2018).
- Certain studies reported on the lack of long-term follow-up (Bruno et al, 2019, Gurm et al, 2019a, Tajti et al, 2019, Zimin et al, 2020).
- Certain studies reported that there was a lack of a Clinical Event Committee on the study (Briguori et al, 2020).
- Certain studies reported absence of randomization as being a limitation of the analysis (Bruno et al, 2019).

9 References

Please include all references below using NICE's standard referencing style.

Allen DW, Ma B, Leung KC, et al. (2017) Risk prediction models for contrast-induced acute kidney injury accompanying cardiac catheterization: systematic review and meta-analysis. Canadian Journal of Cardiology 33(6):724-736. doi:10.1016/j.cjca.2017.01.018.

Amin AP, Bach RG, Caruso ML, et al. (2017) Association of variation in contrast volume with acute kidney injury in patients undergoing percutaneous coronary intervention. Journal of the American Medical Association Cardiology Sep 1;2(9):1007-1012. doi: 10.1001/jamacardio.2017.2156. PMID: 28678988; PMCID: PMC5815045.

Amin AP, McNeely C, Spertus JA, et al. (2020) Incremental cost of acute kidney injury after percutaneous coronary intervention in the United States. American Journal of Cardiology Jan 1;125(1):29-33. doi: 10.1016/j.amjcard.2019.09.042. Epub 2019 Oct 10. PMID: 31711633.

Amoroso G, Christian J, Christopher A (2020) First European experience using a novel contrast reduction system during coronary angiography with automated contrast injection. EuroIntervention Supplement 16 (AC):Euro20A-POS426.

Arribas J, Alegria-Barrero E (2009). How to prevent contrast-induced nephropathy in patients undergoing invasive cardiac procedures. E-Journal of Cardiology Practice 7(25). Accessed on January 20, 2021 from: https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-7/How-to-prevent-contrast-induced-nephropathy-in-patients-undergoing-invasive-card.

Bath A, Bobba K, Gautam S, et al. (2019) Gupta V. Use of DyeVert Plus to reduce contrast exposure in high-risk patients undergoing coronary angiography. Journal of the American College of Cardiology 73(9 Supplement 1):1193. doi:10.1016/s0735-1097(19)31800-5.

Briguori C, Golino M, Porchetta N, et al. (2020) Impact of a contrast media volume control device on acute kidney injury rate in patients with acute coronary syndrome. Catheterization and Cardiovascular Interventions [published online ahead of print, 2020 Jul 18]. doi:10.1002/ccd.29136.

Bruno RR, Nia AM, Wolff G, et al. (2019) Early clinical experiences with a novel contrast volume reduction system during invasive coronary angiography. International Journal of Cardiology Heart and Vasculature 23:100377. doi:10.1016/j.ijcha.2019.100377.

Bunney R, Saenger E, Shah C, et al. (2019) Contemporary use of contrast dye reduction technology in a tertiary academic hospital: patient characteristics and acute kidney injury outcomes following percutaneous coronary interventions. Poster presented at: American College of Cardiology (ACC) Quality Summit; March 2019; New Orleans, LA. Poster 2018-063 presentation https://cvquality.acc.org/docs/default-source/quality-poster-awards-2019/2018-063_bunney-robert_rn.pdf?sfvrsn=582f86bf_2.

Cameron A, Espinosa TJ (2020) Reducing contrast-induced acute kidney injury in a cardiac catherization laboratory: a quality improvement initiative. Society for Cardiac Angiography & Interventions Scientific Sessions Virtual Conference. E-poster abstract presented https://virtual2020.scai.org/p/46024. Catheterization and Cardiovascular Interventions 95 (Supplement 2):I-34.

Castro D, Dang TT (2018) Reducing contrast-induced acute kidney injury in the cath lab. Poster presented at: American Academy of Cardiology (ACC) National Cardiovascular Data Registry (NCDR) 2018 Annual Conference; March 2018; Orlando, FL.

Corcione N, Biondi-Zoccai G, Ferraro P, et al. (2017) Contrast minimization with the new-generation DyeVert Plus System for contrast reduction and real-time monitoring during coronary and peripheral procedures: first experience. Journal of Invasive Cardiology 29(8):259-62. PMID: 28756419.

Desch S, Fuernau G, Pöss J, et al. (2018) Impact of a novel contrast reduction system on contrast savings in coronary angiography - The DyeVert randomised controlled trial. International Journal of Cardiology 257:50-3. doi: 10.1016/j.ijcard.2017.12.107.

Elbadawi A, Elgendy IY, Ha LD, et al. (2019) National trends and outcomes of percutaneous coronary intervention in patients ≥70 years of age with acute coronary syndrome (from the National Inpatient Sample Database). American Journal of Cardiology 123(1):25-32. doi:10.1016/j.amjcard.2018.09.030.

Garg S, Anderson SG, Oldroyd K, et al. (2015) British Cardiovascular Intervention Society; National Institute for Cardiovascular Outcomes Research. Outcomes of percutaneous coronary intervention performed at offsite versus onsite surgical centers in the United Kingdom. Journal of the American College of Cardiology Jul 28;66(4):363-72. doi: 10.1016/j.jacc.2015.05.052. PMID: 26205593.

Gurm HS, Dixon SR, Smith DE, et al. (2011) Renal function-based contrast dosing to define safe limits of radiographic contrast media in patients undergoing percutaneous coronary interventions. Journal of the American College of Cardiology 58:907-914. doi: 10.1016/j.jacc.2011.05.023.

Gurm HS, Seth M, Mehran R, et al. (2016) Impact of contrast dose reduction on incidence of acute kidney injury (AKI) among patients undergoing PCI: a modeling study. Journal of Invasive Cardiology 28:142-146. PMID: 26773238.

Gurm HS, Mavromatis K, Bertolet B, et al. (2019) Minimizing radiographic contrast administration during coronary angiography using a novel contrast reduction system: a multicenter observational study of the DyeVert™ plus contrast reduction system. Catheterization and Cardiovascular Interventions 93(7):1228-35. doi: 10.1002/ccd.27935.

Gurm HS, Seth M, Dixon SR, et al. (2019) Contemporary use of and outcomes associated with ultra-low contrast volume in patients undergoing percutaneous coronary interventions. Catheterization and Cardiovascular Interventions 93:222-230. doi: 10.1002/ccd.27819.

Hsu RK, Siew ED (2017) The growth of AKI: half empty or half full, it's the size of the glass that matters. Kidney International 92:550–3.

James MT, Samuel SM, Manning MA, et al. (2013) Contrast-induced acute kidney injury and risk of adverse clinical outcomes after coronary angiography: a systematic review and meta-analysis. Circulation: Cardiovascular Interventions Feb;6(1):37-43.

Javanbakht M, Hemami MR, Mashayekhi A, et al. (2020) DyeVert™ PLUS EZ System for preventing contrast-induced acute kidney injury in patients undergoing diagnostic coronary angiography and/or percutaneous coronary intervention: a UK-based cost-utility analysis. PharmacoEconomics Sep;4(3):459-472. doi: 10.1007/s41669-020-00195-x. PMID: 31989464; PMCID: PMC7426357.

Kang Y, Chen T, Mui D, et al. (2020) Cardiovascular manifestations and treatment considerations in COVID-19. Heart Aug;106(15):1132-1141. doi: 10.1136/heartjnl-2020-317056. Epub 2020 Apr 30. PMID: 32354800; PMCID: PMC7211105.

Kerr M, Bedford M, Matthews B, et al. (2014) The economic impact of acute kidney injury in England. Nephrology Dialysis Transplantation Jul;29(7):1362-8. doi: 10.1093/ndt/gfu016. Epub 2014 Apr 21. PMID: 24753459.

Kerr M (2017) Chronic kidney disease in England: The human and financial cost. Accessed on January 20, 2021 from: https://www.england.nhs.uk/improvement-hub/wp-content/uploads/sites/44/2017/11/Chronic-Kidney-Disease-in-England-The-Human-and-Financial-Cost.pdf.

Knuuti J, Wijns W, Saraste A, et al. (2019) European Society of Cardiology Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. European Heart Journal Jan 14;41(3):407-477. doi: 10.1093/eurheartj/ehz425. PMID: 31504439.

Kutschman R (2019) Clinical and economic outcomes of a comprehensive clinical quality initiative for reducing acute kidney injury in chronic kidney disease patients undergoing coronary angiography. Journal of the American College of Cardiology 74(13 Supplement):B605. doi: 10.1016/j.jacc.2019.08.731.

Kutschman R, Davison L, Beyer J (2019) Comprehensive clinical quality initiative for reducing acute kidney injury in at-risk patients undergoing diagnostic coronary angiogram and/or percutaneous coronary interventions. Poster presented at Society for Cardiac Angiography & Interventions 2019 Scientific Sessions; May 2019; Las Vegas, NV. Accessed on January 20, 2021 from: https://scai.confex.com/scai/2019/webprogram/Paper2030.html.

Locklear J, Lee K (2018) Minimizing risk of kidney injury during cardiac evaluation in a kidney transplant patient. Cath Lab Digest 26(8). Accessed January 20, 2020 from: www.cathlabdigest.com/article/Minimizing-Risk-Kidney-Injury-During-Cardiac-Evaluation-Kidney-Transplant-Patient.

Mahmud E, Dauerman HL, Welt FGP, et al. (2020) Management of acute myocardial infarction during the COVID-19 pandemic: a consensus statement from the Society for Cardiovascular Angiography and Interventions (SCAI), the American College of Cardiology (ACC), and the American College of Emergency Physicians (ACEP). Catheterization and Cardiovascular Interventions Aug;96(2):336-345. doi: 10.1002/ccd.28946. Epub 2020 May 13. PMID: 32311816.

Leung TYM, Chan AYL, Chan EW, et al. Short- and potential long-term adverse health outcomes of COVID-19: a rapid review. Emerging Microbes & Infections Dec;9(1):2190-2199. doi: 10.1080/22221751.2020.1825914. PMID: 32940572; PMCID: PMC7586446.

National Institute of Health and Care Excellence (NICE) (2014) Acute kidney injury [QS76]. Accessed on January 20, 2021 from: https://www.nice.org.uk/guidance/qs76.

National Institute of Health and Care Excellence (NICE) (2019) Acute kidney injury: prevention, detection and management [NG148]. Accessed on January 20, 2021 from: https://www.nice.org.uk/guidance/ng148.

Prasad A, Sohn A, Morales J, et al. (2017) Contemporary practice patterns related to the risk of acute kidney injury in the catheterization laboratory: results from a survey of Society of Cardiovascular Angiography and Intervention (SCAI) cardiologists. Catheterization and Cardiovascular Interventions 89:383-392. doi: 10.1002/ccd.26628.

Prasad A, Rosenthal NA, Kartashov A, et al. (2020) Contemporary trend of acute kidney injury incidence and incremental costs among US patients undergoing percutaneous coronary procedures [published online ahead of print, 2020 Mar 4]. Catheterization and Cardiovascular Interventions 10.1002/ccd.28824. doi:10.1002/ccd.28824.

Rao S (2019) DyeVert Plus Contrast Reduction System use in patients undergoing highly complex peripheral vascular interventions. Poster presented at the International Symposium on Endovascular Therapies (ISET). Journal of Vascular and Interventional Radiology 30:e16. doi:10.1016/j.jvir.2018.11.033.

Rajani R, Lindblom M, Dixon G (2011) Evolving trends in percutaneous coronary intervention British Journal of Cardiology 18:73−6.

Sapontis J, Sujith S, Cameron J, et al. (2017) A first-in-human evaluation of a novel contrast media saving device. Catheterization and Cardiovascular Interventions 90(6):928-934. doi: 10.1002/ccd.27033.

Sattar A, Schnatz R, Darby M, et al. (2018) Impact of using DyeVert PLUS on incidence of acute kidney injury after cardiac catheterization with coronary interventions in high-risk patients. American College of Cardiology Annual Meeting; April 2018; Charleston, WV. Poster #3 presentation https://jcesom.marshall.edu/media/56993/2018-abstracts.pdf.

Sawhney S, Mitchell M, Marks A, et al. (2015) Long-term prognosis after acute kidney injury (AKI): what is the role of baseline kidney function and recovery? A systematic review. British Medical Journal Open Jan 6;5(1):e006497. doi: 10.1136/bmjopen-2014-006497. Erratum in: BMJ Open. 2015;5(1):e006497corr1. PMID: 25564144; PMCID: PMC4289733.

Sawhney S, Robinson HA, van der Veer SN, et al. (2018) Acute kidney injury in the UK: a replication cohort study of the variation across three regional populations. British Medical Journal Open Jun 30;8(6):e019435. doi: 10.1136/bmjopen-2017-019435. PMID: 29961002; PMCID: PMC6042563.

See EJ, Jayasinghe K, Glassford N, et al. (2019) Long-term risk of adverse outcomes after acute kidney injury: a systematic review and meta-analysis of cohort studies using consensus definitions of exposure. Kidney International Jan;95(1):160-172. doi: 10.1016/j.kint.2018.08.036. Epub 2018 Nov 23. PMID: 30473140.

Stewart J, Findlay G, Smith N, et al. (2009) Adding insult to injury: a review of the care of patients who died in hospital with a primary diagnosis of acute kidney injury. London: National Confidential Inquiry into Patient Outcome and Death. Accessed on January 20, 2021 from: https://www.ncepod.org.uk/2009aki.html

Tajti P, Xenogiannis I, Hall A, et al. (2019) Use of the DyeVert system in chronic total occlusion percutaneous coronary intervention. Journal of Invasive Cardiology 31(9):253-9.

Turner C, Tucker PA (2020) Real-world impact of a quality improvement program for AKI prevention in the cardiac cath lab. Society for Cardiac Angiography & Interventions Scientific Sessions Virtual Conference. Catheterization and Cardiovascular Interventions 95(Supplement 2):S112-S3.

Valle JA, McCoy LA, Maddox TM, et al. (2017) Longitudinal risk of adverse events in patients with acute kidney injury after percutaneous coronary intervention: insights from the national cardiovascular data registry. Catheterization and Cardiovascular Interventions 10(4):e004439. doi:10.1161/CIRCINTERVENTIONS.116.004439.

Zimin VN, Jones MR, Richmond IT, et al. (2020) A feasibility study of the DyeVert™ plus contrast reduction system to reduce contrast media volumes in percutaneous coronary procedures using optical coherence tomography. Cardiovascular Revascularization Medicine Oct 3:S1553-8389(20)30592-3. doi: 10.1016/j.carrev.2020.09.040. Epub ahead of print. PMID: 33046416.

10 Appendices

Appendix A: Search strategy for clinical evidence

Describe the process and methods used to identify and select the studies relevant to the technology. Include searches for published studies, abstracts and ongoing studies in separate tables as appropriate. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	November 05, 2020
Date span of search:	See date span of search in search strategies below.

List the complete search strategies used, including all the search terms: text words (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.

Database: Ovid MEDLINE(R) ALL <1946 to November 05, 2020>

Medline ® and Medline in press ALL search strategy

#	Search terms	Results
1	Acute Kidney Injury.mp. or Acute Kidney Injury/	56774
2	(contrast-induced* or radiocontrast-induced* or ci).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	622920
3	1 and 2	5055
4	Contrast Media/ae	9795
5	(ciaki or cin or ciraf or ci-aki or ci-arf or ci 114ephropathy* or cinephropath* or rci 114ephropathy* or rcinephropath*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	11114
6	(aki or arf or acute kidney or acute renal or early kidney or early renal or necrosis or tubul*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	626876
7	Acute Kidney Injury/ae	0
8	3 or 4 or 5 or 6 or 7	643800
9	Dyevert.mp.	9
10	Osprey Medical.mp.	6
11	9 or 10	11

12	8 and 11	10

Database: Embase <1974 to November 05, 2020>

Embase search strategy

#	Search terms	Results
1	exp acute kidney failure/	92515
2	exp acute kidney tubule necrosis/	5315
3	1 or 2	96137
4	(contrast-induced* or radiocontrast-induced* or ci).tw.	921760
5	3 and 4	8894
6	contrast medium/ae	6579
7	contrast induced nephropathy/	4979
8	(ciaki or cin or ciraf or ci-aki or ci-arf or ci nephropath* or cinephropath* or rci nephropath* or rcinephropath*).tw.	16184
9	(contrast-induced adj4 (aki or arf or acute kidney or acute renal or early kidney or early renal or necrosis or tubul*)).tw.	1311
10	(radiocontrast-induced adj4 (aki or arf or acute kidney or acute renal or early kidney or early renal or necrosis or tubul*)).tw.	61
11	(radiocontrast* adj4 (nephropath* or nephrotoxi*)).tw.	363
12	5 or 6 or 7 or 8 or 9 or 10 or 11	32183
13	Dyevert.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	19
14	12 and 13	16

Database: Cochrane <to November 05, 2020>

Cochrane Library (CDSR and CENTRAL) search strategy

1	Acute Kidney Injury.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	3850
2	(contrast-induced* or radiocontrast-induced* or ci).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	133188
3	1 and 2	1062
4	Contrast Media.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	3934
5	(ciaki or cin or ciraf or ci-aki or ci-arf or ci nephropath* or cinephropath* or rci nephropath* or rcinephropath*).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	1624
6	radiocontrast-induced.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	61
7	(aki or arf or acute kidney or acute renal or early kidney or early renal or necrosis or tubul*).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	29049

8	contrast*.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	505 41
9	(nephropath* or nephrotoxi*).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	115 63
10	radiocontrast*.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	234
11	(nephropath* or nephrotoxi*).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	115 63
12	3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	870 19
13	Dyevert.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	6
14	12 and 13	5

Database: ClinicalTrials.gov <to November 05, 2020>

ClinicalTrials.gov search strategy

1	Dyevert (6)

Database: ICTRP <to November 05, 2020>

ICTRP search strategy

1	Dyevert (6)

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

The company was consulted with to aid in the identification of additional unpublished studies.

Inclusion and exclusion criteria:

Inclusion criteria	
Population	Adult patients undergoing CAG and/or PCI procedures which require injection of contrast media, who are at risk of CI-AKI.
Interventions	DyeVert™, DyeVert™ Plus, DyeVert™ Plus EZ.
Outcomes	• CI-AKI incidence and severity • Volume of contrast received and saved • Image quality • Length of hospital stay • Rates of re-admission as a result of CI-AKI or cardiac complications • Rate of renal replacement therapy as a result of CI-AKI • Long term complications as a result of CI-AKI • Device-related adverse events.
Study design	All types of study designs.
Language restrictions	English language only.
Search dates	No restriction.
Exclusion criteria	
Outcomes	Costs and cost-effectiveness analysis.
Study design	Editorials, reviews, letters, book chapters.

