National Institute for Health and Care Excellence

Medical technologies evaluation programme

GID-MT550 DyeVert Systems for reducing the risk of acute kidney injury in coronary and peripheral angiography
Consultation comments table

Final guidance MTAC date: 23rd July 2021

There were 20 consultation comments from 3 consultees:

- 2 Healthcare professionals
- 1 Company representative

The comments are reproduced in full and arranged in the following groups:

- Recommendations (comments 1-5, n=5)
- Clinical validity of CI AKI (comments 6-11, n=6)
- Power XT system (comments 12-13, n=2)
- At risk population (comments 14, n=1)
- Clinical evidence base (comments 15, n=1)
- Cost model and cost impact of CI-AKI (comments 16, 17, n=2)
- General comments (comments 18-20, n=3)

Comment #	Consultee ID	Role	Section	Comments	NICE response FINAL

RECOMMENDATIONS					
1	2	Health care profes sional	1.2	***Recommendations*** I would suggest most benefit is in patients undergoing coronary angioplasty as compared to diagnostic coronary angiography where relatively more contrast volume is required.	Thank you for your comment. The committee decided the recommendation should remain unchanged. Section 1.2 states that research should include people who need elective coronary or peripheral angiography. Section 4.8 of the guidance was amended to state that DyeVert Systems could be considered for procedures that are expected to use larger contrast volumes. Procedures which use larger contrast volumes, such as more complex procedures including percutaneous coronary intervention, could lead to a higher risk of AKI.
2	2	Health care profes sional	1.2	***Are the recommendations sound and a suitable basis for guidance to the NHS?*** In my view from clinical point of view Dyevert is a promising device and could be used in select group of patients with CKD undergoing coronary angioplasty (Complex coronary intervention, Acute MI angioplasty etc.), pending the results of RCT and wider adoption.	Thank you for your comment. The committee decided the recommendations should remain unchanged. Please see NICE's response to comment 1 on procedure type. Sections 1.2 and 4.11 of the guidance state that an RCT is recommended and should include people with stage 4 CKD who are at risk of AKI and need elective coronary or peripheral angiography.
3	2	Health care profes sional	1.2	***Recommendations*** RCT will be a good idea and will further explore the clinical applications and outcomes but will be time consuming and difficult to recruit patients. However, in my view DyeVert should be allowed a trial in complex coronary angioplasty procedures with CKD 4 which are anticipated to require high volume of contrast agents. Similar to being considered in complex peripheral endovascular graft procedures.	Thank you for your comment. The committee heard that recruitment could be difficult, especially as people included are likely to have multiple risk factors. However, the experts and the committee still agreed that an RCT was

					the most appropriate study design needed to address the uncertainties. The committee decided the recommendations should remain unchanged. Please see NICE's response to comment 1 and 2.
4	3	Company	1.2	***Recommendations*** Randomized clinical trials are not appropriate for the study of CI-AKI reduction through contrast volume reduction due to the multiple ethical and feasibilities factors. The subject systems pose essentially no additional risk to the patient while minimizing exposure to total contrast agent volumes during contrast injections; all while achieving the desired level of image opacification. The clinical feasibility to achieve goals as stated by NICE draft guidance is not reasonable for a low cost, low risk, disposable device that offers more benefit than risk.	Thank you for your comment. Please see NICE's response to comment 2 and 3 on the research recommendations. The committee noted that RCTs are reported in the current literature and that there is an on-going RCT being done in Italy. The committee felt that an RCT would be ethical. As a result, the committee decided to keep its recommendation for further RCT evidence. The committee acknowledged that recruitment may be challenging but felt that an RCT was still appropriate and feasible and would best address the uncertainties in the evidence. The committee decided the recommendations should remain unchanged.
5	2	Health care professional	1.1	Dyevert reduces contrast volume during coronary/peripheral angiography and angioplasty. There are several studies showing contrast volume as an important predictor of AKI following the procedures which require contrast injections. Therefore, Dyevert will be effective in patients requiring large quantities of contrast volume during coronary angioplasty and with chronic kidney disease (eGFR< 30). Therefore, DyeVert use will be clinically relevant in complex coronary angioplasty cases with underlying CKD which require large volumes of contrast volumes.	Thank you for your comment. Please see NICE's response to comment 1 and 2.
CLINICAL VALIDITY OF CI AKI					
6	1	Health care	4.1	Hope you are well, I would first like to thank you all for involving me in the above. I found it to be a great experience and enjoyed it. I wonder if I may	Thank you for your comment.