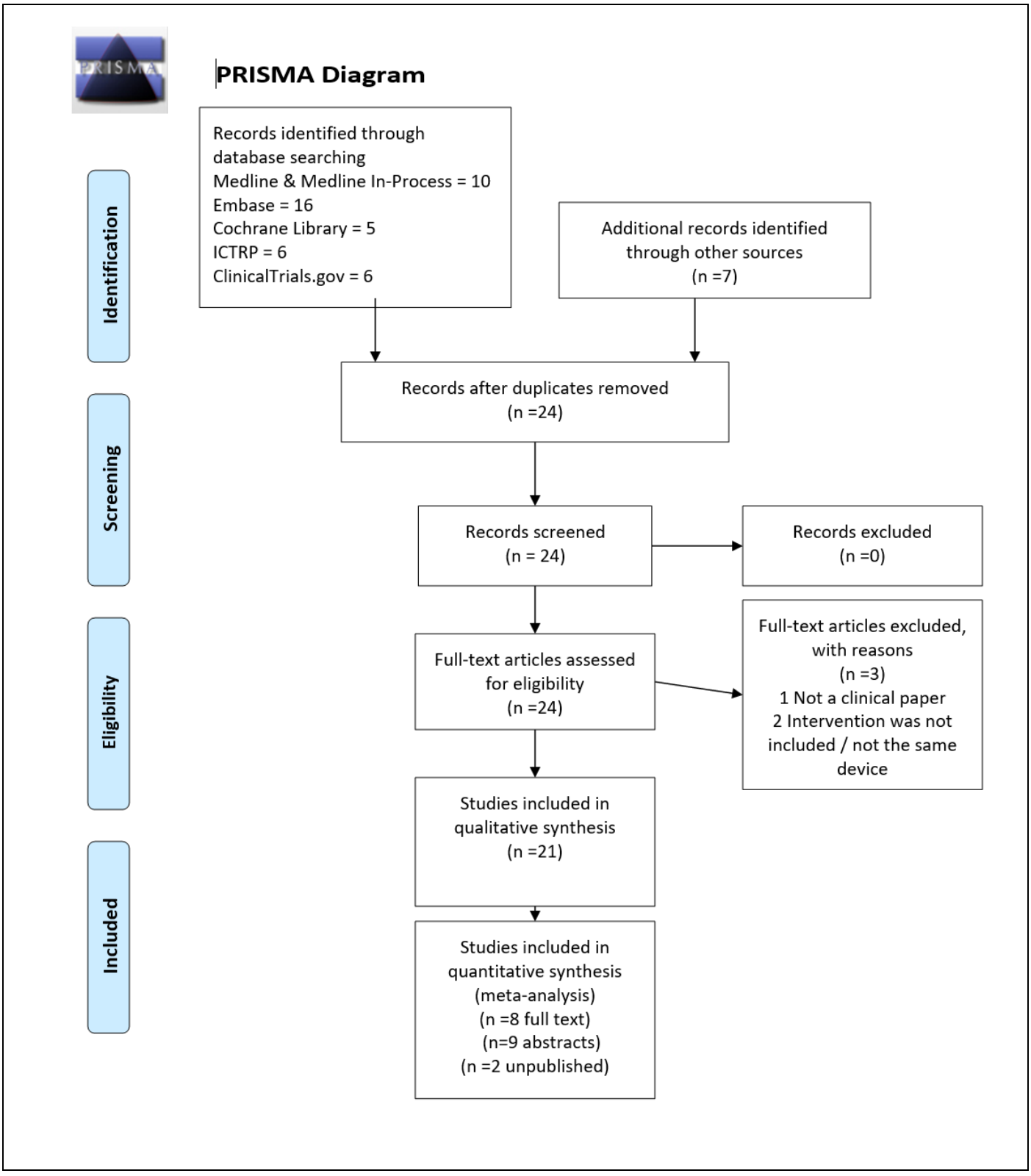
Enter text.
Data abstraction strategy:
Data from all included studies were extracted using a pre-designed form. Data extraction was undertaken by one reviewer and checked by a second independent reviewer. Disagreements between the review authors were resolved by discussion, and the consensus was reached with the involvement of a third review author where necessary.

Excluded studies

List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review but were later excluded for specific reasons.

Excluded study	Design and intervention(s)	Rationale for exclusion	Company comments
DyeVert TM PLUS EZ System for Preventing Contrast-Induced Acute Kidney Injury in Patients Undergoing Diagnostic Coronary Angiography and/or Percutaneous Coronary Intervention: A UK-Based Cost-Utility Analysis.	Economic modelling study	Not a clinical study	Text
Validation of a Novel Monitoring System to Measure Contrast Volume Use During Invasive Angiography.	Non-randomised prospective study	Not the right device/intervention	Text
The use of the AVERT system to limit contrast volume administration during peripheral angiography and intervention.	Non-randomised prospective study	Not the right device/intervention	Text

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).



Structured abstracts for unpublished studies

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Appendix B: Search strategy for adverse events

Date search conducted:	20th November 2020
Date span of search:	Please see section 6
List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.	
Please see section 6	
Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):	
Please see section 6	
Inclusion and exclusion criteria:	
Enter text.	
Data abstraction strategy:	
Enter text.	

Adverse events evidence

List any relevant studies below. If appropriate, further details on relevant evidence can be added to the adverse events section.

Study	Design and intervention(s)	Details of adverse events	Company comments
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

Enter text.

Appendix C: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No ☐ If no, please proceed to declaration (below)

Yes ☒ If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document and match the information in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
Refer to highlighted areas (yellow)	☐ Commercial in confidence ☒ Academic in confidence	Outcomes not yet in the public domain	Anticipate publication in 2021
Details	Reducing contrast-induced acute kidney injury in the cardiac cath lab: preliminary results from a multidisciplinary quality improvement initiative		
Refer to highlighted areas (blue)	☒ Commercial in confidence ☐ Academic in confidence	Outcomes not in the public domain	Indefinately
Details	DyeVert™ Contrast Reduction System Unpublished Market Acceptance Evaluation Summary Report 2020		

Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included, then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*: ** Must be Medical Director or equivalent*		**Date:**	26 January 2021
Print:	Melanie Hess	**Role / organisation:**	VP, Regulatory, Compliance and Quality
Contact email:	[redacted]		

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

GID-MT550 DyeVert for reducing contrast media in coronary and peripheral angiography

Company evidence submission

Part 2: Economic evidence

Company name	Osprey Medical
Submission date	23/02/2021
Contains confidential information	Yes

Contents

1 Published and unpublished economic evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used, and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		9
Number of studies identified as being relevant to the decision problem.		4
Of the relevant studies identified:	Number of published studies.	1
	Number of abstracts.	2
	Number of ongoing studies.	1

List of relevant studies

In table 1, provide brief details of any published or unpublished economic studies or abstracts identified as being relevant to the decision problem.

For any unpublished studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data provided.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix C.

Table 1 Summary of all relevant studies (published and unpublished)

Data source	Author, year and location	Patient population and setting	Intervention and comparator	Unit costs	Outcomes and results	Sensitivity analysis and conclusion
DyeVert™ PLUS EZ System for Preventing Contrast-Induced Acute Kidney Injury in Patients Undergoing Diagnostic Coronary Angiography and/or Percutaneous Coronary Intervention: A UK-Based Cost–Utility Analysis	(Javanbakht et al., 2020) Location: UK.	A hypothetical cohort of patients with chronic kidney disease (CKD) stage 3–4 undergoing diagnostic coronary angiography (CAG) and/or percutaneous coronary intervention (PCI).	Intervention: DyeVert PLUS EZ, Comparator: Standard of care.	The cost of the DyeVert™ PLUS EZ technology was estimated to be £350, including the cost of the smart syringe and module.	The results of the base-case analysis indicate that the introduction of the DyeVert™ PLUS EZ system leads to cost savings of £448 per patient over a lifetime time horizon. Additionally, the intervention leads to improved effectiveness over the patient's lifetime (+ 0.028 QALYs). Therefore, DyeVert™ PLUS EZ system is considered a dominant strategy compared to current practice. The scatter plot produced from the probabilistic analysis shows that the vast majority of points from the 10,000 iterations of the model are in the southeast quadrant of the cost-effectiveness plane (less costly, more effective), while all simulations indicate that the intervention is less costly than the comparator. Additionally, the cost-effectiveness acceptability curve (CEAC) indicates that the DyeVert™ PLUS EZ system has a 100% probability of being cost-effective across all WTP thresholds. The overall long-term cost savings for the NHS for the annual cohort of patients who are at risk of CI-AKI is over £19.7 million.	The probability of contrast-induced acute kidney injury (CI-AKI) post PCI/CAG and the absolute risk reduction for CI-AKI due to the use of the DyeVert™ PLUS EZ system have the greatest impact on the incremental cost of the intervention (± 45.1%). All other parameters have moderate or minimal impact on the incremental costs. The intervention was still cost saving (−£203) when an alternative value (15.1%) was used to estimate the reduction in risk of CI-AKI associated with 40.1% reduction in contrast media. For all the parameters included in the analysis, the NMB of the DyeVert™ PLUS EZ system remains positive, meaning that it is preferable to current practice from a health economic perspective. DyeVert has the potential to improve short-term health outcomes and to achieve cost savings and improved clinical outcomes in the longer term. The probabilistic results were conclusive in that the device had a 100% probability of being cost-effective following 10,000 iterations of the model in a Monte Carlo simulation. Similarly, results of the

						deterministic sensitivity analyses indicated that the intervention would still be cost saving and result in a positive net monetary benefit in all scenarios assessed.
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Clinical and economic outcomes of a comprehensive clinical quality initiative for reducing acute kidney injury in chronic kidney disease patients undergoing coronary angiography	(Kutschman, 2019) Location: USA.	Sample size (n=206). Chronic kidney disease patients who underwent diagnostic coronary angiography and/or PCI. Patients on dialysis were excluded. Baseline characteristics: Age (years), Mean ± SD: 69 ± 11. Male gender, (%): 57%. eGFR (mL/min/1.73 m^2), Mean ± SD: 43 ± 13. Procedure type, PCI: 63% Diagnostic angiography: 37%.	Intervention: With DyeVert (n=128), Comparator: Without DyeVert (n=78).	None provided.	Protocol Followed subgroup had an 11.8% absolute CI-AKI reduction compared to the Protocol Not Followed subgroup. The DyeVert System Used subgroup had a 12.4% absolute CI-AKI reduction compared to the DyeVert Not Used subgroup. Incremental cost offset associated with CI-AKI avoidance was estimated to be at least $2,000 lower per case in the subgroups in which the full Protocol was followed and DyeVert was used.	Implementation of the CI-AKI reduction protocol involving the DyeVert Systems resulted in positive clinical and economic outcomes.
Real-world impact of a quality improvement program for acute kidney injury prevention in the cardiac cath lab	Tucker & Turner, 2020 (Turner and Tucker, 2020) Location: USA.	Sample size (n=703). PCIs, all comers, DyeVert use in n=536 patients with CKD or STEMI. Approximately 30% of the cath lab population is at risk for CI-AKI.	Intervention: PCI with DyeVert ™ PLUS Contrast Reduction System, Comparator: None.	The cost of the DyeVert™ PLUS was estimated to be $350, including the cost of the smart syringe and module.	Estimated incremental cost of CI-AKI per event: $10,000. With an absolute reduction of 10.46% and a number-needed-to-treat (NNT) to avoid 1 CI-AKI event of 10, program cost for 10 patients (assumes $350/case): $3,500. Net savings: $6,500 or $650/case. **Cost neutrality assessment:** -Absolute reduction of 3.6% (higher ARs = cost savings). -NNT of 28 (lower NNTs = cost savings). -CI-AKI event costs of $3,500 (higher CI-AKI costs = cost savings).	Results of this analysis highlighted the clinical and economic effectiveness of the real-world initiative involving the DyeVert™ PLUS Contrast Reduction System in improving outcomes for at-risk patients undergoing angiography. The cost neutrality assessment demonstrates tolerance for cost savings at effect sizes >50% lower than those observed.

2 Details of relevant studies

Please give details of all relevant studies (all studies in table 1). Copy and paste a new table into the document for each study. Please use 1 table per study.

DyeVert™ PLUS EZ System for Preventing Contrast-Induced Acute Kidney Injury in Patients Undergoing Diagnostic Coronary Angiography and/or Percutaneous Coronary Intervention: A UK-Based Cost–Utility Analysis (Javanbakht et al., 2020)	
What are main differences in resource use and clinical outcomes between the technologies?	The results of the base-case analysis presented indicate that the introduction of the DyeVert™ PLUS EZ system leads to cost savings of £448 per patient over a lifetime time horizon. Additionally, the intervention leads to improved effectiveness over the patient's lifetime (+ 0.028 QALYs). Therefore, DyeVert™ PLUS EZ system is considered a dominant strategy (less costly and more effective) compared to current practice. Base-case probabilistic results are presented below, which highlight the strong probability of the intervention being cost-effective. Base-case probabilistic results (lifetime time horizon) Current practice cost = £23,932 DyeVert™ PLUS EZ system cost = £23,484 Incremental cost (£) = − £448 Current practice QALYs = 4.633 DyeVert™ PLUS EZ system QALYs = 4.661 Incremental QALYs = + 0.028 ICER (£) (ΔCost/ΔQALYs): DyeVert™ PLUS EZ system is dominant, i.e. less costly and more effective Probability of being cost-effective at £20,000 WTP threshold = 100%

	Probability of being cost saving = 99.8% Costs included in the model were costs associated with use of the initial DyeVert™ PLUS EZ system amongst patients undergoing CAG and/or PCI, costs associated with CI-AKI (and appropriate treatment), and costs for all modelled health states. Differences in costs and clinical outcomes (complication rates and utility values) are driven by the reduced risk of patient's experiencing CI-AKI (short-term savings associated with reduced complication rate and longer-term savings due to the relationship between CI-AKI and CKD).
How are the findings relevant to the decision problem?	Patients undergoing CAG and/or PCI who are at-risk for CI-AKI may benefit from procedure-based CI-AKI prevention strategies used as an adjunct to the current standard of care pathway. Introduction of the intervention has the potential to result in cost savings for the health care system, and improved clinical outcomes for patients.
Does this evidence support any of the claimed benefits for the technology? If so, which?	This study highlights the cost savings that can be made through a reduction in the onset of CI-AKI. Claimed benefits of the technology include the potential for the system to reduce the risk of CI-AKI due to a significant reduction in contrast media volume use amongst patients undergoing CAG and/or PCI. This analysis highlights the economic benefits of incident CI-AKI reduction and associated sequelae in at-risk patients.
Will any information from this study be used in the economic model?	Yes.
What cost analysis was done in the study? Please explain the results.	This analysis explored the cost of delivering the intervention (£350 per patient, including the cost of the smart syringe and module), the cost of undergoing CAG and PCI, the cost of modelled health states (different stages of CKD), and the cost of relevant complications (MI and CI-AKI). All costs were modelled, in combination with the clinical impact of the intervention on patient outcomes, to understand the long-term cost-effectiveness of the system. See results presented earlier.

What are the limitations of this evidence?	Firstly, it was unknown how the risk of developing CI-AKI changes depending on whether the patient receives CAG, PCI or a combination of both. Therefore, in the model it was assumed that this risk was the same regardless of the intervention initially received. Secondly, there were no data to inform the utility value of patients with CKD stage 3–4 who have experienced a MI. Therefore, for the purpose of this analysis, it was assumed that the utility value of those patients would be same as the utility value of patients with CKD stage 3–4 who have not experienced this adverse event. Although the data used to inform the effectiveness of the DyeVert™ PLUS EZ system were derived from robust published clinical evidence, the number of studies available to inform the clinical effectiveness of the device were limited. Finally, although evidence exists on the relationship between CI-AKI and long-term clinical outcomes, information is limited, which means that there is also a degree of uncertainty around the relevant data included in the model. However, to address this limitation, an extreme sensitivity analysis was performed in which the main input parameters were changed by ±50%, but the conclusion remained stable. Additional minor assumptions were made when populating the model, but none of those were likely to have a major impact on the final model results.
How was the study funded?	Funding received from Osprey Medical, Inc.

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[redacted]	[redacted]
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[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Clinical and economic outcomes of a comprehensive clinical quality initiative for reducing acute kidney injury in chronic kidney disease patients undergoing coronary angiography

(Kutschman, 2019)

What are main differences in resource use and clinical outcomes between the technologies?	This was a comprehensive, cross-functional CI-AKI prevention quality improvement project in the cardiac cath lab involving screening for risk, pre- and post-procedure hydration, maximum contrast dose setting of 3x baseline eGFR, and DyeVert System use. Results were presented for the overall CKD population and by subgroup. The Protocol Followed Group had all elements of the CI-AKI prevention protocol implemented. The Protocol Not Followed Group failed to receive one or more of the protocol elements. The cohort was also analysed based on whether a DyeVert System was used as part of their procedure (according to the protocol, all patients should have received the DyeVert System). The DyeVert System Used subgroup had a mean 40.5% contrast volume savings and 12.4% absolute CI-AKI reduction compared to the DyeVert Not Used subgroup. The Protocol Followed subgroup had an 11.8% absolute CI-AKI reduction compared to the Protocol Not Followed subgroup. The DyeVert System Used subgroup had a 12.4% absolute CI-AKI reduction compared to the DyeVert Not Used subgroup. The incremental cost offset associated with CI-AKI avoidance, following introduction of the intervention protocol, was at least $2,000 per case in the Protocol Followed and DyeVert Used subgroups.
How are the findings relevant to the decision problem?	This program demonstrates real-world, procedure-based strategies for CI-AKI prevention, when consistently applied, are effective in reducing incident CI-AKI; therefore, providing further evidence that a significant proportion of CI-AKI is preventable in at-risk patients. Specifically, in cases using the DyeVert System, contrast savings and CI-AKI reduction were reported. Specifically, they show the potential for the intervention to reduce the rate of CI-AKI, and the associated cost savings.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. This study shows that the intervention has the potential to reduce the rate of adverse clinical outcomes (CI-AKI) and lead to cost savings for the health care provider.

Will any information from this study be used in the economic model?	No.
What cost analysis was done in the study? Please explain the results.	Full details of the cost analysis are unavailable, but an overview of an incremental cost offset analysis was provided. Based on the number-needed-to-treat findings offered it would appear the study explored the cost offset of DyeVert System acquisition costs against the cost savings of CI-AKI avoidance. A reduction of $2,000 per case is reported.
What are the limitations of this evidence?	This study was conducted in the USA and the estimated cost saving need to be interpreted
How was the study funded?	Not reported in abstract.

Real-world impact of a quality improvement program for acute kidney injury prevention in the cardiac cath lab (Turner and Tucker, 2020)	
What are main differences in resource use and clinical outcomes between the technologies?	This was a longitudinal, CI-AKI prevention quality improvement project in the cardiac cath lab involving screening for risk (implemented in April 2018), pre- and post-procedure hydration (April 2018), maximum contrast dose setting of 3x baseline eGFR (July 2018), and DyeVert System use in patients with CKD or acute presentation (October 2018). Results were presented for the overall PCI population by quarter from Q1 2018 through Q3 2019. Clinical results indicate that the protocol resulted in the following outcomes: - DyeVert System use (n=536) resulted in a mean 42 mL of contrast savings per case - 82% of cases with DyeVert System use stayed under the max contrast dose target versus 62% that would have stayed under the max dose based on the contrast media volume attempted to be injected. - CI-AKI rate reduction occurred in the first quarter of implementation,

	- 10.46% absolute reduction (AR) or 83.7% relative reduction in CI-AKI, - Number Needed to Treat to prevent one CI-AKI event (NNT, 1/AR) = 10, - Quarterly rates now below the national average (Q3 2019, 3.7%).
How are the findings relevant to the decision problem?	This program demonstrates real-world, procedure-based strategies for CI-AKI prevention are effective in reducing incident CI-AKI; therefore, providing further evidence that a significant proportion of CI-AKI is preventable in at-risk patients. During the same time period, this program also illustrates a reduction in leading contrast-related risk factors, contrast media volume and contrast media volume/eGFR ratio, as well as shifting the population to lower contrast volume/eGFR ratios. As a result, this hospital went from being well above the US national average risk-adjusted CI-AKI rate to well below the national average. Longitudinal results also demonstrate the impact of CI-AKI prevention strategies when implemented over time with the lowest rates occurring after the DyeVert System was added to the program. The results of the analysis presented indicate that the quality improvement protocol being assessed (including use of the DyeVert System) results in net cost savings of $650 per case (based on the occurrence of CI-AKI events).
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. DyeVert System use resulted in contrast media volume savings, and when used as part of a CI-AKI prevention quality improvement program, resulted in a reduced rate of CI-AKI and economic cost savings.
Will any information from this study be used in the economic model?	No.
What cost analysis was done in the study? Please explain the results.	Economic outcomes involved a cost offset model using the number-needed-to-treat of 10. The model assumed an incremental cost of CI-AKI to be $10,000 per event and a DyeVert System acquisition cost of $3,500 for 10 patients. The offset calculation resulted in a cost saving of $650 per case. Further sensitivity analysis of cost neutrality boundaries estimated absolute

	reductions in CI-AKI down to 3.6%, NNTs of up to 28, and incremental cost of CI-AKI down to $3,500 would still result in cost neutrality.
What are the limitations of this evidence?	This is a non-randomised study which was conducted in the USA therefore the results may not be 100% generalisable to the UK context.
How was the study funded?	Not reported in abstract.

3 Economic model

This section refers to the de novo economic model that you have submitted.

Description

Patients

Describe which patient groups are included in the model.

People at risk of contrast-induced acute kidney injury (CI-AKI) who need coronary or peripheral angiography with contrast media. We have included chronic kidney disease (CKD) patients in the model because, as per NICE guideline (NG148), CKD is a good representation of a population 'at risk' of CI-AKI.

Technology and comparator(s)

State the technology and comparators used in the model. Provide a justification if the comparator used in the model is different to that in the scope.

Application of the DyeVert Systems during coronary or peripheral angiography and/or percutaneous coronary intervention are compared to current standard care (i.e., conventional hand or automated injection of contrast media with the absence of the DyeVert Systems).

Model structure

Provide a diagram of the model structure you have chosen in Appendix B.

Justify the chosen structure of the model by referring to the clinical care pathway outlined in part 1, section 3 (Clinical context) of your submission.

The model structure consists of a decision tree followed by a Markov model with six health states. This model has a lifetime time-horizon with costs and benefits estimated in the decision tree for the first three months, and in the Markov model for the remainder of the patient's lifetime. A cycle length of 3 months is used in the Markov model**. The model was used to simulate the management of patients undergoing** diagnostic coronary or peripheral angiography (CAG) and/or percutaneous coronary interventions (PCI) **with reduced kidney function (i.e., eGFR 15 - 60 ml/min/1.73m^2).** **In each strategy, patients may or may not experience a CI-AKI event requiring further treatment. Patients may then either remain in state 'CKD stage 3-4' (or state 'CKD stage 3-4 (AKI history)' if they previously had CI-AKI) or progress according to the natural progression of CKD to state 'CKD stage 5'. Patients whose renal insufficiency is not severe (i.e., 'CKD stage 3-4') can experience a recurrent AKI or a myocardial infarction (MI) at any point. Patients who enter the 'CKD stage 5' are assumed to either remain in this state or die, as they will be receiving dialysis**

and treatments to prevent MI. Associated costs are incurred for patients in each health state, and upon the occurrence of clinical complications.

Simulated patients are at risk of death from all causes during any model cycle. Risk of death is conditional on CKD stage, history of AKI and/or MI, and age. The all-cause mortality rates were derived from general population mortality statistics reported in national life tables and were adjusted to reflect the extra mortality associated with CI-AKI and renal insufficiency. In order to evaluate the face validity of the model, the model structure, input parameters and results were presented to clinical experts in the team, who are well-respected in this field in the UK and who have significant experience. The experts were asked to evaluate the model structure and assumptions in comparison to real-world circumstances. A wide range of sensitivity analyses was also conducted to explore uncertainty in the model results and to assess the internal validity of the model. Null and extreme values were assigned to input parameters and the model was run to test the robustness of the outputs.

Table 2 Assumptions in the model

In this table, list the main assumptions in the model and justify why each has been used

Assumption	Justification	Source
Patients can develop CI-AKI due to the procedure which is captured in the decision tree component of the model. Recurrent CI-AKI is captured in the model also.	Possibility of having additional scan has been modelled in the previous economic model (NG148). Previous studies have also shown that people who have had CI-AKI are at a higher risk of recurrent AKI.	(NG148, 2019) & (Valle et al., 2017)
It is assumed that the risk of developing CI-AKI in CAG, in PCI, and in CAG with PCI is the same since no differential information was found.	Clinical Expert opinion.	Expert opinion
It is assumed that 26% of patients in the 'CKD 3-4 stage' are in stage 4 (NICE, 2013), of whom 60% will require Furosemide as diuretics.	As per NICE guideline CG169.	(CG169, 2013)
An increased early resource use for patients entering the 'CKD 5 stage' is assumed due to access procedures. For CKD stage 5, it is also assumed that 90% of patients will be receiving renal replacement therapy (RRT) (NICE CG169, 2013). Finally, patients in this stage are assumed to have more frequent eGFR measurements and home visits than patients in CKD stage 3-4, as well as 33% of them receiving Epoetin alfa.	As per NICE guideline CG169.	(CG169, 2013)

Table 3 Clinical parameters, patient and carer outcomes and system outcomes used in the model

In this table, describe the clinical parameters, patient and carer outcomes and system outcomes used in the model.

Parameter/outcomes	Source	Relevant results	Range or distribution	How are these values used in the model?
Baseline risk of CI-AKI	(Mehran et al., 2004)	30%	27.7%-32.4% Beta	Applied as the baseline risk of CI-AKI in standard care (control arm).
Relative risk reduction of CI-AKI (due to DyeVert Systems)	Meta-analysis	0.41	0.110-0.620 Log Normal	Used to estimate the risk of CI-AKI in the intervention arm (DyeVert Systems).
Hazard ratio of CI-AKI to Death	(Valle et al., 2017)	2.13	2.010 2.260 Log Normal	Used to estimate the mortality rate in the first three months post CI-AKI for those who had AKI.

If any outcomes listed in table 4 are extrapolated beyond the study follow-up periods, explain the assumptions that underpin this extrapolation.

No outcomes were extrapolated beyond the study follow-up period.

Table 4 Other parameters in the model

Describe any other parameters in the model. Examples are provided in the table. You can adapt the parameters as needed.

Parameter	Description	Justification	Source
Time horizon	Lifetime	As per NICE recommendation and in order to capture all the potential clinical and cost outcomes associated with using the technology.	NICE Scope document
Discount rate	3.5%	As per NICE recommendation	(NICE, 2013)

Perspective (NHS/PSS)	NHS and personal social services perspective.	As specified in the final scope	NICE Scope document
Cycle length	3 months	As per previous model (CG169)	(CG169, 2013)
Transition probabilities	**Markov Model (long-term)** CI-AKI to CKD 5 CKD 3-4 to CKD 5 <69 years 70–79 years >79 years RR of CKD 5 after CI-AKI CKD 5 to CKD 3-4 Risk of recurrent AKI, first 3 months (without previous CI-AKI) Risk of recurrent AKI, subsequent (without previous CI-AKI) Risk of recurrent AKI, first 3 months (with previous CI-AKI) Risk of recurrent AKI, subsequent (with previous CI-AKI) Risk of MI, acute phase (with previous CI-AKI) Risk of MI, subsequent (with previous CI-AKI) Risk of MI, acute phase (without previous CI-AKI) Risk of MI, subsequent (without previous CI-AKI) Risk of AKI requiring dialysis, acute phase (with previous CI-AKI) Risk of AKI requiring dialysis, subsequent (with previous CI-AKI) Risk of AKI requiring dialysis, acute phase (without previous CI-AKI) Risk of AKI requiring dialysis, subsequent (without previous CI-AKI)	The incidence of CI-AKI in patients with CKD undergoing PCI was based on a cohort study of 1,473 patients and was estimated to be 30% (Mehran et al., 2004). Due to the limited evidence, it was assumed that the risk for those patients who are receiving PCI and diagnostic coronary or peripheral angiography are the same and equal 30% in the base-case analysis. Different source of baseline risk of CI-AKI was explored in the sensitivity analyses. The baseline transition probability associated with the progression of patients from CKD stage 3-4 to CKD stage 5 for different age groups, was based on a ten-year cumulative incidence rate in a cohort study of 3,047 patients (Eriksen and Ingebretsen, 2006). The probability of transitioning to Stage 5 CKD following a CI-AKI after the first cycle (first 3 months) was obtained from clinical guidelines from CG169 and James et al., 2010 (James et al., 2010) and from the study by (Valle et al., 2017). The probability of MI for patients with a history of CI-AKI was taken from Valle et al., 2017 (Valle et al., 2017). For patients who had not experienced an AKI throughout the model, the probability of MI was 1.42% and 0.67% in the first 3 months and the subsequent cycles respectively (Valle et al., 2017). For patients who had experienced CI-AKI in the previous cycles, the equivalent probabilities were 2.58% and 1.23% respectively (Valle et al., 2017). The probability of recurrent AKI was taken from the same study as the probability of MI (Valle et al., 2017). Based on the cumulative incidence in the 3rd month and the first year of the study follow-up, we estimated the probability of recurrent AKI in the first 3 months after the CAG and/or PCI, and for	(Valle et al., 2017) (James et al., 2010) (Eriksen and Ingebretsen, 2006) (CG169, 2013)

	CKD 3–4 to death RR (conditional on age & gender) Male <69 years Female <69 years Male 70-79 years Female 70-79 years Male >79 Female >79 CKD 5 to death RR (conditional on age & gender) Male 18-64 years Female 18-64 years Male >64 years Female >64 years MI (acute) to death SMR MI (subsequent) to death SMR	subsequent 3-month cycles. For patients who had not experienced a CI-AKI after the procedure, the probability of recurrent AKI was 1.78% and 0.91% in the first 3 months and the subsequent cycles respectively. For patients who had experienced CI-AKI during the procedure, the equivalent probabilities were 6.6% and 2.3% respectively.	
Health states	CKD stage 3-4 with and without CI-AKI history CKD stage 5 MI and Post MI Death Recurrent CI-AKI	**In each strategy, patients may or may not experience a CI-AKI requiring further treatment. Patients may then either remain in state 'CKD stage 3-4' (or state 'CKD stage 3-4 (AKI history)' if they previously had CI-AKI) or progress according to the natural progression of CKD to state 'CKD stage 5'. Patients whose renal insufficiency is not severe (i.e. 'CKD stage 3-4') can experience a recurrent AKI or a myocardial infarction (MI) at any point. Patients who enter the 'CKD stage 5' are assumed to either remain in this state or die, as they will be receiving dialysis and treatments to prevent an MI.**	(Javanbakht et al., 2020)
Sources of unit costs	• Device manufacturer (cost of DyeVert Systems) • NHS reference costs	Unit costs for all resource use estimates were extracted from the literature or obtained through other relevant sources such as NHS reference	(Department of Health and Social Care, 2019) (Walker et al., 2016)

	• BNF • PSSRU • Published economic and costing study	costs (Department of Health and Social Care, 2019), Personal Social Services Research Unit (Curtis, 2018), British National Formulary and manufacturer price list (Joint Formulary Committee London, 2017). Costs were measured in Sterling (£) for the year 2019-20. The choice of cost items was mainly informed by a NICE clinical guidelines model developed for the evaluation of prevention strategies of CI-AKI using different hydration methods (NG148, 2019). However, updated unit costs and dosages of drugs were extracted from the literature. In the instances where unit costs of relevant outcomes were not available, the cost of items used in the NICE guidelines model (CG169, 2013) were inflated to reflect current prices. This was done by applying an inflation index provided by the National bank of England (Bank of England, 2018).	Osprey Medical, Inc. (Curtis and Burns, 2019) (British National Formulary, 2019)

Explain the transition matrix used in the model and the transformation of clinical outcomes, health states or other details.

Patients at model entry were those undergoing diagnostic coronary or peripheral angiography and/or PCI with some kidney function impairment (CKD stage 3-4). The base-case population was 65 years old. Evidence has shown that when DyeVert Systems is used in patients undergoing coronary or peripheral angiography and/or PCI the contrast media volume is significantly reduced (Amoroso et al 2020. Bath et al., 2019, Bruno et al., 2019, Bunney et al., 2020, Cameron and Espinosa, 2020, Corcione et al., 2017, Desch et al., 2018, Gurm et al., 2018, Kutschman et al., 2019, Rao, 2019, Sapontis et al., 2016, Sattar et al., 2018, Tajti et al., 2019, Turner and Tucker, 2020, Zimin et al., 2019). Also, several studies have shown reduction in CI-AKI rate after using DyeVert Systems (Briguori et al., 2020, Bunney et al., 2020, Cameron and Espinosa, 2020, Gurm et al., 2018, Kutschman et al., 2019, Rao, 2019, Sattar et al., 2018, Turner and Tucker, 2020). To estimate the reduction in risk of CI-AKI after using DyeVert Systems, we analyzed the risk reduction rate reported in four double arm studies (Briguori et al., 2020, Bunney et al., 2020, Kutschman et al., 2019, Sattar et al., 2018). The estimated absolute risk reduction was used to adjust the risk of CI-AKI in the intervention arm for the base-case analysis.

Transition probabilities

The incidence of CI-AKI in patients with CKD undergoing PCI was based on a cohort study of 1,473 patients and was estimated to be 30% (Mehran et al., 2004). Due to the limited evidence, it was assumed that the risk for those patients who are receiving PCI and CAG at the same time, or CAG alone or peripheral angiography are the same and equal 30% in the base case analysis. Different level of risk of CI-AKI were explored in the sensitivity analyses. The baseline transition probability associated with the progression of patients from CKD stage 3-4 to CKD stage 5 for different age groups, was based on a ten-year cumulative incidence rate in a cohort study of 3,047 patients (Eriksen and Ingebretsen, 2006). The probability of transitioning to Stage 5 CKD following a CI-AKI after the first cycle (first 3 months) was obtained from clinical guidelines from (CG169, 2013) and James et al., 2010 (James et al., 2010) and from the study by Valle et al., 2017 (Valle et al., 2017). The probability of MI for patients with a history of CI-AKI was taken from Valle et al., 2017 (Valle et al., 2017). For patients who had not experienced an AKI throughout the model, the probability of MI was 1.42% and 0.67% in the first 3 months and the subsequent cycles respectively (Valle et al., 2017). For patients who had experienced CI-AKI in the previous cycles, the equivalent probabilities were 2.58% and 1.23% respectively (Valle et al., 2017).
The probability of recurrent AKI was taken from the same study as the probability of MI (Valle et al., 2017). Based on the cumulative incidence in the 3rd month and the first year of the study follow-up, we estimated the probability of recurrent AKI in the first 3 months after the CAG and/or PCI, and for subsequent 3-month cycles. For patients who had not experienced a CI-AKI after the procedure, the probability of recurrent AKI was 1.78% and 0.91% in the first 3 months and the subsequent cycles respectively. For patients who had experienced CI-AKI during the procedure, the equivalent probabilities were 6.6% and 2.3% respectively. Standardised mortality ratios for each health state included in the model were applied to the relevant age-dependent mortality rates and are shown in Table 2 below. These mortality ratios were derived from the literature.

Parameters	Mean	Distribution	Lower limit	Upper limit	Source
Transition probabilities					
Decision tree (3 month) probabilities					
CKD 3-4 to CI-AKI	30%	Beta	27.7%	32.4%	(Mehran et al., 2004)
RR reduction of CI-AKI due to DyeVert	0.41	Log Normal	0.11	0.62	Meta-analysis
HR of CI-AKI to Death	2.13	Log Normal	2.01	2.260	(Valle et al., 2017)
Markov Model (long-term)					
CI-AKI to CKD 5	3.28%	Beta	3.10%	3.46%	(James et al., 2010)

CKD 3-4 to CKD 5					
<69 years	0.02%	Beta	Alpha 5.50	Beta 3043.00	(Eriksen and Ingebretsen, 2006) & (CG169, 2013)
70–79 years	0.10%	Beta	Alpha 3.1	Beta 3045.0	(Eriksen and Ingebretsen, 2006) & (CG169, 2013)
>79 years	0.08%	Beta	Alpha 2.3	Beta 3046.0	(Eriksen and Ingebretsen, 2006) & (CG169, 2013)
RR of CKD 5 after CI-AKI	4.81	Log Normal	3.04	7.62	(See et al., 2018)
Risk of recurrent AKI, first 3 months (without previous CI-AKI)	1.78%	Beta	1.74%	1.82%	(Valle et al., 2017)
Risk of recurrent AKI, subsequent (without previous CI-AKI)	0.91%	Beta	0.49%	0.50%	(Valle et al., 2017)
Risk of recurrent AKI, first 3 months (with previous CI-AKI)	6.61%	Beta	6.24%	6.96%	(Valle et al., 2017)
Risk of recurrent AKI, subsequent (with previous CI-AKI)	2.26%	Beta	2.20%	2.32%	(Valle et al., 2017)
Risk of MI, acute phase (with previous CI-AKI)	2.58%	Beta	2.35%	2.82%	
Risk of MI, subsequent (with previous CI-AKI)	1.23%	Beta	1.18%	1.28%	
Risk of MI, acute phase (without previous CI-AKI)	1.42%	Beta	1.36%	2.35%	(Valle et al., 2017)
Risk of MI, subsequent (without previous CI-AKI)	0.67%	Beta	0.64%	1.11%	
Risk of AKI requiring dialysis, acute phase (with previous CI-AKI)	0.79%	Beta	0.65%	0.93%	
Risk of AKI requiring dialysis, subsequent (with previous CI-AKI)	0.16%	Beta	0.15%	0.18%	
Risk of AKI requiring dialysis, acute phase (without previous CI-AKI)	0.11%	Beta	0.11%	0.12%	
Risk of AKI requiring dialysis, subsequent (without previous CI-AKI)	0.04%	Beta	0.04%	0.04%	
Mortality					
CKD 3–4 to death RR (conditional on age & gender)					
Male <69 years	3.60	Log Normal	2.60	5.000	
Female <69 years	2.70	Log Normal	2.00	3.700	
Male 70-79 years	2.40	Log Normal	2.00	2.900	
Female 70-79 years	1.80	Log Normal	1.50	2.100	
Male >79	2.30	Log Normal	2.00	2.600	
Female >79	2.10	Log Normal	1.90	2.300	
CKD 5 to death RR (conditional on age & gender)					(Villar et al., 2007) (See et al., 2018)
Male 18-64 years	10.00	Log Normal	7.10	13.700	
Female 18-64 years	16.40	Log Normal	9.60	26.300	
Male >64 years	4.80	Log Normal	3.90	5.800	
Female >64 years	7.10	Log Normal	5.40	9.200	
MI (acute) to death SMR	5.84	Log Normal	4.38	7.300	(TA236, 2011)
MI (subsequent) to death SMR	2.21	Log Normal	1.66	2.763	(TA236, 2011)

AKI: Acute Kidney Injury; CAG: Diagnostic Coronary Angiography; CI-AKI: Contrast-Induced Acute Kidney Injury; CKD: Chronic Kidney Disease; HR = Hazard Ratio; MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention; RR: Relative Risk; SMR = <add>

Resource identification, measurement and valuation

Technology costs

Provide the list price for the technology (excluding VAT).

Cost of the DyeVert Systems used in the model (including cost of smart syringe and module) = £350 (as provided by Osprey Medical, Inc.).

If the list price is not used in the model, provide the price used and a justification for the difference.

Not applicable.

NHS and unit costs

Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs, the national tariff and unit costs (from PSSRU and HSCIC). Please provide relevant codes and values (e.g. OPCS codes and ICD codes) for the operations, procedures and interventions included in the model.

Included in the table below are the costs associated with defined model health states, interventions, procedures and complications. Relevant values and sources for all costs included in the model are presented below:

Cost	Value	Source
Health-state costs/cycle		
CKD stage 3-4/cycle	£260	See below
CKD stage 5 first cycle/cycle	£7,135	See below
CKD stage 5 subsequent cycles/cycle	£6,113	See below
Event costs & other		
Cost of MI (initial)/cycle	£6,364	(Walker et al., 2016)
Cost of MI (subsequent)/cycle	£512	(Walker et al., 2016)

CI-AKI cost of index admission	£2,834	(Department of Health and Social Care, 2019) (HRG codes: LA07H, LA07J, LA07K, LA07L, LA07M, LA07P)
CI-AKI cost of extended hospital admission	3.75 (days)*379=£1,421	(Kerr et al., 2014, Subramanian et al., 2007)
CI-AKI cost of hospital day	£379	NHS Reference Cost, 2019 (Department of Health and Social Care, 2019) (HRG codes: LA07H, LA07J, LA07K, LA07L, LA07M, LA07P)
DyeVert Cost	£350	Osprey Medical, Inc.
Cost of CAG	£1,786	(Department of Health and Social Care, 2019) (HRG codes: EY40A, EY40B, EY40C, EY40D, EY41A, EY41B, EY41C, EY41D)
Cost of PCI	£2,836	(Department of Health and Social Care, 2019) (HRG codes: EY42A, EY42B, EY42C, EY42D, EY43A, EY43B, EY43C, EY43D, EY43E, EY43F)

'CKD stage 3-4' costs

Patients in CKD stage 3-4 are expected to incur costs associated with consultations with nephrologist (CG169, 2013), combined with lab resources costs and an assumed 5-minute phlebotomist time to measure the patient's eGFR. Additional costs would include a 9% of patients requiring Epoetin-alfa to treat anaemia as recommended by the clinical guidelines for anaemia treatment in patients with CKD (CG169, 2013) Epoetin-alfa dosage was estimated for a 77kg individual on average, according to ONS. This aggregated to a cost of £86 per cycle. To take into consideration also the patients who require diuretics, an assumption was made based on the guidelines model (CG169, 2013) that about a quarter of patients (26%) in the CKD 3-4 stage were in stage 4 of which 60% would be on 40mg daily dose of Furosemide. The latter resulted in a cost of £0.27 per cycle. The total cost of CKD stage 3-4 per cycle was estimated to be *£260*. Cost of care for 'CKD stage 3-4' are summarised in table below.