		profes sional		make a couple of comments please about the draft guidance particularly one particular aspect that worries me with the way it currently reads. I have quoted the text I am referencing and highlighted one particular area. *"However, 1 expert maintained that contrast-induced AKI has not been proven clinically, and that the link between contrast agent and AKI may only be an association. This was a key uncertainty and as a result the committee was not confident that a reduction in contrast dye received would lead to reduced incidence of AKI."* I agree with the outcome of the guidance and can see how it is in keeping with the overall discussions in the meetings except in relation to the area highlighted above. The above could be read by individuals as a green light to use as much contrast as they like based on their personal beliefs seeing as the opinion of one expert is being used as one of the "key" points to make a decision about whether contrast and contrast volume are linked to post procedure AKI. At the end of the day every country's renal, cardiac, and radiology societies recommend reducing contrast use and volume. This is echoed by the European Society of Cardiology and American equivalent. These recommendations are not made lightly but indeed are reflective of general belief and the best knowledge of a variety of experts that draft these guidance. Whereas the renal expert at this consultation maybe correct that contrast and contrast volume don't cause harm, this needs to be taken in the context of being out of line with the general consensus as evidenced by guidelines. I don't think NICE should be using this or quoting it as a "key" issue as I feel one experts personal view point is not in line with general accepted wisdom currently. Please understand that I am totally open minded to the idea that contrast may not be an issue, though my personal experience leads me to follow the accepted guidelines. We did discuss at length in our first group meeting of experts the above issue but I don't feel that in the "official" meeting we reflected these discussions well. It would have been good had there been more air time to discuss this complex issue. As an example one expert was very keen to point out that any view that contrast is associated with AKI was personal and went as far as to ask the other experts for examples of their published work. I think it is equally pertinent to have that reflected back. Animal studies have shown harm to kidneys from contrast and I can't see why human kidneys would be any different. More importantly the general consensus (ie of most experts) is that we should avoid and minimise contrast as much as possible to try and minimise AKI. People take a sensible view that we should not put patients at risk unless we know for	Establishing the clinical relevance of CI-AKI is outside of NICE's MTEP evaluation of DyeVert. The committee acknowledged that national and international guidance, including NICE's guideline on acute kidney injury (NG146), recognised increasing volumes of contrast media as a risk factor for AKI development. However, the committee also heard that the cause of AKI is multifactorial and complex. Although contrast media is 1 risk factor for AKI, it can be difficult to identify its direct cause (or causes), given other confounding factors such as comorbidities (which are often significant in people having angiography) and procedural complexities. As a result, it was uncertain whether reducing the contrast dye received using DyeVert Systems would directly lead to reduced incidence of AKI. The committee amended section 4.1 of the guidance to acknowledge clinical guidelines and the accepted practice of reducing contrast dye given where possible. The committee also acknowledged that people with impaired renal function, namely an eGFR less than 30 would be at the greatest risk of AKI and would most benefit from DyeVert use (section 4.7).

				a fact that contrast use does not cause harm. The onus is equally on individuals who feel contrast causes no harm to perform a RCT of patients with an eGFR of 25 or less and give half of them 300ml of contrast and the other half saline through an artery. Then we can have an answer. Such a study may have some minor issues getting through an ethics committee but will also have lots of issues in terms of recruitment as what patient would be happy to take a risk that they might need dialysis (renal physicians currently quote a risk between 1 and 10% depending on eGFR) to be part of a trial?! I really do feel that the issue of whether contrast leads to AKI is beyond the remit of the DyeVERT consultation and would need a whole review in its own right. As such I think it is unreasonable to place so much emphasis on 1 experts view on this when it is not in keeping with current guidance. As such the above highlighted statement can lead to patient harm if misinterpreted by clinicians as a green light to give as much contrast as they like. That aside I think the recommendations made are sound. I have attached below a few papers and link to uptodate that I think are reasonably well rounded in their assessment. If I have more time I will send more. Let me know if the links don't work and I will send the actual references. https://www.jacc.org/doi/full/10.1016/j.jcin.2013.06.016?keytype2=tf_ipsecsha&ijkey=61b0b4bcf63fe9063db6486049258c33e4e91d56 Older article from 2014 but does show the importance of contrast volume: https://www.uptodate.com/contents/prevention-of-contrast-induced-acute-kidney-injury-associated-with-computed-tomography Above is fair summary focusing on CT scans which is less risk than angioplasty https://www.mdcalc.com/mehran-score-post-pci-contrast-nephropathy References for this widely adopted calculator demonstrate contrast volume as a predictor of post PCI CIB https://journals.sagepub.com/doi/full/10.1177/1179546819878680#abstract Summarises things acknowledging the deficiencies in knowledge and discrepancy in opinion about causation and association. Contrast-associated acute kidney injury - BJA Education Also points to contrast volume as a risk factor for AKI The important point is that association is not to be sniffed at until we know more regarding causation. It is also important to note that contrast use for	