Costs of care for patients in 'CKD stage 3-4'

Unit	Unit Cost	Resource use per cycle	Cost per cycle	Source
Nephrologist appointment	£169	1	£169	(Department of Health and Social Care, 2019)
Biochemistry	£1	1	£1	(Department of Health and Social Care, 2019) (DAPS04)
Phlebotomist time	£3	1	£3	(Department of Health and Social Care, 2019) (DAPS08)
eGFR measurement	£4			Phlebotomist cost + biochemistry cost

Drug	Dose	Frequency	% of patients	BNF cost per dose	Cost per cycle
Diuretics Stage 4	40 mg	1 per day	60%	£0.02	£0.27
Epoetin α Stage 3–4 [1]	112.5 (75-300) IU/kg	Per week	9%	£79.85	£86.2

CKD stage 5' costs

Patients in stage 5 CKD will incur the drug costs mentioned in **Error! Reference source not found.** above. However, patients in this stage will also occur costs associated with Renal Replacement Therapy (RRT) or Conservative Management (CMa). In this stage patients are expected to incur costs such as RRT procedures, anaemia management, specialist appointments, eGFR measurements and diuretics.

In the first cycle that a patient enters the CKD stage 5 state, it is assumed that the intensity of treatment will be increased compared to later stages, as costs of initiating treatment are captured. In is assumed based on the NICE guidelines model, that a percentage of 90% of patients will be receiving RRT in this model state. For the estimation of RRT costs, a pooled average was taken from NHS reference costs (2018-19) accounting for national usage of different treatment modalities, such as haemodialysis and filtration.

RRT modalities for Haemodialysis and Peritoneal dialysis - NHS Reference Costs 2018-19

RRT Modality (LDA01-12)	National usage Weight by modality	Unit cost	Weighted cost per session (£)
Haemodialysis			
Hospital Haemodialysis / Filtration, with Access via Haemodialysis Catheter	13.40%	£148	19.88
Hospital Haemodialysis / Filtration, with Access via Arteriovenous Fistula / Graft	22.07%	£157	34.57
Hospital Haemodialysis / Filtration, with Access via Haemodialysis Catheter, with Blood-B/ne Virus	0.60%	£154	0.92
Hospital Haemodialysis / Filtration, with Access via Arteriovenous Fistula / Graft, with Blood-B/ne Virus	0.75%	£166	1.24
Satellite Haemodialysis / Filtration, with Access via Haemodialysis Catheter	17.98%	£145	26.12
Satellite Haemodialysis / Filtration, with Access via Arteriovenous Fistula / Graft	37.71%	£157	59.24
Satellite Haemodialysis / Filtration, with Access via Haemodialysis Catheter, with Blood-B/ne Virus	0.78%	£139	1.08
Satellite Haemodialysis / Filtration, with Access via Arteriovenous Fistula / Graft, with Blood-B/ne Virus	1.54%	£160	2.47
Home Haemodialysis / Filtration, with Access via Haemodialysis Catheter	1.30%	£200	2.59
Home Haemodialysis / Filtration, with Access via Arteriovenous Fistula / Graft	3.88%	£149	5.81
Weighted Average cost of Haemodialysis per session			***£153.92***
Peritoneal dialysis			
Continuous Ambulatory Peritoneal Dialysis (CAPD)	35.16%	£66	£23
Automated Peritoneal Dialysis (API)	64.84%	£73	£47
Pooled average cost of peritoneal dialysis per day			***£70.72***

[1] Assumed for an average weight of 77 kg, the average UK weight according to Office of National Statistics
Company evidence submission (part 2) for GID-MT550 DyeVert for reducing contrast media in coronary and peripheral angiography.

Frequency		Source
Frequency of haemodialysis per week	3 days	(CG169, 2013)
Frequency of peritoneal dialysis per week	7 days	(CG169, 2013)
Proportion of patients receiving each strategy		**Source**
Peritoneal dialysis	21%	(CG169, 2013)
Haemodialysis	79%	(CG169, 2013)
	Cost per 3-month cycle (weekly frequency * cost per day * 12)	**Weighted cost per cycle (cost per cycle * proportion)**
Haemodialysis	£5,521	£4,377
Peritoneal dialysis	£6,145	£1,248
TOTAL COST OF RRT		***£5,625***

Table 1. Total cost of RRT based on frequency and usage of treatment.

Patients entering the CKD stage 5 will receive an access procedure which will then allow for permanent access for RRT. This varies according to the type of dialysis a patient is having.

Costs of RRT access procedures

Procedure	Cost	%patients receiving	Source
Peritoneal access	£845	79%	(Department of Health and Social Care, 2019)
Haemodialysis vascular access	£1,643	21%	NHS Reference Costs 2010/11 * inflated
Weighted average			***£1,013***

In subsequent cycles it is assumed that there will be no further access procedure related costs. Drugs and check-ups are also required and are more frequent in 'CKD stage 5'. It was assumed all patients in this stage would have an eGFR more frequently (on a weekly basis), and two nephrologist appointments per three months. In this state, Epoetin was assumed to be administered to 33% of the patients in the same dosage as for patients in CKD 3-4 stages (CG169, 2013). Patients on conservative management (10%) will be receiving monthly home visits by a specialist nurse as well as telephone calls on a weekly basis. It was assumed (CG169, 2013) that diuretics will be used by 90% of the patients with the double dosage compared to CKD 3-4 stages (80mg).

Costs of RRT and CMa

Resource	Frequency	Cost per cycle	Source of unit cost
Patients on RRT cycle 1			
Nephrologist appointment	2 per cycle	£338	(Department of Health and Social Care, 2019)
eGFR	12 per cycle	£48	Phlebotomist cost + biochemistry cost
Epoetin alpha	1,788 units per week (£0.005 per unit)	£319	NICE BNF
Access procedure	1	£1,013	See above
RRT		£5,625	See above
Sub Total		***£7,343***	
Patients on RRT cycle 2 and onwards			

Subtotal		***£6,330***	(Cost of RRT cycle 1) – (cost of access procedure)
Patients on Conservative Management (CMa)			
Nephrologist appointment	2 per month	£338	(Department of Health and Social Care, 2019)
Phone call	12 per cycle	£73	{Curtis, 2019 #287}
Home visits	3 per cycle	£75	{Curtis, 2019 #287}
eGFR	12 per cycle	£48	(Department of Health and Social Care, 2019)
Diuretics	80mg per day	£319	{British National Formulary, 2019 #281}
Epoetin alpha	1,788 units per week	£3.1	{British National Formulary, 2019 #281}
Sub Total		**£856**	

Based on calculations the cost of stage CKD5 was estimated for patients who enter the CKD 5 state, and for the subsequent cycles in CKD 5 state.

Costs of state CKD 5

Resource	Cost	Patients on RRT	Patients on CT	Source of cost
CKD stage 5 (1st cycle)	£6,749	90%	10%	Above tables
CKD stage 5 (subsequent cycles)	£5,783	90%	10%	Above tables

CI - AKI

For the estimation of CI-AKI event cost, two different methods were used in the model. 1) For patients who have to be re-admitted to the hospital due to CI-AKI after a CAG and/or PCI procedure, the cost of an index admission due to AKI was used. 2) For patients admitted for CAG and/or PCI who have a prolonged length of stay due to CI-AKI, the cost of these additional bed days was considered.
For the cost of the 'AKI' state, the cost of an index admission to due AKI was used in combination with the cost of CKD stage 3-4.

Cost of new admission

For the cost of CI-AKI the weighted average of the costs of AKI from the NHS reference costs LA07 (H-P) was used. Since this cost is closely associated with the introduction of the intervention, because of the disaggregation of this cost and the inherent uncertainty in the cost estimate, it's value was varied in the sensitivity analysis as described later. The aggregate cost of a hospitalisation due to AKI based on the HRG currency descriptions – (Non-Elective Long Stay) associated with AKI was used (Table below). The estimated cost of an admission associated with an AKI episode was ***£2833.75***.

Table 2. Cost of Index admission with primary diagnosis of AKI

Currency Description - Non-Elective Long Stay	Weight (A)	Unit cost (B)	Weighted cost (A*B)
Acute Kidney Injury with Interventions, with CC Score 11+	3%	£5,656	£202.28
Acute Kidney Injury with Interventions, with CC Score 6-10	7%	£4,695	£301.46

Acute Kidney Injury with Interventions, with CC Score 0-5	6%	£3,693	£202.89
Acute Kidney Injury without Interventions, with CC Score 12+	8%	£3,513	£301.85
Acute Kidney Injury without Interventions, with CC Score 8-11	22%	£2,854	£587.54
Acute Kidney Injury without Interventions, with CC Score 4-7	35%	£2,313	£735.45
Acute Kidney Injury without Interventions, with CC Score 0-3	19%	£1,956	£342.33
Pooled average (per episode)			***£2833.75***

Cost of prolonged length of stay

The second estimate used for the cost of CI-AKI is the estimated cost per day in hospital for patients experiencing AKI (Table below). This estimate was used for patients who are not discharged after the CAG and/or PCI procedure, but rather have a prolonged length of stay. This cost was estimated based on the unit cost and the activity of excess bed days in each of the HRG currencies, according to the NHS reference costs 2017-18 (excess bed days cost was not reported in NHS reference costs 2018-19).

According to a systematic literature review conducted by Subramanian et al. 2007 (Subramanian et al., 2007), the incremental in-hospital length of stay in patients with hospital acquired CI-AKI was 3.75 days (95% CI 1.9 5.6). Consequently, the incremental (additional) cost of CI-AKI in an admission for CAG and/or PCI, is estimated to be £1,421.

Costs and activity of excess days in currencies in NHS reference costs (2017-18) associated with CI-AKI

Currency Code	Currency Description	Excess Bed days	National Average Unit Cost
LA07H	Acute Kidney Injury with Interventions, with CC Score 11+	47.0	£135
LA07J	Acute Kidney Injury with Interventions, with CC Score 6-10	61.0	£542
LA07K	Acute Kidney Injury with Interventions, with CC Score 0-5	57.0	£490
LA07L	Acute Kidney Injury without Interventions, with CC Score 12+	50.0	£330
LA07M	Acute Kidney Injury without Interventions, with CC Score 8-11	146.0	£342
LA07N	Acute Kidney Injury without Interventions, with CC Score 4-7	427.0	£354
LA07P	Acute Kidney Injury without Interventions, with CC Score 0-3	270.0	£349
Pooled average (per episode)			£358 Inflated to 2019 price =£379

Cost of AKI state

The cost of AKI state was considered to be £1,681 the sum of an AKI related admission (£1,421) and CKD stage 3-4 (£260).

Resource use

Describe any relevant resource data for the NHS in England reported in published and unpublished studies. Provide sources and rationale if relevant. If a literature search was done to identify evidence for resource use then please provide details in appendix A.

See above

Describe the resources needed to implement the technology in the NHS. Please provide sources and rationale.

Other than use of the technology itself, the only additional resource use required to implement the technology in the NHS would be introduction of staff to use the technology through product evaluation processes within hospital sites. Osprey Medical, Inc. have indicated that product evaluations are provided free of charge and therefore, no additional costs related to use of the technology (other than the cost of the technology itself) are included in the model.

Describe the resources needed to manage the change in patient outcomes after implementing the technology. Please provide sources and rationale.

No additional resources will be required to manage the change in patient outcomes. The model captures the change in clinical outcomes (progression of the condition, as well as occurrence of adverse events) following introduction of the intervention. However, increased resource use will only be required if the intervention results in increased complication rates and worsens progression of the clinical condition. This is not the case, as complication rates are reduced through introduction of the intervention. Resource use associated with clinical complications, and health states, included in the model are presented in a later section.

Describe the resources needed to manage the change in system outcomes after implementing the technology. Please provide sources and rationale.

Not applicable. Please see previous paragraph; the same applies to impact on system outcomes.

Table 5 Resource use costs

In this table, summarise how the model calculates the results of these changes in resource use. Please adapt the table as necessary.

Response: Please see table below for details on cost of the intervention, and the modelling results section later on for full details on impact of the intervention on resource use costs over the patient lifetime.

	Technology costs (£)	Comparator 1 costs	Comparator 2 costs	Difference in resource use costs (technology vs comparator 1) (£)	Difference in resource use costs (technology vs comparator 2)
Cost of resource use to implement technology	350	0	N/A	350	N/A
Cost of resource use associated with patient outcomes	See modelling results	See modelling results	N/A	See modelling results	N/A
Cost of resource use associated with system outcomes	See modelling results	See modelling results	N/A	See modelling results	N/A
Total costs	350	See modelling results	N/A	See modelling results	N/A

Adverse event costs

If costs of adverse events were included in the analysis, explain how and why the risk of each adverse event was calculated.

The following adverse events were included in the model, based on the fact that these are the most commonly occurring complications amongst this patient population undergoing the outlined procedures:

(1) CI-AKI: The baseline risk of experiencing a CI-AKI in the model was derived from previous literature (Mehran et al., 2004) (base-case analysis: 30%). A range of alternative baseline values were also explored in the scenario analyses (Maioli et al., 2008, Rashid et al., 2004, Dangas et al., 2005, NG148, 2019). The probability of experiencing a recurrent AKI was sourced from a study by Valle et al, 2017 exploring the longitudinal risk of adverse events in patients with acute kidney injury after percutaneous coronary intervention. A parameter to account for the reduction in the risk of experiencing a CI-AKI following use of the intervention was also included in the model (base-case: 41%).

(2) MI: The probability of patients experiencing MI (initial and subsequent) was sourced from the study by Valle et al, 2017.

(3) Additional complications including the need to undergo dialysis, and the occurrence of End-Stage Renal Disease were also modelled.

Complications included in the model had implications on resource use, and quality-of-life and therefore, they were modelled. Please see earlier table, and Table 6, for details on costs associated with adverse events.

Table 6 Adverse events and costs in the model

In this table, summarise the costs associated with each adverse event included in the model. Include all adverse events and complication costs, both during and after long-term use of the technology. Please explain whether costs are provided per patient or per event.

Adverse event	Items	Cost	Source
CI-AKI index admission	Technology	not applicable	not applicable
	Staff	not applicable	not applicable
	Hospital costs	not applicable	not applicable
	[Other items]	not applicable	not applicable
	Total	£2,834	(Department of Health and Social Care, 2019) (HRG codes: LA07H, LA07J, LA07K, LA07L, LA07M, LA07P)
CI-AKI cost of hospital day	Technology	not applicable	not applicable
	Staff	not applicable	not applicable
	Hospital costs	not applicable	not applicable
	[Other items]	not applicable	not applicable
	Total	£379	(Department of Health and Social Care, 2019) (HRG codes: LA07H, LA07J, LA07K, LA07L, LA07M, LA07P)
CI-AKI cost of extended hospital admission (it was assumed that 50% of CI-AKI will lead to an extended hospital admission and the rest (50%) will lead to a new admission)	Technology	not applicable	not applicable
	Staff	not applicable	not applicable
	Hospital costs	not applicable	not applicable
	[Other items]	not applicable	not applicable
	Total	£1,421	(Department of Health and Social Care, 2019)
Cost of MI (initial)/cycle	Technology	not applicable	not applicable
	Staff	not applicable	not applicable
	Hospital costs	not applicable	not applicable
	[Other items]	not applicable	not applicable
	Total	£6,364	(Walker et al., 2016)
Cost of MI (subsequent)/cycle	Technology	not applicable	not applicable
	Staff	not applicable	not applicable
	Hospital costs	not applicable	not applicable
	[Other items]	not applicable	not applicable
	Total	£512	(Walker et al., 2016)

Miscellaneous costs

Describe any additional costs or resource considerations that have not been included elsewhere (for example, PSS costs, and patient and carer costs). If none, please state.

Not applicable.

Are there any other opportunities for resource savings or redirection of resources that have not been possible to quantify?

As highlighted in the limitations of the analysis (presented in the next section), it was not possible to quantify how the risk of developing CI-AKI changes depending on whether the patient receives CAG, PCI or a combination of both. Therefore, in the model it was assumed that this risk was the same regardless of the intervention initially received. However, it is possible that further resource savings could be made following introduction of the intervention if it was found that the risk of developing CI-AKI was reduced further depending on the initial procedure.

*Total costs

In the following tables, summarise the total costs:

- Summarise total costs for the technology in table 7.
- Summarise total costs for the comparator in table 8. This can only be completed if the comparator is another technology.

Table 7 Total costs for the technology in the model

Description	Cost	Source
Cost per treatment/patient over lifetime of device	£350	Osprey Medical, Inc.
Consumables per year (if applicable) and over lifetime of device	£0	Osprey Medical, Inc.
Maintenance cost per year and over lifetime of device	£0	Not Applicable.
Training cost over lifetime of device	£0	Not Applicable.
Other costs per year and over lifetime of device	£0	Not Applicable.
Total cost per treatment/patient over lifetime of device	£350	Osprey Medical, Inc.

Table 8 Total costs for the comparator in the model

The technology being evaluated is a technology that would be used in addition to existing procedures, and therefore there are no immediate costs associated with the comparator. Therefore, no costs have been added to the table below.

Description	Cost	Source
Cost per treatment/patient over lifetime of device	Not Applicable.	Not Applicable.
Consumables per year (if applicable) and over lifetime of device	Not Applicable.	Not Applicable.
Maintenance cost per year and over lifetime of device	Not Applicable.	Not Applicable.
Training cost over lifetime of device	Not Applicable.	Not Applicable.
Other costs per year and over lifetime of device	Not Applicable.	Not Applicable.
Total cost per treatment/patient over lifetime of device	Not Applicable.	Not Applicable.

Results

Table 9 Base-case results

In this table, report the results of the base-case analysis. Specify whether costs are provided per treatment or per year. Adapt the table as necessary to suit the cost model. If appropriate, describe costs by health state.

	Mean discounted cost per patient using the technology over a lifetime time horizon (£)	**Mean discounted cost per patient using the comparator 1 over a lifetime time horizon (£)**	**Mean discounted cost per patient using the comparator 2 over a lifetime time horizon (£)**	**Difference in mean discounted cost per patient over a lifetime time horizon (£): technology vs comparator 1***	**Difference in mean discounted cost per patient over a lifetime time horizon (£): technology vs comparator 2***
Device cost per procedure	£350	0	N/A	£350	N/A
Adverse events (first 3 months of model)	£668	£947	N/A	-£279	N/A
Subsequent disease management	£24,164	£25,586	N/A	-£1,421	N/A
Total**	£28,701	£30,051	N/A	-£1,350	N/A

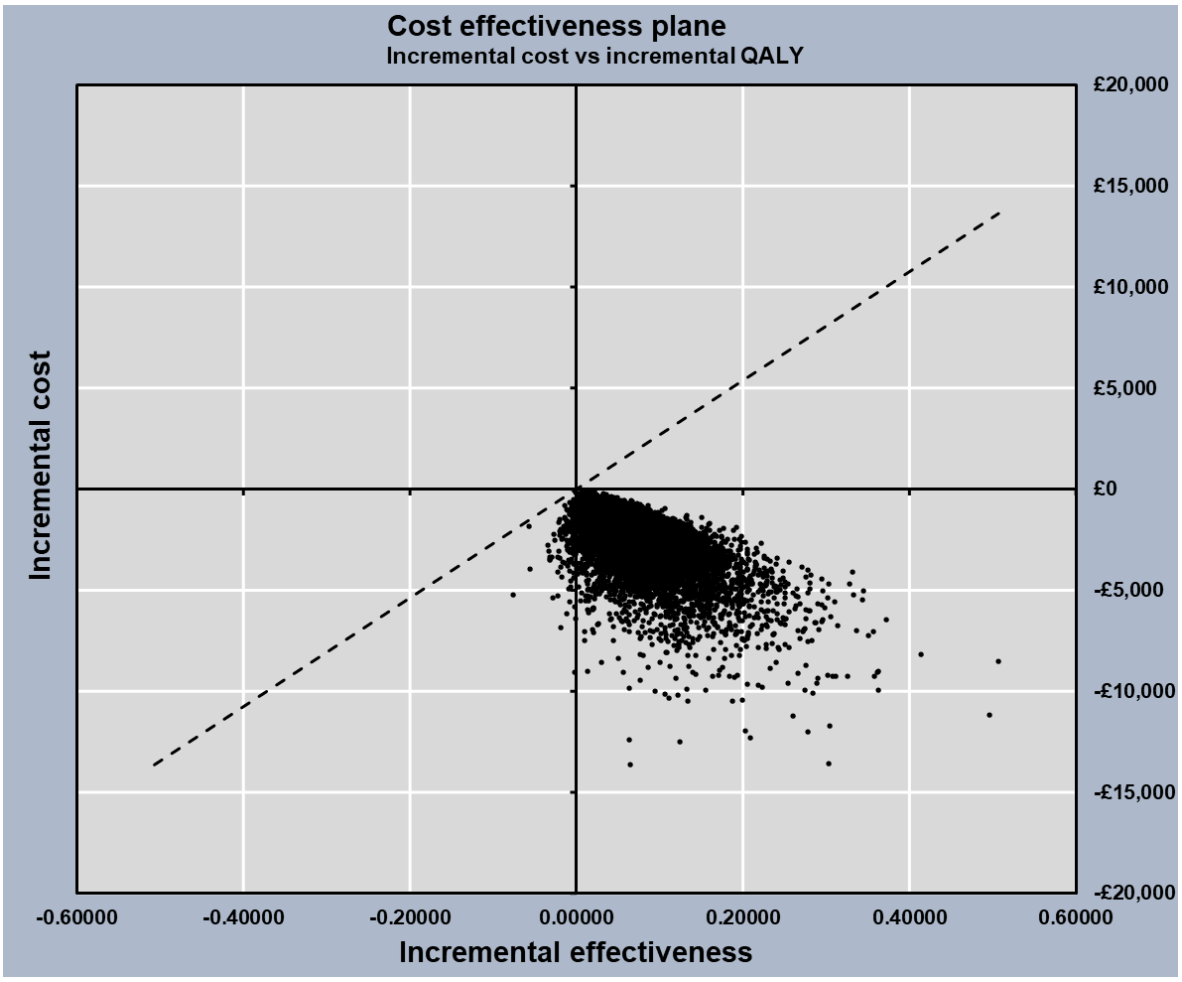
* Negative values indicate a cost saving.

Adapt this table as necessary.

** Note that there are additional costs associated with undergoing the original procedure which are not outlined in the table above. This is the reason why the total costs across the categories presented will not equal the total. The cost of undergoing the procedure is the same for patients in both arms of the model.

The economic modelling focussed on impact of introduction of the technology on health system costs, as well as patients' outcomes (quality adjusted life years). Base-case results from the model indicated that the technology is cost saving and results in improved patient outcomes. Probabilistic results (which account for uncertainty in the model/parameter estimates based on a number of model simulations) from the model indicated that the intervention would have a high probability of being cost saving (>99%) over the patient lifetime. Probabilistic results following 10,000 model simulations are presented below. The first graph (cost-effectiveness plane) shows that the majority of points (representing individual iterations of the model) are in

the south-east quadrant indicating that the intervention is less costly and more effective than the comparator.



Scenario analysis

If relevant, explain how scenario analyses were identified and done. Cross-reference your response to the decision problem in part 1, section 1 of the submission.

Various sensitivity analyses exploring uncertainty in model parameters, and impact on the model outputs, are presented in the next section. In the following table we have reported the estimated incremental cost for different level of baseline risk of CI-AKI and the absolute risk reduction associated with using the DyeVert Systems.

Describe the differences between the base case and each scenario analysis.

In these scenario analyses, different assumptions have been made for the baseline risk of CI-AKI and absolute risk reduction associated with using DyeVert Systems. The results from these scenario analyses indicate that in most of the scenarios the technology is still cost saving which is consistent with the base-case analysis.

Describe how the scenario analyses were included in the cost analysis.

By applying different baseline risk of CI-AKI and risk reduction associated with DyeVert Systems, the overall incremental cost per patients were estimated and reported in the following table.

Describe the evidence that justifies including any scenario analyses.

Different baseline risks of CI-AKI were used to inform the economic model that was included in the latest NICE guideline (NG148, 2019). In addition, we explored the impact of different level of risk reduction associated with application of the DyeVert Systems.

Table 10 Scenario analyses results

In this table, describe the results of any scenario analyses that were done. Adapt the table as necessary.

The estimated incremental cost for different level of baseline risk of CI-AKI and the absolute risk reduction associated with using DyeVert Systems is presented in the table below.

		Risk reduction (source)			
Scenario (Source)	**Baseline CI-AKI risk**	**Javanbakht et al. 2020 (21.4%)**	**Assumption (25%)**	**Assumption (30%)**	**Assumption (35%)**
Mehran et al. 2004	30.00%	**-£537.4**	**-£686.7**	**-£894.0**	**-£1,101.4**
Maioli et al. 2008	11.50%	**£9.8**	**-£47.4**	**-£126.9**	**-£206.4**
Rashid et al. 2004	14.30%	**-£73.0**	**-£144.2**	**-£243.0**	**-£341.8**
Pooled RCT data, all trials	13.10%	**-£37.5**	**-£102.7**	**-£193.2**	**-£283.8**
Pooled RCT data, elective trials	10.80%	**£30.5**	**-£23.2**	**-£97.9**	**-£172.5**
Pooled RCT data, emergency trials	19.60%	**-£229.8**	**-£327.3**	**-£462.8**	**-£598.2**
Dangas et al. 2005	19.20%	**-£217.9**	**-£313.5**	**-£446.2**	**-£578.9**

Sensitivity analysis

Describe what kinds of sensitivity analyses were done. If no sensitivity analyses have been done, please explain why.

Multiple sensitivity analyses were conducted to explore the impact of parameter variations on the model outputs. In the first analysis (multiple one-way sensitivity analyses), all model parameters were varied by 25% (increased and decreased) to explore the impact that this had on the incremental cost of the intervention (with results presented in the form of a tornado diagram). In subsequent analyses, alternative parameter values were assigned to parameters for which there some uncertainty (one-way sensitivity analyses). The impact of these variations on the overall cost-effectiveness results are presented. The range of sensitivity analyses are presented in the next paragraph, with results presented afterwards.

Summarise the variables used in the sensitivity analyses and provide a justification for them. This may be easier to present in a table (adapt as necessary).

Sensitivity analysis:
Multiple one-way sensitivity analyses, in which all model parameters were varied by 25% (increased and decreased) to look at the impact that this had on the incremental cost of the intervention.

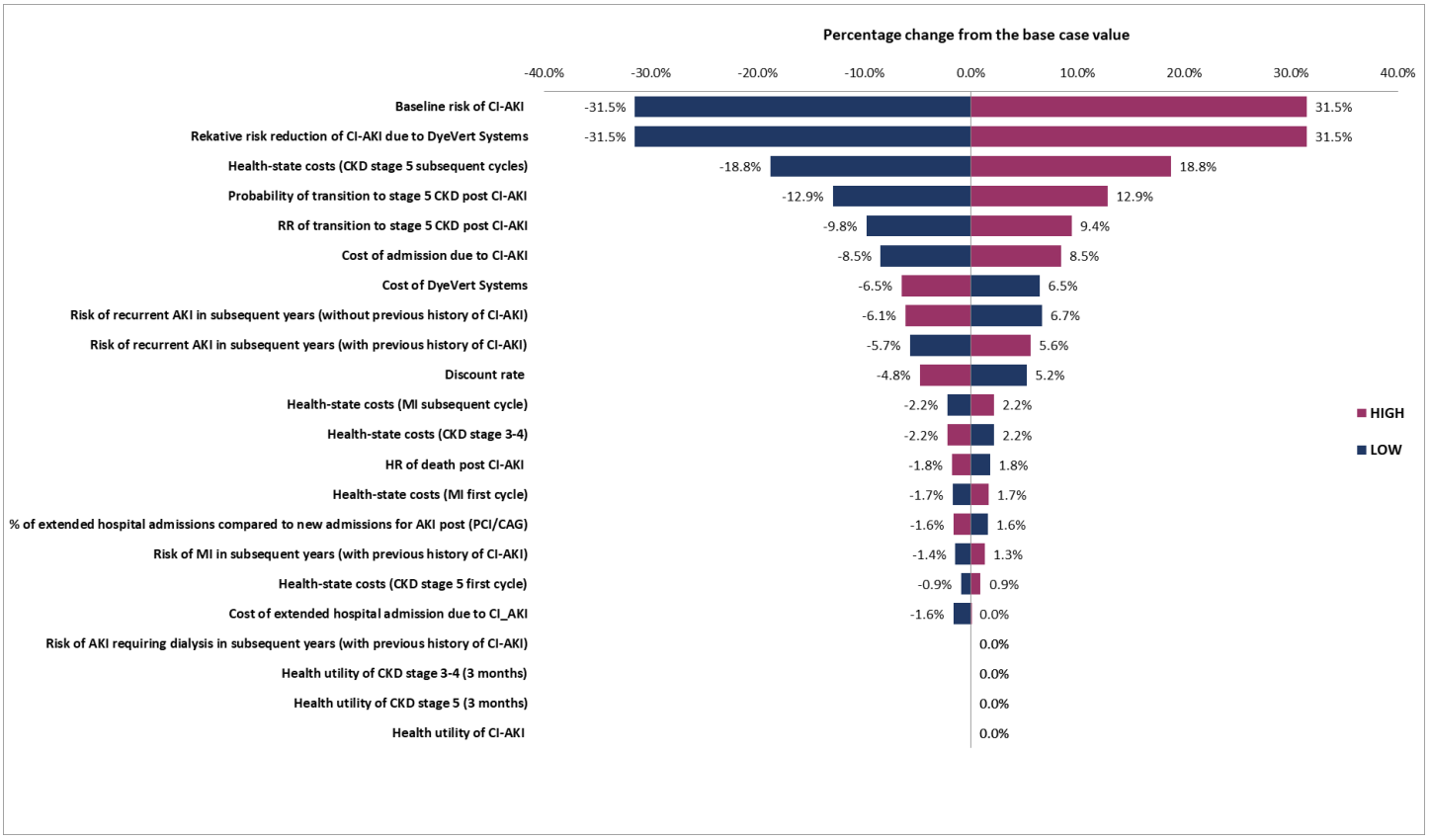
If any parameters or variables listed in table 3 were omitted from the sensitivity analysis, please explain why.

All relevant parameters were included in the multiple one-way sensitivity analyses.

Sensitivity analyses results

Present the results of any sensitivity analyses using tornado plots when appropriate.

Sensitivity analysis: Impacts of changing the input parameters by ± 25% on the estimated incremental cost.



What were the main findings of each of the sensitivity analyses?

Sensitivity analysis: In the tornado diagram which shows the results of the multiple one-way sensitivity analyses (25% parameter variations), parameters are displayed in order, with those which have the greatest impact on incremental cost displayed at the top and those with have the least impact displayed at the bottom of the graph. The results show that the parameters which have the largest impact on cost results are the baseline probability of CI-AKI following the initial procedure and the risk reduction in experiencing CI-AKI following use of the DyeVert Systems. When these parameter values are reduced, cost savings associated with implementing the intervention are reduced also. However, as Table 10 illustrates, the DyeVert System is predicted to be a cost saving intervention at levels of baseline CI-AKI rates and relative reductions in CI-AKI much lower than those observed thus far.

Results from all sensitivity analyses highlight that the baseline risk of CI-AKI, and the risk reduction associated with introduction of the DyeVert Systems have the greatest impact on the model results. However, the overall conclusion (i.e., DyeVert Systems is a cost saving intervention) will stay the same in all scenarios in the one-way sensitivity analysis.

What are the main sources of uncertainty about the model's conclusions?

As described in detail in the later section, there is uncertainty surrounding the values associated with a number of model parameters (please refer to Section 4). However, extensive sensitivity analyses were conducted with little impact on the overall results identified.

Miscellaneous results

Include any other relevant results here.

Not applicable.

Validation

Describe the methods used to validate, cross-validate (for example with external evidence sources) and quality assure the model. Provide sources and cross-reference to evidence when appropriate.

In order to evaluate the face validity of the model, the model structure, input parameters and results were presented to clinical experts with significant experience working in this clinical area, and who are well-respected in this field of research. They evaluated the model structure and assumptions in comparison to real-world circumstances. A large number of sensitivity analyses were also conducted to assess the internal validity of the model. Null and extreme values were assigned to input parameters and the model was run to test the robustness of the results.

Give details of any clinical experts who were involved in validating the model, including names and contact details. Highlight any personal information as confidential.

Azfar Zaman[1]· Yahya Al-Najjar[2] · Donal O'Donoghue[2] · Farzin Fath-Ordoubadi[2] · Stephen Wheatcroft[3] Kimberly Knish[4] 1. Freeman Hospital, Newcastle upon Tyne, UK 2. Manchester University, Manchester, UK 3. Leeds Teaching Hospitals NHS Trust, Leeds, UK 4. Clinical Affairs, Osprey Medical, USA

4 Summary and interpretation of economic evidence

Describe the main findings from the economic evidence and cost model. Explain any potential cost savings and the reasons for them.

Findings from the economic modelling indicate that introduction of the technology results in cost savings for the UK health care service and improved patient outcomes (both a reduction in the clinical complication rate, and an increase in quality-adjusted life-years gained). A probabilistic model was developed, which allows one to quantify the uncertainty present in the model results. However, based on 10,000 iterations of the model, results indicate that the intervention has a >99% probability of being cost saving. Base-case model results indicate that cost savings of £1350 per patient would be made over a lifetime time horizon, as well an increase of 0.057 QALYs per patient. Therefore, the intervention can be considered to be a 'dominant' strategy in that it is less costly and more effective than the comparator (current practice).

Following introduction of the DyeVert Systems, cost savings are largely driven by the reduction in the risk of experiencing CI-AKI during the index cath lab procedure and the reduction in risk associated with subsequent short- and long-term complications (i.e., CKD progression, recurrent CI-AKI and MI), which are expensive complications. Thus, both short- and long-term health care savings are projected.

In summary, the high incremental cost of CI-AKI and associated complications when viewed against a relatively low technology acquisition cost for the DyeVert System (£350 per procedure) results in meaningful improvements to patient quality of life and clinical outcomes as well as a significant reduction in healthcare burden.

Briefly discuss the relevance of the evidence base to the scope.

Clinical and economic consequences of CI-AKI are a significant and growing public health problem due to a perfect storm of multifactorial causes, such as: increasing demand for angiography services, increasing age of the patient population undergoing angiography and increasing prevalence of comorbidities that increase patient risk for CI-AKI, such as chronic kidney disease, with the burden disproportionately born by the most vulnerable patients.

The technology-enabled solution provided by the DyeVert System offers a new approach to CI-AKI prevention that provides real-time clinical decision support and attunes everyone in the cath lab to the importance of risk screening, contrast media use monitoring and management, and overall contrast dose minimization.

A robust decision-analytic model projects the introduction of the DyeVert System to be less costly and more effective in reducing the lifetime health care burden associated with CI-AKI compared to current standard of care in at-risk patients undergoing angiography. These findings are further supported by real-world evidence summarized herein in the target demographic undergoing angiography. Therefore, the evidence provided directly aligns with the scope.

Briefly discuss if the results are consistent with the published literature. If they are not, explain why and justify why the results in the submission be favoured over those in the published literature.

Two abstracts involving an analysis of use of the DyeVert Systems were identified in the search for relevant economic evidence. A study of at-risk patients by Kutschman et al, 2019 (Kutschman, 2019) reported a 12.4% absolute and 57% relative reduction in CI-AKI in cases using the DyeVert System compared to cases in which the DyeVert System was not used, which translated into an estimated savings of $2,000 per case based on the cost savings associated with CI-AKI avoidance during the index procedure.

A study by (Turner and Tucker, 2020) reported an overall 10.46% absolute and 83.7% relative reduction in CI-AKI for a quality improvement protocol that included use of the DyeVert Systems in CKD and acute presentation cases, which translated into a net cost savings of $650 per case due to CI-AKI avoidance during the index procedure.

Results presented in the two abstracts identified are, therefore, largely consistent with the results from the economic modelling study presented here. While neither look at the long-term cost-effectiveness, or impact on quality-of-life, associated with introduction of the DyeVert System (as we have presented in our model), both show that a reduction in CI-AKI incidence amongst the target population can lead to cost savings for the health care provider. Similarly, [redacted]. Finally, the publication by (Javanbakht et al., 2020) showed that the DyeVert PLUS EZ system had a high probability of being cost-saving which again is consistent with our own results.

Very few studies exploring alternative interventions aimed at preventing/reducing the onset of CI-AKI are available from the literature. A model was developed by the National Clinical Guideline Centre (UK) in 2013 as part of their guidelines on AKI, exploring the cost-effectiveness of alternative intravenous fluids for the prevention of the condition (NG148, 2019). However, other than the model presented by Javanbakht et al, 2020 no other analyses have been identified focussing on the cost-effectiveness of an intervention designed to reduce contrast media volume.

Describe if the cost analysis is relevant to all patient groups and NHS settings in England that could potentially use the technology as identified in the scope.

The analysis is relevant to all patients at risk of CI-AKI who need coronary or peripheral angiography and/or percutaneous coronary intervention with contrast media. It is relevant to all NHS settings which deliver the procedure(s) and intervention(s) outlined.

Briefly summarise the strengths and limitations of the cost analysis, and how these might affect the results.

A number of assumptions were made when populating the model due to data limitations. Firstly, it was unknown how the risk of developing CI-AKI changes depending on whether the patient receives CAG, PCI or a combination of both or peripheral angiography. Therefore, in the model it was assumed that this risk was the same regardless of the initial intervention. This may have the effect of over- or underestimating the risk of developing this complication, depending on the initial intervention received, and the direction of this effect is unknown.

The data used to inform the effectiveness of the DyeVert Systems were derived from robust published clinical evidence and real-world evidence. All these clinical evidences have consistently showed reduction in CI-AKI rate.

Finally, information on the relationship between AKI and long-term clinical outcomes (i.e. MI and recurrent AKI and ESRD) is limited, which means that there is a degree of uncertainty around the relevant data included in the model. However, to address this limitation, an extreme sensitivity analysis was performed in which the main input parameters were changed by ±25%.

Despite the limitations highlighted above, a robust decision-analytic model was developed. The model was informed by clinical guidelines, published literature and expert clinical input, and any assumptions that were made in the analysis can be rectified by using more robust data in later studies, as a model now exists for re-analysis once additional information becomes available.

Additionally, it is important to consider the model does not account for additional complexities related to the full scope of downstream events following CI-AKI, such as other high-burden health states like heart failure and other major adverse cardiovascular events, the prevalence of all known CI-AKI risk factors, or the increasing proportion of patients who are undergoing repeat procedures involving contrast media over their lifetime. The model also does not account for the fact that patients experiencing a CI-AKI event are more likely to be discharged to higher burden care facilities such as skilled nursing or hospice; and therefore, represents a conservative model of cost savings.

Detail any further analyses that could be done to improve the reliability of the results.

The structure of the economic model, and the methods used, are robust enough to allow for re-analysis. Further analyses should focus on identifying more reliable data to inform the parameters outlined in the limitations above, to ensure that the conclusions are reliable.

5 References

Please include all references below using NICE's standard referencing style.

Bank of england. (2020). Inflation Calculator [Online]. Available: https://www.bankofengland.co.uk/monetary-policy/inflation/inflation-calculator [Accessed 17 November 2020].

Bath A, Bobba K, Gautam S, et al. (2019) Gupta V. Use of DyeVert Plus to reduce contrast exposure in high-risk patients undergoing coronary angiography. Journal of the American College of Cardiology 73(9 Supplement 1):1193. doi:10.1016/s0735-1097(19)31800-5.

Briguori C, Golino M, Porchetta N, et al. (2020) Impact of a contrast media volume control device on acute kidney injury rate in patients with acute coronary syndrome. Catheterization and Cardiovascular Interventions [published online ahead of print, 2020 Jul 18]. doi:10.1002/ccd.29136.

British national formulary. (2019). Available: https://www.bnf.org/ [Accessed October 2019].

Bruno RR, Nia AM, Wolff G, et al. (2019) Early clinical experiences with a novel contrast volume reduction system during invasive coronary angiography. International Journal of Cardiology Heart and Vasculature 23:100377. doi:10.1016/j.ijcha.2019.100377.

Bunney R, Saenger E, Shah C, et al. (2019) Contemporary use of contrast dye reduction technology in a tertiary academic hospital: patient characteristics and acute kidney injury outcomes following percutaneous coronary interventions. Poster presented at: American College of Cardiology (ACC) Quality Summit; March 2019; New Orleans, LA. Poster 2018-063 presentation https://cvquality.acc.org/docs/default-source/quality-poster-awards-2019/2018-063_bunney-robert_rn.pdf?sfvrsn=582f86bf_2.

Cameron A, Espinosa TJ (2020) Reducing contrast-induced acute kidney injury in a cardiac catherization laboratory: a quality improvement initiative. Society for Cardiac Angiography & Interventions Scientific Sessions Virtual Conference. E-poster abstract presented https://virtual2020.scai.org/p/46024. Catheterization and Cardiovascular Interventions 95 (Supplement 2):I-34.

CG169. (2013). Acute kidney injury: prevention, detection and management [Online]. Available: https://www.nice.org.uk/guidance/cg169 [Accessed].