				diagnostic tests is clearly different from use in interventional procedures where larger volumes are used and there is no “set” amount. This is particularly of relevance in patients with an eGFR<30 which are mostly excluded from trials. Whereas for patients with better eGFRs I don’t think that CI-AKI is an issue at all. For those patients with established renal impairment it is not at all controversial to recommend reduction in contrast use and avoidance where possible until someone proves otherwise.	
7	3	Company	Draft Guidance	Of critical note, the initial MT SCOPE of the guidance development did not include the need to demonstrate the clinical relevance of Contrast Induced Acute Kidney Injury (CI-AKI) as that has been previously established in current NICE guidelines and was not asked to be part of the DyeVert System guidance scope. In fact, the NICE scope document of this project acknowledged the clinical validity in “prolonged hospital stay, increased mortality and increased health care costs” along with other NICE guidelines for the reduction of Acute Kidney Injury (AKI); leading Osprey Medical to believe that this was not a scope question (refer to section 1.2 of the scope document). As such additional information is provided herein to address committee member comments and draft language (through-out the guidance) regarding the clinical validity of CI-AKI for patients undergoing coronary and peripheral angiography as well as concern regarding identification of at-risk patients and alignment with global professional society guidelines in both cause of AKI and risk factors. CI-AKI is clinically relevant and validated in that: 1) International professional societies recognize the growing concern of CI-AKI for Catherization Laboratories, including within Current NICE guidelines and other worldwide professional society guidelines. NICE ***current*** Guideline state to ‘consider delay of imaging of eGFR <40 and strong consideration for AKI risks when giving intra-arterial administration of contrast’ along with other various CI-AKI prevention strategies. Both NICE and UK Renal Association state CI-AKI risks should be identified, and contrast volume reduced for purposes of reducing CI-AKI. As such, the current draft guidance does not align with current guidelines. Please see figure a, page 4, company supporting document. 2) Published literature identifies CI-AKI as a leading cause of hospital-acquired acute renal failure and is associated with prolonged length of stay, accelerated onset of end-stage renal disease, need for dialysis, increased health care costs and higher morbidity/mortality rates. *3)* In review of large epidemiological propensity-controlled studies, found that the rate of CI-AKI is less clinically meaningful in its relationship to	Thank you for your comment. The committee heard from clinical experts who felt that the risk of AKI was only high for those with an eGFR of less than 30. The experts felt that this group would be most appropriate for DyeVert Systems use. Please see NICE’s response to comment 6. Please see NICE’s response to comment 14 and 17 on at-risk populations and long-term health outcomes following an AKI event, respectively.