Corcione N, Biondi-Zoccai G, Ferraro P, et al. (2017) Contrast minimization with the new-generation DyeVert Plus System for contrast reduction and real-time monitoring during coronary and peripheral procedures: first experience. Journal of Invasive Cardiology 29(8):259-62. PMID: 28756419.

Curtis, I. & Burns, a. (2019). Unit Costs of Health and Social Care 2019, Personal Social Services Research Unit, University of Kent, Canterbury [Online]. Available: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/ [Accessed].

Dangas, G., Iakovou, I., Nikolsky, E. et al (2005). Contrast-induced nephropathy after percutaneous coronary interventions in relation to chronic kidney disease and hemodynamic variables. Am J Cardiol, 95, 13-9.
Department of Health and Social Care. (2019). NHS Reference costs [Online]. Available: https://www.england.nhs.uk/national-cost-collection/#ncc1819 [Accessed April 2020].

Desch S, Fuernau G, Pöss J, et al. (2018) Impact of a novel contrast reduction system on contrast savings in coronary angiography - The DyeVert randomised controlled trial. International Journal of Cardiology 257:50-3. doi: 10.1016/j.ijcard.2017.12.107.

Eriksen, B. O. & Ingebretsen, O. C. (2006). The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age. Kidney Int, 69, 375-82.

Amoroso G, Christian J, Christopher A (2020) First European experience using a novel contrast reduction system during coronary angiography with automated contrast injection. EuroIntervention Supplement 16 (AC):Euro20A-POS426.

Gurm HS, Dixon SR, Smith DE, et al. (2011) Renal function-based contrast dosing to define safe limits of radiographic contrast media in patients undergoing percutaneous coronary interventions. Journal of the American College of Cardiology 58:907-914. doi: 10.1016/j.jacc.2011.05.023.

Gurm HS, Seth M, Mehran R, et al. (2016) Impact of contrast dose reduction on incidence of acute kidney injury (AKI) among patients undergoing PCI: a modeling study. Journal of Invasive Cardiology 28:142-146. PMID: 26773238.

Gurm HS, Mavromatis K, Bertolet B, et al. (2019) Minimizing radiographic contrast administration during coronary angiography using a novel contrast reduction system: a multicenter observational study of the DyeVert™ plus contrast reduction system. Catheterization and Cardiovascular Interventions 93(7):1228-35. doi: 10.1002/ccd.27935.

James MT, Samuel SM, Manning MA, et al. (2013) Contrast-induced acute kidney injury and risk of adverse clinical outcomes after coronary angiography: a systematic review and meta-analysis. Circulation: Cardiovascular Interventions Feb;6(1):37-43.

Javanbakht M, Hemami MR, Mashayekhi A, et al. (2020) DyeVert™ PLUS EZ System for preventing contrast-induced acute kidney injury in patients undergoing diagnostic coronary angiography and/or percutaneous coronary intervention: a UK-based cost-utility analysis. PharmacoEconomics Sep;4(3):459-472. doi: 10.1007/s41669-020-00195-x. PMID: 31989464; PMCID: PMC7426357.

Kerr M, Bedford M, Matthews B, et al. (2014) The economic impact of acute kidney injury in England. Nephrology Dialysis Transplantation Jul;29(7):1362-8. doi: 10.1093/ndt/gfu016. Epub 2014 Apr 21. PMID: 24753459.

Kutschman R (2019) Clinical and economic outcomes of a comprehensive clinical quality initiative for reducing acute kidney injury in chronic kidney disease patients undergoing coronary angiography. Journal of the American College of Cardiology 74(13 Supplement):B605. doi: 10.1016/j.jacc.2019.08.731.

Maioli, M., Toso, A., Leoncini, M., et al. (2008). Sodium bicarbonate versus saline for the prevention of contrast-induced nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. J Am Coll Cardiol, 52, 599-604.

Mehran, R., Aymong, e. D., Nikolsky, e., et al. (2004). A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. J Am Coll Cardiol, 44, 1393-9.

NG148. (2019). Acute kidney injury: prevention, detection and management [Online]. Available: https://www.nice.org.uk/guidance/ng148/history [Accessed].

National Institute for Health and Care Excellence (NICE) (2013). Guide to the Methods of Technology Appraisal 2013. London.

Rao S (2019) DyeVert Plus Contrast Reduction System use in patients undergoing highly complex peripheral vascular interventions. Poster presented at the International Symposium on

Endovascular Therapies (ISET). Journal of Vascular and Interventional Radiology 30:e16. doi:10.1016/j.jvir.2018.11.033.

Rashid, s. T., Salman, M., Myint, F.et al.2004). Prevention of contrast-induced nephropathy in vascular patients undergoing angiography: a randomized controlled trial of intravenous N-acetylcysteine. J Vasc Surg, 40, 1136-41.

Sapontis J, Sujith S, Cameron J, et al. (2017) A first-in-human evaluation of a novel contrast media saving device. Catheterization and Cardiovascular Interventions 90(6):928-934. doi: 10.1002/ccd.27033.

Sattar A, Schnatz R, Darby M, et al. (2018) Impact of using DyeVert PLUS on incidence of acute kidney injury after cardiac catheterization with coronary interventions in high-risk patients. American College of Cardiology Annual Meeting; April 2018; Charleston, WV. Poster #3 presentation https://jcesom.marshall.edu/media/56993/2018-abstracts.pdf.

See EJ, Jayasinghe K, Glassford N, et al. (2019) Long-term risk of adverse outcomes after acute kidney injury: a systematic review and meta-analysis of cohort studies using consensus definitions of exposure. Kidney International Jan;95(1):160-172. doi: 10.1016/j.kint.2018.08.036. Epub 2018 Nov 23. PMID: 30473140.

SUBRAMANIAN, S., TUMLIN, J., BAPAT, B. & ZYCZYNSKI, T. (2007). Economic burden of contrast-induced nephropathy: implications for prevention strategies. J Med Econ, 10, 119-34.

TA236. (2011). Ticagrelor for the treatment of acute coronary syndromes [Online]. Technology appraisal guidance [TA236]. Available: https://www.nice.org.uk/guidance/ta236 [Accessed March 2019].

Tajti P, Xenogiannis I, Hall A, et al. (2019) Use of the DyeVert system in chronic total occlusion percutaneous coronary intervention. Journal of Invasive Cardiology 31(9):253-9.

Turner C, Tucker PA (2020) Real-world impact of a quality improvement program for AKI prevention in the cardiac cath lab. Society for Cardiac Angiography & Interventions Scientific Sessions Virtual Conference. Catheterization and Cardiovascular Interventions 95(Supplement 2):S112-S3.

Valle JA, McCoy LA, Maddox TM, et al. (2017) Longitudinal risk of adverse events in patients with acute kidney injury after percutaneous coronary intervention: insights from the national cardiovascular data registry. Catheterization and Cardiovascular Interventions 10(4):e004439. doi:10.1161/CIRCINTERVENTIONS.116.004439.

Villar, E., Remontet, L., Labeeuw, M. et al. (2007). Effect of Age, Gender, and Diabetes on Excess Death in End-Stage Renal Failure. Journal of the American Society of Nephrology, 18, 2125.

Walker, S., Asaria, M., Manca, A.,. et el. (2016). Long-term healthcare use and costs in patients with stable coronary artery disease: a population-based cohort using linked health records (CALIBER). Eur Heart J Qual Care Clin Outcomes, 2, 125-40.

Zimin VN, Jones MR, Richmond IT, et al. (2020) A feasibility study of the DyeVert™ plus contrast reduction system to reduce contrast media volumes in percutaneous coronary procedures using optical coherence tomography. Cardiovascular Revascularization Medicine Oct 3:S1553-8389(20)30592-3. doi: 10.1016/j.carrev.2020.09.040. Epub ahead of print. PMID: 33046416.

6 Appendices

Appendix A: Search strategy for economic evidence

Describe the process and methods used to identify and select the studies relevant to the technology being evaluated. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	28/01/2021
Date span of search:	Until Jan 2021

List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.

Database: Ovid MEDLINE(R) ALL <1946 to January 26, 2021>

Table 3 MEDLINE(R) and Medline in press ALL search strategy

NEW

#	terms	# of hits
1	Acute Kidney Injury.mp. or Acute Kidney Injury/	57262
2	(contrast-induced* or radiocontrast-induced* or ci).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	625901
3	1 and 2	5120
4	Contrast Media/ae	9858
5	(ciaki or cin or ciraf or ci-aki or ci-arf or ci nephropath* or cinephropath* or rci nephropath* or rcinephropath*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	11161
6	(aki or arf or acute kidney or acute renal or early kidney or early renal or necrosis or tubul*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	629030
7	Acute Kidney Injury/ae	0
8	3 or 4 or 5 or 6 or 7	646026
9	Dyevert.mp.	8
10	Osprey Medical.mp.	5
11	9 or 10	10
12	Economics/	27279
13	exp "Costs and Cost Analysis"/	241657
14	exp Economics, Hospital/	24896
15	exp Economics, Medical/	14237
16	Budgets/	11380
17	expenditure$.tw.	57994
18	(cost or costs or costing$ or costly or costed).tw.	588836

19	(price$ or pricing$).tw.	41668
20	(pharmacoeconomic$ or (pharmaco adj economic$)).tw.	4077
21	(value adj3 (money or monetary)).tw.	2589
22	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	801546
23	8 and 11 and 22	3

Database: Embase <1974 to January 27, 2021>

Table 4 Embase search strategy

#	terms	# of hits
1	contrast induced nephropathy/	5080
2	(((contrast or radiocontrast) adj induc* adj2 (nephropath* or nephrotoxi* or aki or arf or acute kidney injury or acute renal failure)) or cin or ciaki or ciraf or ci-aki or ci-arf or ((contrast or radiocontrast) adj2 prophyla*)).ti,ab.	18362
3	1 or 2	19872
4	DyeVert.mp.	19
5	Osprey Medical.mp.	19
6	4 or 5	30
7	3 and 6	17
8	health economics/	33317
9	exp economic evaluation/	314527
10	exp health care cost/	298889
11	exp fee/	40693
12	budget/	30081
13	funding/	50912
14	resource allocation/	21603
15	budget*.ti,ab.	40266
16	cost*.ti,ab.	859570
17	(economic* or pharmaco?economic*).ti,ab.	363925
18	(price* or pricing*).ti,ab.	60193
19	(financ* or fee or fees or expenditure* or saving*).ti,ab.	335779
20	(value adj2 (money or monetary)).ti,ab.	3415
21	resourc* allocat*.ti,ab.	12381
22	(fund or funds or funding* or funded).ti,ab.	148298
23	(ration or rations or rationing* or rationed).ti,ab.	16908
24	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	1753706
25	7 and 24	9

Database: NHS Economic Evaluation Database (NHS EED), Database of Abstracts of Effects (DARE) and Health Technology Assessments (HTA) via CRD Database

Table 5 NHS EED, DARE, HTA search strategy

#	terms	# of hits
1	MeSH DESCRIPTOR Acute Kidney Injury EXPLODE ALL TREES	138
2	(acute kidney injur*) IN DARE, NHSEED, HTA	177
3	(acute renal injur*) IN DARE, NHSEED, HTA	3
4	(acute kidney failure*) IN DARE, NHSEED, HTA	5
5	(acute renal failure*) IN DARE, NHSEED, HTA	89
6	(acute kidney insufficiency*) IN DARE, NHSEED, HTA	0
7	(acute renal insufficiency*) IN DARE, NHSEED, HTA	2
8	(acute kidney tubular necrosis*) IN DARE, NHSEED, HTA	0
9	(acute tubular necrosis*) IN DARE, NHSEED, HTA	5
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	246
11	MeSH DESCRIPTOR Contrast Media EXPLODE ALL TREES WITH QUALIFIER AE	77
12	(contrast NEAR induc*) OR (radiocontrast NEAR induc*) IN DARE, NHSEED, HTA	77
13	(ciaki or ciraf or ci-aki or ci-arf) OR (contrast NEAR prophyla*) OR (radiocontrast NEAR prophyla*) IN DARE, NHSEED, HTA	7
14	#11 OR #12 OR #13	106
15	#10 AND #14	42
16	DyeVert	0
17	Osprey Medical	0
18	#16 OR #17	0
19	#15 AND #18	0

Database: Cost-Effectiveness Analysis registry (CEA registry) via Centre for the Evaluation of Value and Risk in Health

Table 6 CEA Registry search strategy

#	terms	# of hits
1	kidney injury	6
2	renal injury	0
3	kidney failure	3
4	renal failures	0
5	kidney insufficiency	0
6	renal insufficiency	5
7	tubular necrosis	0
8	1 or 2 or 3 or 4 or 5 or 6 or 7	9
9	contrast media	2
10	contrast induced	0
11	radio contrast	0
12	ciaki	0
13	ciraf	0
14	ci-aki	0
15	ci-arf	0
16	9 or 10 or 11 or 12 or 13 or 14 or 15	2
17	8 and 16	0

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

We checked the references of identified studies too

Inclusion and exclusion criteria:

A SLR was conducted to identify relevant published economic evidence studies comparing DyeVert contrast reduction systems with other strategies to minimize the risk of CI-AKI in patients undergoing coronary angiography (CAG) and/or percutaneous coronary intervention (PCI) procedures.

Inclusion criteria

Population

Adult patients undergoing CAG and/or PCI procedures which require injection of contrast media who are at risk for CI-AKI.

Interventions DyeVert™, DyeVert™ Plus, DyeVert™ Plus EZ, DyeVert Power XT

Outcomes

- Life years gained
- Quality adjusted life years gained (QALYs)
- Incremental Cost-Effectiveness Ratios (ICERs)
- Clinical effectiveness (e.g. survival rates, healing rates, etc.)
- Details of the results of sensitivity analyses

Study design

- Cost-effectiveness analyses (CEA)
- Cost-utility analyses (CUA)
- Cost-benefit analyses (CBA)
- Cost-minimization analyses (CMA)
- Cost-consequence studies
- Budget impact models
- Cost studies

Language restrictions English language only

Search dates No restriction

Country No restriction

Exclusion criteria

Outcomes Data unrelated to safety or efficacy

Study design Editorials, reviews, letters, book chapters, conference abstracts

Data abstraction strategy:

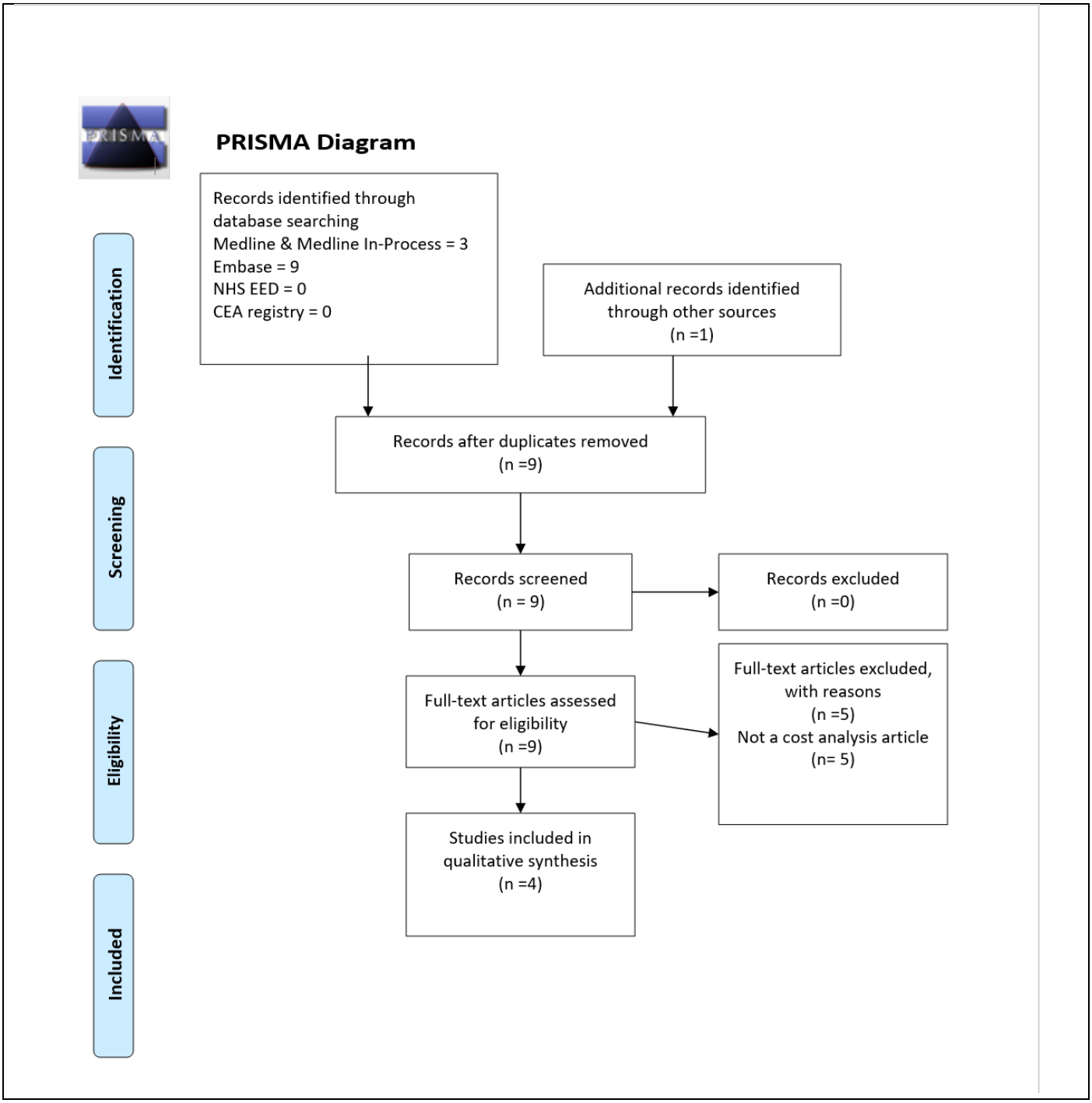
N/A

Excluded studies

List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review, but were later excluded for specific reasons.

Excluded study	Design and intervention(s)	Rationale for exclusion	Company comments
Use of DyeVert Plus to reduce contrast exposure in high-risk patients undergoing coronary angiography.	Prospective, single-center, randomised controlled trial	No cost analysis/data	Text
A Feasibility Study of the DyeVert Plus Contrast Reduction System to Reduce Contrast Media in Optical Coherence Tomography-Guided Percutaneous Coronary Interventions.	Prospective, post-market, single-arm, clinical feasibility study	No cost analysis/data	Text
Impact of a novel contrast reduction system on contrast savings in coronary angiography - The DyeVert randomised controlled trial	Prospective, single-center, open-label, randomised controlled study	No cost analysis/data	Text
A first in human evaluation of a novel contrast media saving device	Prospective, multicenter, single-arm, clinical pilot study	No cost analysis/data	Text
Contrast Minimization With the New-Generation DyeVert Plus System for Contrast Reduction and Real-Time Monitoring During Coronary and Peripheral Procedures: First Experience	Retrospective, observational, single-arm, single-center study	No cost analysis/data	Text

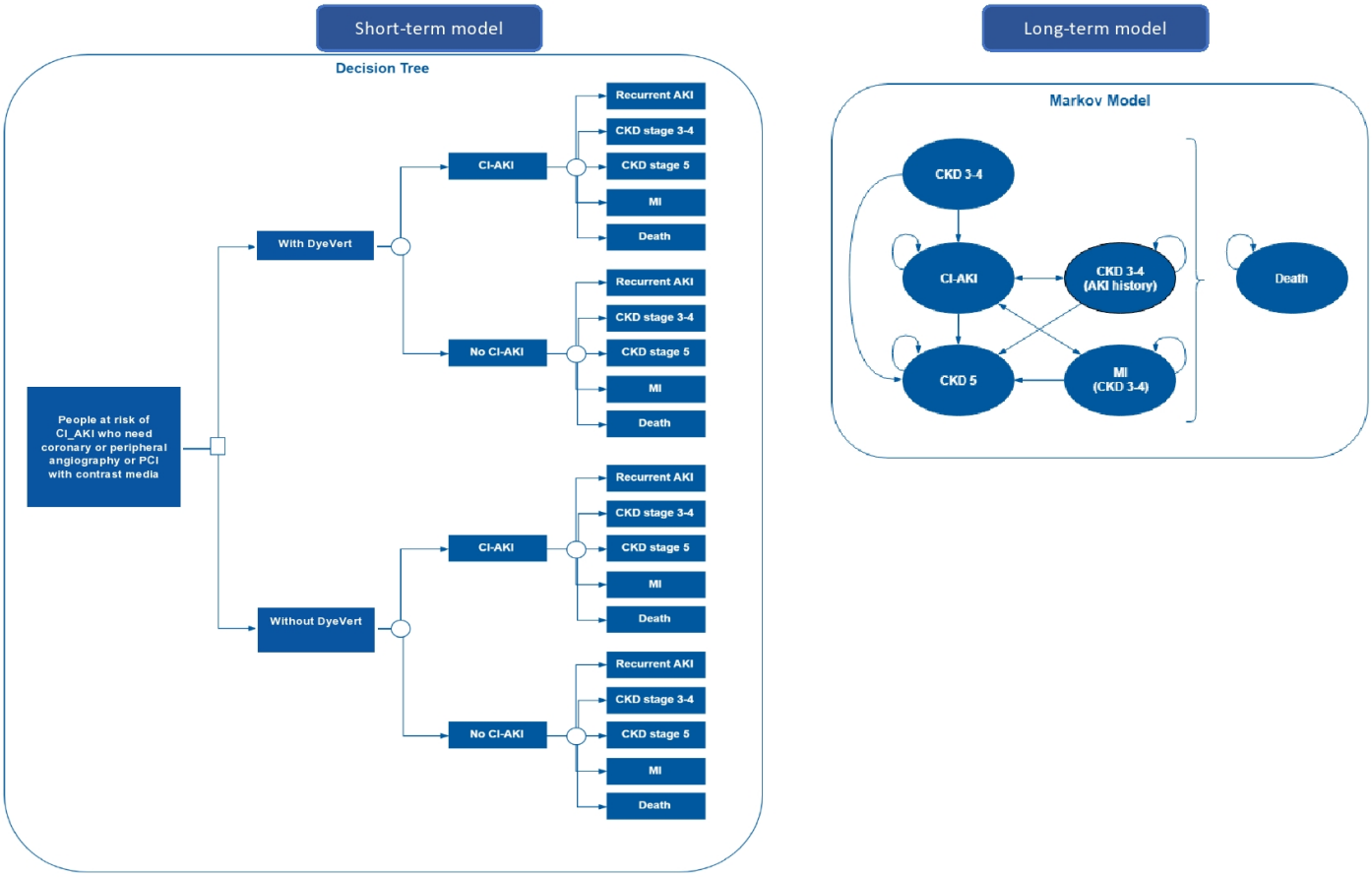
Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).