				contrast volume only as patient at-risk profiles have less risk. This is to be expected and identifies the criticality of all CI-AKI analysis to review *at-risk* patients using *validated at-risk models* (e.g., eGFR status, angiography vs CT, co-morbidities, etc).	
8	3	Company	Draft Guidance (4.1 and 4.4)	***Contrast Volume (CV) is not related to AKI*** Detailed review of data shows CV is related to AKI. The associative conclusions are based on the issue of data that is available, mostly includes all-comers and does not provide detailed subpopulation analysis. But even when assessing all-comers (i.e., no limitation to at-risk patients), the totality of the data continues to support and suggest contrast exposure as a single independent factor is critical in determining *and influencing* the patient AKI outcome post-procedure. Even under the worst-case scenario, associative data is consistently used in the development of standard of care. Support for innovative technology in context of the totality of the data must be considered (and is normal in innovation adoption) and is appropriate for a simple/low-cost and *extremely low risk* device such as the DyeVert Systems. Data demonstrates contrast volume to AKI outcome association is substantiated enough to endorse contrast minimization in the efforts of AKI reduction. Especially in light of lack of AKI treatment options or other proactive means to prevent AKI post intra-arterial contrast administered angiographic procedures. NICE ***current*** Guidelines state to 'consider delay of imaging of eGFR <40 and strong consideration for AKI risks when giving intra-arterial administration of contrast' along with other various CI-AKI prevention strategies. Both NICE and UK Renal Association state CI-AKI risks should be identified, and contrast volume reduced for purposes of reducing CI-AKI. As such, the current draft guidance does not align with current guidelines.	Thank you for your comment. The committee decided the recommendations should remain unchanged. Please see NICE's response to comment 6 on the association of contrast volume and AKI incidence. The committee felt that the evidence on a direct causal relationship between contrast agent volume and AKI incidence was not robust enough to determine whether reducing the amount of contrast media with DyeVert Systems use would lead to a reduction in AKI incidence. It felt that the current evidence on the technology was not strong enough to support adoption of the device.
9	2	Health care professional	Draft guidance	***Clinical evidence to demonstrate contrast associated AKI*** Majority of the evidence has been taken into account and there is emerging evidence (Ref below) linking the AKI to contrast volume usage during complex coronary interventions. Current evidence shows DyeVert reduces contrast volume with no compromise in image quality and could potentially be trialled in select sub group of patients, pending the results of RCT.	Thank you for your comment. Please see NICE's response to comments 7 and 8.

				A prospective study on the incidence of contrast-associated acute kidney injury after recanalization of chronic total coronary occlusions with contemporary interventional techniques. Werner GS, Lorenz S, Yaginuma K, Koch M, Tischer K, Werner J, Keuser T, Moehlis H, Riegel W. Int J Cardiol. 2021 May 17:S0167-5273(21)00842-1. doi: 10.1016/j.ijcard.2021.05.030.	
10	3	Company	1.1, 3.5, 4.10	***Association between contrast media and AKI*** Part of a recent Cleveland Clinic (world renown clinical academic center in the USA) debate of CI-AKI. The conclusion in the review of data demonstrates CI-AKI remains a real issue albeit at a slightly lower rate than what has been seen in previous decades. In review of large epidemiological propensity-controlled studies, the assessment found that the rate of CI-AKI is less clinically meaningful in its relationship to contrast volume only as patient at-risk profiles have less risk. This is to be expected and identifies the criticality of all CI-AKI analysis to review at-risk patients using validated at-risk models well established as noted below (e.g., eGFR status, angiography vs CT, co-morbidities, etc.). Despite the lack of ideal propensity-controlled studies to identify the singular risk profile and contrast volume to trigger AKI events, the data continues to collaborate contrast exposure is critical in determining *and influencing* the patient outcome post-procedure, even when *not* considering risk profiles of the patients (i.e. assessing all comers). The following tables demonstrate contrast volume to AKI outcome association/relationship is substantiated enough to endorse contrast minimization in the efforts of proactive means to reduce AKI in light of no known AKI treatment. Please see table 3, company consultation response, page 6. Gurm et al. evaluated 45,429 patients as part of a 31-hospital regional registry. The results of this analysis showed that as the ratio or contrast volume/eGFR approached 2 there was a strong trend toward the development of CI-AKI and a ratio >3 was a significant predictor of increased incidence with an odds ratio of 1.46 suggesting 46% greater adjusted odds of developing CI-AKI. Gurm et al. recently published a modeling study of the impact of contrast dose reduction	Thank you for your comment. Please see NICE's response to comments 7 and 8.

				on the incidence of CI-AKI. They retrospectively analyzed a cohort of 95,625 patients from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium. Similar to their previous analysis, they found that a CV/CrCl >2.99 resulted in a significant increase in the risk of CI-AKI. Based on their modeling, a 30% reduction in contrast dose would be expected to reduce the incidence of CI-AKI by 12.5%. Please see figure 1, page 7 of company consultation response. In addition, the following table (please see table 4 and 5, page 8-15 of company consultation response document) demonstrates the link of contrast volume to CI-AKI rates continues to be consistent over the decades in demonstrating a tipping point when assessing contrast volume as an independent factor. Furthermore, Raposeiras-Roubin et al. found that for each 10 cc of contrast media administered up to 158 cc, the risk of CI-AKI increased by 5.0% and for every one-tenth increase of contrast volume/estimated glomerular filtration rate up to 2.7, the risk of CI-AKI increased by 4.9%. More recently, Amin et al. showed that physicians who used more contrast had an increased risk (OR 1.42; 95% CI 1.40-1.43) per each incremental 75 ml increase in contrast use ($p<0.001$) despite adjusting for patient characteristics and acute kidney injury risk such as kidney function measurement. Thereby each 75mL incremental increase in contrast raised the risk of acute kidney injury by 42%. These results support a maximum acceptable contrast dose based on kidney function is required to minimize CI-AKI occurrence; and an impact on CI-AKI is directly impacted by contrast volume across an at-risk population. Please see figure 2, page 16 of company consultation response. Despite ongoing data collection demonstrating the relationship between contrast volume and AKI outcome directly, the strongest consensus of determining the clinical impact of contrast volume to AKI occurrence is in consideration of validated multi-variable models (e.g. Yuan et al (2021), Tsia (2014), Mehran (2004)). These models not only support the relationship of contrast volume to AKI outcome, but identify triggers in the complexity of co-morbidities that amplifies the clinical relationship between contrast volume and AKI outcome.	
11	3	Company	4.1, page 8	***Clinical incidence*** Contrast media is an essential part of investigative radiology. The discovery of x-ray imaging found that radiopacity was enhanced using elements of high atomic numbers. However, bismuth, lead and barium salts used to create the	Thank you for your comment. The committee acknowledged NICE guidelines on Acute Kidney Injury

				first angiogram of an amputated hand in 1896 were unsafe for living human use . Initial efforts to develop safe contrast agents led to the discovery and use of iodine salts in the early 1920's when iodine containing compounds were used to treat syphilis at the Mayo Clinic, Osborne et al. 1923 . Then in 1933, a chemist by the name of Wallingford created an iodine derivative with up to three atoms per molecule that was less toxic than the early iodine agents and started the beginning of modern contrast agents. Further research in the 1950's and 1960's made improvements to water solubility (i.e. osmolality) as well as changes in viscosity and ionic character3. The resulting contrast agents developed are still in use today. Today, contrast is among the most highly used medications with a global market expected to reach $5.53 billion by 2022 from an estimated $4.57 billion in 2017 at a compound annual growth rate of 3.9%. The iodinated contrast media segment is expected to account for the largest share of the contrast media market. The growth is attributed to the increasing number of diagnostic imaging units, examinations, and procedures along with the growth in average age of the population and rising prevalence of chronic conditions. This on-going growth increases patient risk of contrast volume exposure significantly and increases the risk of patients to contrast related adverse events. There is recognition among practitioners that patients are receiving increasingly more accumulative dosing through repetitive or serial studies in addressing complex co-morbidities and disease severity. The use of contrast in repetitive exposure also emphasizes the growing concern for the minimization of contrast volumes. CI-AKI in Angiography is Recognized Internationally in Guidelines International professional societies have recognized the overwhelming associative cause of contrast volume to AKI after intra-arterial procedures for years. These organizations have deemed the evidence is strong enough to provide state of the art clinical guidelines to recommend minimizing contrast load to patients undergoing intra-arterial contrast exposure. The reduction of occurrence of CI-AKI is critical as there is no specific treatment available today. Published literature and medical professional guidelines and consensus statements have consistently identified intravenous volume expansion and/or minimizing contrast volume as the only two-modifiable primary preventative measures. Other drugs or imaging techniques have received little endorsement and failed to meet study endpoints. Due to the growing issue of hospital-acquired renal injury and in alignment with ongoing data collection, professional medical societies have issued numerous guidance to physicians to prevent CI-AKI. The primary recommended actions to reduce CI-AKI is screening patients for risk, hydration of patients and minimization of contrast volume in at-risk patients (including those patients with	(NG148) which stated that intra-arterial contrast administration and contrast volume were risk factors for AKI development. In 4.1 of the guidance clinical experts state that contrast volume is a modifiable parameter which could reduce AKI risk. The committee amended section 4.1 of the guidance to acknowledge current clinical guidelines and the accepted practice of reducing contrast dye given where possible. The committee decided that no further amendment to the guidance was needed.