Structured abstracts for unpublished studies

Appendix B: Model structure

Please provide a diagram of the structure of your economic model.



*CI-AKI = contrast-induced acute kidney injury, CKD = chronic kidney disease, CM = contrast media, MI = myocardial infarction, PCI = percutaneous coronary interventions

Appendix C: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No ☐ If no, please proceed to declaration (below)

Yes ☒ If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document, and match the information provided in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
6,7,11,12,13,58	☒ Commercial in confidence ☐ Academic in confidence	Data owner request	Indefinitely

Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*: ** Must be Medical Director or equivalent*		**Date:**	Click or tap here to enter text.
Print:	Click or tap here to enter text.	**Role / organisation:**	Click or tap here to enter text.

Contact email: Click or tap here to enter text.

National Institute for Health and Care Excellence

Collated comments table

MTG Medtech Guidance: GID-MT550 Dyevert

Expert contact details and declarations of interest:

Expert #1	Dr Bella Huasen, Lancashire University teaching health trusts NHS
	Nominated by: BSIR
	DOI: NONE
Expert #2	Daniel Conroy, Consultant Radiologist, Belfast Health and Social Care Trust
	Nominated by: BSIR
	DOI: NONE
Expert #3	Dr Yahya al-Najjar, Consultant Interventional Cardiologist, Manchester University NHS Foundation Trust
	Nominated by: NICE (from MIB)
	DOI: Non-financial professional interest as co-author of a scientific paper
Expert #4	Professor Azfar Zaman, Consultant Cardiologist, Freeman Hospital, Newcastle upon Tyne,
	Nominated by: NICE (from MIB)
	DOI: Non-financial professional interest as co-author of a scientific paper
Expert #5	Dr Sudhir Rathore, Consultant Cardiologist, NHS Frimley Health Foundation Trust
	Nominated by: NICE (from MIB)
	DOI: NONE
Expert #6	Mark Devonald, Consultant Nephrologist, Liverpool University Hospitals Foundation Trust
	Nominated by: NICE
	DOI: Co-inventor on a patent for urinary biomarkers for the early detection of acute kidney injury.

1	Please describe your level of experience with the procedure/technology, for example:	Expert #1: Yes – Key opinion leader in interventional and endovascular procedures where contrast is used daily as part of the work.

	Are you familiar with the procedure/technology? Have you used it or are you currently using it? Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake? Is this procedure/technology performed/used by clinicians in specialities other than your own? − If your specialty is involved in patient selection or referral to another specialty for this procedure/technology, please indicate your experience with it.	No I do not have this system.
		Expert #2 I have never used this device in my currently clinical practice as an interventional radiologist. I am unaware of its use in other interventional radiology or cardiology departments in the UK. According to information on the NICE website, in Nov 2019 it was in use in 5 hospitals in the UK. I am familiar with standard methods of contrast injection using a standard contrast injection pump. All interventional radiology and cardiology departments across the UK would use the above as a baseline device.
		Expert #3 I have used the technology and have demonstrated it at a UK national live conference (Heart Live). I am not currently using it as it is going through our procurement process. It is used in a handful of centres in a limited fashion (in those patients with significant renal impairment).
	−	Expert #4 I have evaluated the device as part of a technology assessment exercise in approximately 10 patients. I am not currently using. It is a simple and effective (at reducing contrast load) device. I am not aware of any centres using this device routinely.

	–	Expert #5 Yes, Familiar with the technology. Yes, used in several cases Being used by several operators in my trust and have heard of usage in other hospitals
	–	Expert #6 I am a nephrologist with a particular interest in acute kidney injury (AKI), including contrast associated AKI (CA-AKI) which is relevant to this technology. I am not familiar with this particular device and, as I am not a cardiologist, I would not personally use it, but I am frequently consulted by cardiologists about the risks of CA-AKI. I have developed local and national guidelines (including with NICE) on CA-AKI (e.g. NICE CG169 management of AKI and DAP43, point of care serum creatinine testing for contrast studies). My research programme on AKI has included studies on patients undergoing coronary angiography. As a nephrologist I don't use it nor would I if adopted more widely. I am not aware of its use in the NHS but I would not necessarily know. The technology would be used by interventional cardiologists not by nephrologists. My specialty is involved in decisions about assessing risk of undergoing procedures involving intravascular contrast, including coronary angiography.
2	– Please indicate your research experience relating to this procedure (please choose one or more if relevant):	Expert #1: I have done research on this procedure in laboratory settings (e.g. device-related research). I have done clinical research on this procedure involving patients or healthy volunteers.
		Expert #2 I have done bibliographic research on this procedure. I have done research on this procedure in laboratory settings (e.g. device-related research). I have done clinical research on this procedure involving patients or healthy volunteers. I have published this research. I have had no involvement in research on this procedure.

		Expert #3 I have not been involved with any research using it.
	–	Expert #4 I have not been involved in R&D projects specific to this device.
	–	Expert #5 No
	–	Expert #6 I have done bibliographic research on this procedure – **not on this procedure but on the wider subject of contrast associated AKI.** I have done research on this procedure in laboratory settings (e.g. device-related research). I have done clinical research on this procedure involving patients or healthy volunteers. – **not on this procedure but I have led clinical research investigating biomarkers to detect AKI in patients undergoing coronary angiography.** I have published this research – **the above clinical research is currently being written up for publication** I have had no involvement in research on this procedure.

Current management

3	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design? Which of the following best describes the procedure (please choose one):	Expert #1: Definitely novel and of uncertain safety and efficacy.
		Expert #2 Established practice and no longer new. A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy. Definitely novel and of uncertain safety and efficacy. The first in a new class of procedure.
		Expert #3 It is a novel concept.
		Expert #4 It is a novel yet simple design with no competitors.
		Expert #5 This appears to be a novel concept as this reduces the amount of contrast given to the patient.
		Expert #6 Established practice and no longer new. A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy. – **in terms of risk of AKI, I would say this represents a minor variation because recent evidence suggests that the risk of contrast-induced AKI is low, particularly in patients who have moderate to good renal function (GFR >30 mL/min). For patients with GFR <30 mL/min the degree of risk from contrast procedures remains debatable but it is probably not high.**

		Definitely novel and of uncertain safety and efficacy. The first in a new class of procedure.
4	Does this procedure/technology have the potential to replace current standard care or would it be used as an addition to existing standard care?	Expert #1: an addition to existing standard care
		Expert #2 This would be used as an addition to the current standard of care in a select group of patients
		Expert #3 It is in addition.
		Expert #4 Addition
		Expert #5 This will be addition to the current care.
		Expert #6 Probably an addition to standard care for a limited proportion of patients, namely those with advanced chronic kidney disease and/or other risk factors for AKI.

Potential patient benefits

5	Please describe the current standard of care that is used in the NHS.	Expert #1: Dose calculation per weight or per scan to the amount of contrast used…or as required in a procedure.

		Expert #2 Standard non-disposable contrast injection pump with larger initial outlay but little or no per-patient costs.
		Expert #3 not asked
		Expert #4 not asked
		Expert #5 not asked
		Expert #6 This is best answered by an interventional cardiologist but my understanding is that the minimum volume of contrast required for adequate imaging would be administered manually.
6	Are you aware of any other competing or alternative procedure/technology available to the NHS which have a similar function/mode of action to this? If so, how do these differ from the procedure/technology described in the briefing?	Expert #1: No
		Expert #2 Not using iodinated contrast An alternative method of contrast injection is using an injection of CO2 (carbon dioxide). This eliminates the need for nephrotoxic contrast. At source dilution of contrast with saline can also reduce the volume of contrast given without reduction in image quality.
		Expert #3 I am not aware of any.
		Expert #4

		No
		Expert #5 Not aware of any other similar technology
		Expert #6 No
7	What do you consider to be the potential benefits to patients from using this procedure/technology?	Expert #1: Reduction of contrast = reduction in kidney injury, and reduced fluid volume in those with fluid restriction (dialysis patients/cardiac patients)
		Expert #2 This procedure should reduce the amount of renal toxic contrast injected into the patient. This is turn should reduce the risk of renal failure in at risk patients.
		Expert #3 Reduced contrast load and thus less risk of contrast induced nephropathy.
		Expert #4 Minimising contrast media load in patients with reduced renal function undergoing invasive coronary angiography procedures.
		Expert #5 This technology reduces the amount of contrast given to the patient.
		Expert #6 For a few patients who have a high risk of AKI (e.g. those with stage 4 and 5 chronic kidney disease) there may be some benefit in ensuring that the minimum amount of contrast is delivered, but I am not aware of any convincing evidence to support this.

Potential system impact

8	Are there any groups of patients who would particularly benefit from using this procedure/technology?	Expert #1: Cardiac failure, Renal patients, Allergy patients
		Expert #2 Those with chronic kidney injury who are not currently receiving renal replacement therapy, e.g. dialysis.
		Expert #3 Patients whose renal function is impaired (eg CKD stage 3b) and patients whose procedures are done by new trainees (they tend to inject more dye than experienced operators).
		Expert #4 Those with reduced renal function and patients undergoing prolonged procedures requiring large volumes of contrast media eg CTO procedures.
		Expert #5 Patients with Kidney impairment and failure.
		Expert #6 Possibly those at high risk of AKI such as those with stage 4 or 5 CKD
9	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system?	Expert #1: Potentially yes
		Expert #2 This technology could reduce the incidence of acute on chronic renal failure with can lead to a significant burden on the healthcare system in the short and long term.

	Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	Expert #3 Yes. If it leads to less clinically relevant contrast induced nephropathy (CIN). CIN is a serious issue in patients with renal function and results in a small proportion of these patients requiring multiple hospital visits and very rarely dialysis.
		Expert #4 Yes it has the potential to improve clinical outcomes in the above patients and reduce hospital stay and progression to renal failure.
		Expert #5 This could potentially reduce incidence of contrast nephropathy in select group of patients and thereby improving the outcomes.
		Expert #6 If it did reduce the incidence of AKI then that would be a definite benefit because AKI is associated with increase mortality, increased length of hospital stay, increased risk of developing CKD and end stage kidney disease. AKI costs the NHS probably in excess of £1 billion per year. However, it is not clear to me that this technology would decrease the incidence of AKI.
10	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the procedure/technology likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting etc)	Expert #1: If reduces contrast used and injury overall would be cost effective
		Expert #2 Initial outlay is likely to lead to increased cost per procedure. It is unclear whether this will be balanced by a decrease in long term costs from chronic healthcare issues.
		Expert #3 It is likely to cost more if adopted liberally. If strict criteria are applied for use then it could be cost neutral in the longer run.

		Expert #4 Whilst the device will be an additional cost, the cost benefit will need rigorous evaluation from clinical trials.
		Expert #5 Likely to cost more
		Expert #6 If it significantly reduced the incidence of AKI then very likely it would lead to a net cost saving but my guess, based on recent evidence about risk of contrast-induced AKI, is that it would not do this sufficiently to compensate for the additional cost of the technology.
11	What do you consider to be the resource impact from adopting this procedure/technology (is it likely to cost more or less than standard care, or about same-in terms of staff, equipment, and care setting)?	Expert #1: No change to current setting. I doubt it will cost more to implement.
		Expert #2 This will cost more in terms of equipment cost (£350 per patient). There should be no increased staffing cost or need for any other specialist equipment to use it.
		Expert #3 In a targeted population group with renal impairment it could potentially reduce the need for repeat blood tests and hospital visits/admission.
		Expert #4 There are no resource implication beyond the device itself.
		Expert #5 No significant impact
		Expert #6 More.

12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	Expert #1: Just the system itself and staff training to use it
		Expert #2 None
		Expert #3 Minimal training of cath lab staff in set up of the equipment
		Expert #4 No
		Expert #5 Training of the personnel involved required but easy to use device and no extra risk to the patient.
		Expert #6 This is best answered by a cardiologist but, from reading about the device, it looks like it would not complicate the procedure significantly.

General advice

13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	Expert #1: With any new device training is always required. Though I don't envisage this to be cumbersome with this system.
		Expert #2 Yes, this is a new technology and local training needed prior to use in patients.

		Expert #3 Minimal training of cath lab staff in set up of the equipment
		Expert #4 No
		Expert #5 Training of the personnel involved required but easy to use device and no extra risk to the patient.
		Expert #6 I defer to cardiology opinion

Other considerations

14	What are the potential harms of the procedure/technology? Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence: Adverse events reported in the literature (if possible, please cite literature) Anecdotal adverse events (known from experience) Theoretical adverse events	Expert #1: Technology break down. Poor trouble shooting pathways. Air bubbles?
		Expert #2 Inadequate image quality resulting in repeat contrast administration leading to an increase in total contrast used. There will not be any increase in adverse reactions from drugs administered.
		Expert #3 not asked

		Expert #4 not asked
		Expert #5 not asked
		Expert #6 Presumably the risk of administering an excessive or an inadequate amount of contrast, but I defer to cardiology again.
15	Please list the key efficacy outcomes for this procedure/technology?	Expert #1:
		Expert #2 Reduction in acute kidney injury in at risk patients Cost effectiveness
		Expert #3 not asked
		Expert #4 not asked
		Expert #5 not asked
		Expert #6 Incidence of contrast induced AKI – but the true incidence of this is likely to be low to start with.
16		Expert #1:

	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	Expert #2 I am not sure of any published data on its use in peripheral angiography. Potential benefits in this setting are theoretical.
		Expert #3 Not aware of any.
		Expert #4 No
		Expert #5 None
		Expert #6 not asked
17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	Expert #1:
		Expert #2 No
		Expert #3 not asked
		Expert #4 not asked
		Expert #5 not asked

		Expert #6 The uncertainty is really whether contrast induced AKI is a significant clinical problem. If it is not, then presumably it would not be cost effective to spend limited resources on trying to reduce it.
18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please choose one):	Expert #1: Most or all district general hospitals.
		Expert #2 Most or all district general hospitals. A minority of hospitals, but at least 10 in the UK. Fewer than 10 specialist centres in the UK.
		Expert #3 not asked
		Expert #4 not asked
		Expert #5 not asked
		Expert #6 Most or all district general hospitals – **most hospitals with interventional cardiology**. A minority of hospitals, but at least 10 in the UK. Fewer than 10 specialist centres in the UK.

		Cannot predict at present.
19	Please list any abstracts or conference proceedings that you are aware of that have been recently presented / published on this procedure/technology (this can include your own work). Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings which might not be found using standard literature searches. You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important.	Expert #1: J Invasive Cardiol. 2019 Sep;31(9):253-259. Use of the DyeVert System in Chronic Total Occlusion Percutaneous Coronary Intervention
		Expert #2 I am not aware of any.
		Expert #3 not asked
		Expert #4 not asked
		Expert #5 not asked
		Expert #6
20	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list.	Expert #1: Not that I am aware
		Expert #2 I am not aware of any.
		Expert #3 not asked
		Expert #4 not asked

		Expert #5 We will be conducting Audit at our centre in future.
		Expert #6 not asked
21	Approximately how many people each year would be eligible for an intervention with this procedure/technology, (give either as an estimated number, or a proportion of the target population)?	Expert #1: Every interventional procedure that uses contrast (endovascular, renal, cardiology, neuro intervention etc) It's a lot so I'm uncertain but it's large
		Expert #2 5000 per year in the UK (4000 in the cardiology setting, 1000 in the peripheral angiographic setting)
		Expert #3 I would estimate that 5-15% of patients undergoing coronary intervention/angiography would be eligible. As mentioned above though this is on the assumption of use in patients with CKD stage 3+
		Expert #4 I estimate 20% of all patients undergoing invasive coronary angiography
		Expert #5 10-20% of patients coming for coronary or peripheral procedures.
		Expert #6 I defer to cardiology but many thousands of patients undergo coronary angiography each year.

22	Are there any issues with the usability or practical aspects of the procedure/technology?	Expert#1Uncertain there is
		Expert#2 This is a new technology and therefore local training would be needed prior to use in patients.
		Expert#3 Not really
		Expert #4 No
		Expert #5 Some training required.
		Expert #6
23	Are you aware of any issues which would prevent (or have prevented) this procedure/technology being adopted in your organisation or across the wider NHS?	Expert#1 Expense (I don't know the cost)
		Expert#2 No.
		Expert#3 Cost
		Expert #4
		Expert #5 No issues identified.
		Expert #6 Again, the issue of whether CI-AKI is a significant problem.

24	Is there any research that you feel would be needed to address uncertainties in the evidence base	Expert#1 It really needs to show there is a reduction in contrast use without impacting quality of work
		Expert#2 Clarity of cost effectiveness. i.e. cost of device against cost of acute renal failure
		Expert#3 Would be good to have an outcome randomised control trial in patients with CKD stage3+
		Expert #4 Yes, randomised study to assess
		Expert #5 Prospective multi-centric registries will be beneficial.
		Expert #6 An updated review of incidence, outcomes and risk factors for contrast-induced and contrast-associated AKI.
25	Please suggest potential audit criteria for this procedure/technology. If known, please describe: − Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures and patient-related outcomes. Please suggest the most appropriate method of measurement for each and the timescales over which these should be measured. − Adverse outcome measures. These should include early and late complications.	Expert#1 Beneficial outcome measures: Reduction in contrast use. No compromise to image quality/work quality. Adverse outcome measures: No break down in the system that maybe expelled into the patient.

	Please state the post procedure timescales over which these should be measured	No gas bubble issues.
		Expert#2 Beneficial outcome measures: Reduction in acute kidney injury in those patients most at risk, Adverse outcome measures: Decrease in image quality through use of decreased contrast administration
		Expert#3 not asked
		Expert #4 not asked

		Expert #5 not asked
		Expert #6 Beneficial outcome measures: Reduction in hospital admissions and length of stay Reduction in average volume of contrast used Adverse outcome measures: Incidence of AKI by KDIGO criteria Incidence of admission to hospital within 7 days of procedure Incidence of requirement for renal replacement therapy (RRT) Effect on eGFR 3 months after procedure
26	Please add any further comments on your particular experiences or knowledge of the procedure/technology,	Expert#1 I have not used this system
		Expert# 2 In summary: This is a device that could be used in approximately 5000 patients per year in the UK. I have no personal experience of use of this device. There is limited published evidence of use in the cardiology setting but I am not sure of any published evidence of use in the peripheral angiography setting.

		The device has the potential to reduce the risk of acute kidney injury but only in a select group of patients and would not become the standard of care in patients undergoing angiography. The device has a reasonable per patient cost of £350 in comparison to negligible per patient cost of current techniques. The device could reduce the cost of ongoing management of acute and permanent renal failure. Alternative methods of reducing nephrotoxic contrast volume already exist in the form of dilution, radiographic technique optimisation or the use of CO2 angiography. Cost effectiveness should be confirmed. There are minimal risks of harm from the use of this device.
		Expert#3 not asked
		Expert #4 not asked
		Expert #5 not asked
		Expert #6 My comments are directed towards the renal aspects of the technology rather than having any expert knowledge of practicalities of interventional cardiology.

NICE National Institute for Health and Care Excellence

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

External Assessment Centre Report factual check

DyeVert for reducing contrast media in coronary and peripheral angiography

Please find enclosed the assessment report prepared for this assessment by the External Assessment Centre (EAC).

You are asked to check the assessment report from [insert EAC] to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 12pm, **26 March 2021** using the below proforma comments table. All your comments on factual inaccuracies will receive a response from the EAC and when appropriate, will be amended in the EAC report. This table, including EAC responses will be presented to the Medical Technologies Advisory Committee and will subsequently be published on the NICE website with the Assessment report.

23 March 2021

Issue 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 9 paragraph 3, first sentence "…and mean baseline eGFR (43 – 103 ml/min/1.73m^2)"	CHANGE TO: "…and mean baseline eGFR (43 – **74** ml/min/1.73m^2)"	We do not see a paper reporting a mean baseline eGFR of 103. Briguori's population had the highest mean baseline eGFR.	Thank you for your comment. You are correct, this is a mistake and has been amended throughout.

Issue 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 9 "Again, this is not unexpected; the company suggest that only 10% of their users are using the DyeVert Power XT system."	**Remove statement**	Statement is inaccurate to what the company believes. The company provided estimated market use of *power injectors* vs manual injection and did not provide estimate of DyeVert system use.	Our apologies, we misunderstood this, this has been amended throughout.

Issue 3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 9 last paragraph, first sentence "Mean volume was between 17 – 41% in the DyeVert groups in the comparative studies."	CHANGE TO: "Mean **CMV injected ranged from around** 17% to 41% **less** in the DyeVert group in the comparative studies **(EAC calculated)**."	This sentence is incomplete and does not reflect the source.	Thank you, we have added "(EAC Calculated)".

Issue 4

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 10 "However, there is considerable uncertainty on both the baseline risk of CI-AKI and the effectiveness of hydration measures to reduce this risk."	**Remove statement**	See rationale below and statement is misleading that baseline risk was conservatively considered only in context of CKD and did not account for other comorbidities; and the intent of the economic analysis was not to compare to hydration.	Thank you for your comment. We discussed baseline risk of CI-AKI with several clinical experts, particularly in relation to an evidence review produced as part of the production of the NICE Guideline NG148, which suggested that oral hydration strategies should be used and that the baseline risk may be as low as 2.74% (see page 65 of the assessment report). We concluded that this figure was unlikely to be realistic for several reasons but also concluded that the baseline risk in real practice is uncertain – this is reflected in the economic analysis.

Issue 5

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 10 "In these patients DyeVert is unlikely to be cost saving and may not be cost-effective. Further evidence on the absolute risk of CI-AKI would be required to identify	ADD/CHANGE TO: In these patients DyeVert is unlikely to be cost saving and may not be cost-effective. **However, in patients with additional co-morbidities under validated CI-AKI risk scores, CKD patients may have risk greater than 8%.** Further evidence on the absolute risk of CI-AKI in a CKD stage	See rationale below and statement is misleading that EAC assessment baseline risk is a calculated economic percentage based on the conservative consideration of CKD stage only and does not account for additional co-morbidities. Taking into account co-morbidities it is most likely that stage 3 CKD	Thank you for your comment. We agree that there is uncertainty around this and have not found strong evidence on the baseline risk of CI-AKI, especially not for particular subgroups. We have amended this slightly to read: "It seems probable that the risk of CI-AKI

this subgroup with confidence."	category would be required to identify risk **differentially and by percentage** under each subgroup confidently; **however there are no available clinical criteria for this activity at this time."**	patients would qualify for a greater than 8% risk of CI-AKI. And there are no current clinical criteria to further stratify CKD stage categories for CI-AKI risk.	in some patients with well managed CKD disease, **and no other risk factors** undergoing peripheral angiography may be below 8%."

Issue 6

Description of factual inaccuracy	**Description of proposed amendment**	**Justification for amendment**	**EAC response**
P 15 "…a small grove is present to allow for the difference in dye flow rate."	CHANGE TO: " **a minor adjustment** is present to allow for the difference in dye flow rate."	Please adjust to address to reflect more accurately the difference between the systems.	Thank you, we have accepted this change.

Issue 7

Description of factual inaccuracy	**Description of proposed amendment**	**Justification for amendment**	**EAC response**
P. 17 "Iodine-based CM are administered intravenously for use in x-ray based image modalities such as angiography…"	CHANGE TO: "Iodine-based CM are administered for use in x-ray based image modalities such as angiography…" **Language deleted.**	Angiography is an intra-arterial CM administration; not intravenous.	Thank you, we have accepted this change.

Issue 8

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 19 “The company suggest that DyeVert is not suitable as a replacement for hydration in patients at risk of AKI.”	CHANGE TO: “The company suggests that DyeVert is a preferred approach when replacement for hydration in patients at risk of AKI is not suitable; **but does not consider it a substitute for hydration. And that lack of hydration does not preclude the use of DyeVert.”**	To better reflect the company’s position	This now reads: “The company does not consider DyeVert a suitable substitute for hydration in general but suggests that it can be used as a replacement in patients at risk of CI-AKI in whom hydration is not suitable.” We hope this reflects the company’s position better.

Issue 9

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 2. Participants and setting, We note high risk patient comorbidities are missing from this table beyond age and eGFR while pages 16 and 17 list high risk criteria from NICE guidelines	CHANGE TO: ADD: **Table 1 and 2 of the clinical submission specifically detail patient comorbidities that can be added for each study included.**	Per NICE guidance, eGFR and age are not the only high-risk attributes for CI-AKI. See comment below regarding risk determination and comorbidities.	Thank you for your comment. This table only records age, sex and eGFR as these were consistently reported in the literature. Others were less consistent and were left out to keep the table concise. Where comparative studies reported p values for other baseline characteristics, these were reported in the table if significant. We realise that diabetes, heart failure, hypotension, and MEHRAN risk score (for example) are also reported in some cases, but for this table we have included age, sex and eGFR as standard as these are almost always present in the published papers.

Issue 10

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 22, 4th column, "AKI (≥0.5 mg/dL increase in serum creatinine) at discharge was reported in 11 participants (9.6%)…" **p45, last row of the table, same sentence**	CHANGE TO: "AKI (>0.**3** mg/dL increase in serum creatinine through discharge) was reported in 11 participants (9.6%)…"	Typo correction	Thank you for your comment, this has been corrected.

Issue 11

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 22, 4th column, "Overall difference in CMV per procedure : 40.1ml ± 8.8% (95% CI: 38.4, 41.8; P < 0.0001). **p. 45 last row, same sentence**	CHANGE TO: "Overall **percentage of** contrast volume saved was 40.1 ± 8.8% (95% CI: 38.4, 41.8; P < 0.0001).	Clarification of the outcome and remove ml which is inaccurate.	Thank you for your comment, this has been corrected.

Issue 12

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p.29, Column 3 (outcomes) "Mean CMV saved in DyeVert group: 125.81 ± 47.10 mL (97.5% CI: 158.62 – 273.79), or 37.5 ± 5.3% per procedure."	Change to: "Mean CMV saved in DyeVert group: 125.81 ± 47.10 mL (97.5% **CI: 95.29–156.33**), or 37.5 ± 5.3% per procedure."	Typo correction	Thank you for your comment, this has been corrected.

Issue 13

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p.29, Column 3 (outcomes) secondary endpoint missing	CHANGE TO: ADD: **Results from quantified OCT analysis suggest that the clear region of interest (ROI) in the DyeVert group was non-inferior (p < .0001) to the control group. For all (100%) of the 15 procedures, physicians described the quality of images acquired during use of the DyeVert System as acceptable.**	Additional endpoints are included but the secondary endpoint is missing leading to incomplete data regarding quality image.	Thank you, we have added: "Analysis of OCT images showed the clear region of interest (ROI) in the DyeVert group was non-inferior (p < 0.0001) to the control group. Clinicians described all images in the 15 DyeVert procedures as acceptable." to the table.

Issue 14

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 34, 3rd column (participants and setting) Baseline eGFR was 103 ± 61ml.	CHANGE TO: "Baseline eGFR was **43 ± 13** ml".	The original data is actual contrast volume injected data, not baseline eGFR data.	Thank you for your comment, this discrepancy has been amended throughout and baseline eGFR added here.

Issue 15

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 35 Kutschman 2019b, AKI Incidence "…was an overall 33% relative reduction in AKI compared to the cohort in which DyeVert was not used (6.9% vs 10.3%, respectively)."	CHANGE TO "…**was in the Protocol Followed cohort, the overall relative reduction in AKI was 61% compared to the Protocol Not Followed cohort (p<0.02**).	AKI incidence is incorrectly reported	Thank you for your comment. The 2019b poster reports a figure of 33% - the 2019a abstract reports the 61% figure (and 57% when DyeVert was used, which is reflected in the table).

Issue 16

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p.38, EAC comments, Abstract only	CHANGE TO: "T**his study has been reported through an abstract and a poster."**	Like Cameron et al, this study was reported through an abstract and a poster.	Thank you, we have removed this comment.

Issue 17

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p.43, second paragraph "Mean baseline eGFR ranged from 43ml/min/1.73m2 (Gurm 2019a) to 103ml/min/1.73m2 (Kutschman 2019a), **p. 53 third paragraph, same sentence**	CHANGE TO: "Mean baseline eGFR ranged from 43 ml/min/1.73m2 (Gurm 2019a) to **74 ml/min/1.73m2 (Briguori 2020)"**	The original data is actual contrast volume injected data, not baseline eGFR data.	Thank you, this has been amended throughout.

Issue 18

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p.43, second paragraph, "Notably, Gurm had the oldest, most male population, along with the lowest mean eGFR and highest level of serum creatinine,	CHANGE TO: "**All studies include patients with attributes listed in the NICE AKI guidance as CI-AKI risk factors. CI-AKI risk factors under validated risk**	CI-AKI risk cannot be assessed by just age and eGFR. All of the studies included patients with various combinations of high-risk CI-AKI criteria. The Tajti paper had the highest percentage of male patients at 82%. The Sattar publication had a population with a mean eGFR of 43.3 and Kutschman 2019a had a mean eGFR of 43, similar to the Gurm paper. The Rao publication included the highest percentage of patients with diabetes and heart failure. Kutschman, Bunney, Rao, and Sattar all had populations with a higher proportion of diabetes patients compared to the Gurm paper. In addition, as noted in the business case for the adoption of the DyeVert System as well as Osprey Medical's response to the scope assessment, the risk of CI-AKI is variable with rates varying from 3%-37%	Thank you, this has been amended to: "Notably, Gurm had the oldest, most male population, along with the lowest mean

meaning that it included a higher-risk population than the other studies."

scores include age, diabetes, moderate and severe CKD, MI on presentation, Anemia, Heart Failure, IABP prior to procedure, STEMI, Cardiogenic Shock and CHF".

(Tsai 2014 JACC, Brown 2016, Prasad 2019), the incidence of CI-AKI is increasing due to multifactorial causes including age and CKD [but not limited to].

Published validated risk models determined age, diabetes, moderate and severe CKD and heart failure on presentation as the leading factors for when to consider renal protection measures such as contrast minimization tools and processes. The validity of the data is recognized through the international adoption of the scientific recommendations to reduce contrast volume as a primary modifiable factor in the reduction of CI-AKI. The enclosed table summarizes key publications citing patient risk factors to consider when considering the use of strategies to reduce contrast use. The Tsai model is a validated risk score.

		Patient Risk Factors											
Risk Model reference	**Referenced Publication**	**Age**	**Hypotension**	**Diabetes**	**Moderate CKD**	**Cardiac Arrest on Presentation**	**Anemia**	**Heart Failure on Presentation**	**IABP prior to procedure**	**STEMI**	**Cardiogenic shock**	**Severe CKD**	**CHF**
NCDR Prediction Score	Tsai et al. 2014. J AM Heart Assoc.3:e001380 doi/JAHA.114.00.001380	X		X	X	X	X	X	X	X	X	X	
Mehran Risk Score	Mehran et al. 2004. J AM Coll Cardiol;44:1393-9	X	X	X	X		X		X			X	X
CIN Calculator	Gurm et al. 2013. J AM Coll Cardiol; 61:2242-8	X		X	X	X	X	X		X	X	X	
Freeman	Kooman and Gurm. 2014 Intervent Cardiol Clin 3l 369-377			X				X			X	X	
Bartholomew				X	X			X	X			X	
Merenzi		X				X			X				
Brown		X		X	X			X	X			X	
Maioli		X		X	X			X				X	
Tziakas					X							X	
Chen		X		X	X		X	X				X	

The EAC analysis states the DyeVert begins to save money as the risk of CI-AKI climbs above 8%; and EAC analysis states there are incidences of CKD patients falling within risk of below 8%.

eGFR and highest level of serum creatinine, meaning that it included a population that **may be at a higher-risk than the other studies**."

Please also see our responses to issues 4 and 5.

		To identify risk of CI-AKI with confidence, Osprey Medical strongly suggests that comorbidities as presented in AKI risk validated models are used to identify at risk patients.	

Issue 19

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 3, Procedure time being included instead of a more meaningful outcome like Proportion of the population staying at or below 3x CMV/eGFR ratio	Replace Procedure Time column with a more meaningful outcome such as proportion of the population staying at or below 3x CMV/eGFR ratio	A central benefit of the use of DyeVert is being able to move a greater proportion of the population to lower CMV/eGFR ratios which are associated with lower CI-AKI rates. The statement of procedure time out of context of the fluoroscopy time is misleading and not applicable; and does not account for when the device is used (only during fluoroscopy time).	Thank you for comment. We have removed the procedure time column. In general, we include any outcome that has been reported by several studies in the table. We agree that the procedure time outcome does not have any bearing on the decision problem. CMV/eGFR ratio's have been included in the contrast volume column.

Issue 20

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 45 Gurm, Image Quality Not Reported	CHANGE TO: "**Image quality maintained in 113/114 cases**"	Gurm reported in the publication: Image quality was maintained in all but one diagnostic + PCI case where the DyeVert System was turned off for 1 injection only and then resumed using the DyeVert System for the remainder of the case.	Thank you, this has been amended.

Issue 21

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p.46, Bruno, Image Quality Not Reported	CHANGE TO: **"Clinicians noted no loss in image quality**"	Bruno reports in this paper: The use of the DyeVert Power XT in combination with the ACIST automated injector results in clinically meaningful contrast volume savings, *without loss of image quality in this patient sample.*	Thank you, this has been amended.

Issue 22

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p.46, Sapontis, Procedure Time Not Reported	CHANGE TO: "**Mean ± SD: 20.2 ± 22.9 (Min, Max): (3, 87**)"	Provided in the publication	Thank you, we have removed this column.

Issue 23

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p.46, Corcione, Image Quality Not Reported	CHANGE TO: "**Clinicians noted no loss in image quality**."	Authors note in the paper: All procedures were successfully completed with adequate and high-quality angioscopic and angiographic images.	Thank you, this has been added.

Issue 24

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p.46, Briguori, Image Quality Not Reported	CHANGE TO: "**Clinicians noted no loss in image quality."**	Briguori reported in the publication: The DyeVert system was not turned off under any circumstances due to inadequate/poor image quality or other device-related reasons.	Thank you, this has been added.

Issue 25

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 47, Zimin, Image Quality Not Reported	CHANGE TO: "**Results from quantified OCT analysis by an independent core lab suggest that the clear region of interest (ROI) in the DyeVert group was non-inferior (p < .0001) to the control group. Clinicians noted no loss in image quality**."	Image quality was a secondary endpoint for this study. Authors report: Results from quantified OCT analysis suggest that the clear region of interest (ROI) in the DyeVert group was non-inferior (p < .0001) to the control group. For all (100%) of the 15 procedures, physicians described the quality of images acquired during use of the DyeVert System as acceptable.	Thank you, this has been added.

Issue 26

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p.47 "Procedure time was significantly longer in the DyeVert group, 220 minutes (IQR, 128 - 294) vs 152 minutes in the non-DyeVert Group (IQR, 100 - 225, p=0.03). "	CHANGE TO: "Procedure time was significantly longer in the DyeVert group, 220 minutes (IQR, 128 - 294) vs 152 minutes in the non-DyeVert Group (IQR, 100 - 225, p=0.03, **however fluoroscopy time was equivalent in the non-DyeVert Group (28-73, p=.20)."**	The statement of procedure time out of context of the fluoroscopy time is misleading and not applicable; and does not account for when the device is used (only during fluoroscopy time).	Thank you – we have removed this column.

Issue 27

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 49 Rao, AKI incidence Not Reported	CHANGE TO: "**No patients had worsening of renal function post-procedure**."	In the poster, the author states: No patients had worsening of renal function post-procedure.	Thank you, this has been added.

Issue 28

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 49 Tucker & Turner, Contrast Volume Not Reported	CHANGE TO: "**Mean contrast savings of 42 ± 28 ml per case**"	Authors present this data in the poster	Thank you, this has been added.

Issue 29

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p.49 Kutschman 2019b, Contrast volume Not reported	CHANGE TO: "**Mean contrast savings of 58 ml or 40% per case"**	Data presented in the poster.	Thank you, this has been added.

Issue 30

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 52 “The evidence base is almost completely comprised of data from outside of the UK (largely the US and Germany), meaning that it may not be generalisable to the NHS.”	CHANGE TO: “The evidence base is almost completely comprised of data from outside of the UK (largely the US and Germany).” **Language deleted.**	The language removed is inaccurate in that it is contradictory to EAC expert confirmed generalizability between developed nations.	Thank you for your comment. Despite the expert’s comments, it should still be noted that the evidence base **may** not be generalisable. Practice may be similar, but setting must still be noted.

Issue 31

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 54 “The diversion mechanism is almost identical to that used in the manual injection system; however, it is not clear if the difference in injector would affect clinical results.”	CHANGE TO: “The diversion mechanism is almost identical to that used in the manual injection system. **Language deleted.**	The language removed is inaccurate in that it states that the difference of clinical results is not clear; however, the clinical result is strictly based on the mechanism to decrease contrast volume and that has been demonstrated to be equivalent to the other DyeVert Systems. Also, Osprey Medical has provided NICE information that the devices perform equivalently.	Thank you for this comment. The report notes that % saving in CMV is similar between the systems. However, there is limited published clinical evidence that the systems perform equivalently, and this must be noted.

Issue 32

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 55 “Two studies (Tajti 2019 and Zimin 2020) reported that procedure time with the DyeVert System was increased (220 vs 152 minutes, p=0.03; 63 vs 48 minutes, p=0.09, respectively). Tajti et al. 2019 investigated DyeVert during CTO PCO, while Zimin et al. 2020 reported cases of OCT for diagnostic PCI.”	**Remove statement**	The statement is misleading in that it suggests the device should have influence over overall procedure time and the device is only used during set up and fluoroscopy time which has been shown to be equivalent with non-DyeVert procedures.	Thank you for your comment. We have added: “It should be noted, however, that fluoroscopy time was shown to be equivalent in both groups in Desch et al. 2018.”

Issue 33

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P. 55” The company believes that the Power XT system makes up around 10% of the systems being used.”	CHANGE TO: The company believes that **power injector use in the UK makes up around 10% of the market.**	Statement is inaccurate to what the company believes. The company provided estimated market use of power injectors vs manual injection and did not provide estimate of system use.	Thank you for your comment and apologies for the misunderstanding – this has been amended throughout.

Issue 34

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
p. 56 “which differs from the company suggestion that DyeVert be used in patients with CKD stage 3+ (i.e. eGFR<30).”	CHANGE TO: which differs from the company suggestion that DyeVert be used in patients with CKD stage 3+ (i.e. eGFR<**60**). **Typo correction**	Typo correction	Thank you for your comment, this has been amended.

Issue 35

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 6: Cost parameters used in the company’s model and changes made by the EAC	The EAC price for CI-AKI cost of index admission **should read £2834** not £2.834	Typo correction	Thank you for your comment, this has been amended.