				renal insufficiency). Consensus of minimizing contrast media in the prevention of CI-AKI - considering pre-procedural kidney function and relative to pre-defined thresholds - is well established in peer-reviewed literature. Refer to Table 02, page 34 company consultation comments document, capturing both long standing and recent consensus statements and guidelines as endorsed by professional clinical societies and public health organizations, which includes standing NICE guidelines.	
POWER XT SYSTEM					
12	3	Company	1.2	Regardless of contrast injection source, the DyeVert System pressure-compensating diversion valves are designed to respond to a clinically relevant range of injection pressures even if the injection profile (refer to body of text) changes during the procedure. The diversion valves are similar between the DyeVert Systems in both design and performance specification criteria. When physicians use automated contrast injection systems per their usual practices, the addition of the DyeVert Power XT System resulted in equivalent contrast savings in every procedure. As this contrast savings is the foundational mechanism for AKI reduction it is appropriate to assess the DyeVert Power XT System under the totality of the DyeVert System data.	Thank you for your comment. Section 4.3 of the guidance states 'the company said that the PLUS EZ and Power XT versions work in a similar way, with both devices responding to pressure going through the valve'. The committee decided that no amendment to the guidance was needed.
13	3	Company	3.6 and 4.3	***Evidence on the Power XT version is limited.*** ***Generalisability of Plus EZ to Power XT device is uncertain.*** The two systems are equivalent in mechanism of action, contrast reduction and patient contrast flow rates. (Bruno et al, 2019, Amoroso et al, 2020, Osprey Medical market acceptance evaluation) 	Thank you for your comment. Please see NICE's response to comment 12. The committee considered the additional information provided and concluded it does not answer the uncertainties around the use of the Power XT device in an NHS setting. Clinical experts also expressed uncertainty on the use of the Power XT device as they are not aware of its current use within the NHS. The Bruno et al. (2019), Amoroso et al. (2020), and Osprey Medical market acceptance evaluation were evaluated as part of the EAC's assessment of the

				[redacted] [redacted] In theory, optimization of contrast injection profiles is feasible given that the user has the capacity to modify some attributes of each injection; however, challenges with real-world clinical application remain due to a range of variables that impact the injection profile such as significant variation in coronary artery size and anatomy, disease progression, arterial flow rate, procedure objectives, catheter size and design, and contrast media type. For example, a physician can potentially place focus on flow, volume, rise time and pressure for one injection, but the reality of clinical practice is that physician focus is divided between ongoing assessment of image quality as well as patient safety, radiation exposure, and accomplishing procedural objectives which may include complex, multivessel interventions. Additionally, adequate image quality depends upon dialing in the right combination of these injection profile variables for each vessel and these variables differ from patient-to-patient. Therefore, the clinical reality is that optimization of the contrast injection profile is a complex endeavor specific to each patient and procedure. To date, while some centers may be experimenting with optimizing contrast injection protocols, there is no evidence that active injection profile modulation during coronary angiography is happening in widespread, real-world clinical practice. In our experience interviewing end users, physicians most commonly use manufacturer recommended automated injector settings. Some experienced users may use a hand controller to dial back flow rate settings after the initial injection or as needed during a case; however, use of the hand	evidence, detailed in its assessment report, and presented to the committee. The committee decided that no amendment to the guidance was needed.

				controller is variable from case-to-case for a given physician and across physician users. Regardless, DyeVert System pressure-compensating diversion valves are designed to respond to a clinically relevant range of injection pressures even if the injection profile changes during the procedure. In real-world clinical settings, when physicians used automated contrast injection systems per their usual practices, the addition of the DyeVert Power XT System resulted in contrast savings in every procedure. Osprey Medical, Inc. conducted initial commercial Market Acceptance Evaluations of the DyeVert™ Power XT Contrast Reduction System following commercial launch in Europe in 2018. The purpose of the evaluation was to obtain initial market feedback from product end users in standard commercial use settings. Data collection included procedure and contrast elements relevant to assess contrast use and DyeVert System performance. No private or identifying patient health records or data were collected throughout these evaluations. Users include interventional cardiologists and cardiac cath lab staff. Participating hospitals were large urban academic medical centers and tertiary care facilities. [redacted] [redacted] As such, Osprey Medical disagrees with the NICE draft guidance suggesting that there is no comparability as the devices are equivalent. In fact, Osprey Medical Systems are the only devices that have demonstrated statistically significant and equivalent contrast reduction regardless of contrast injection source as presented to regulatory authorities. Regardless of contrast injection source, the DyeVert System pressure-compensating diversion valves are designed to respond to a clinically relevant range of injection pressures even if the injection profile (refer to body of text) changes during the procedure. The diversion valves are similar between the DyeVert Systems in both design and performance specification criteria. When physicians use automated contrast injection systems per their usual practices,	

				the addition of the DyeVert Power XT System resulted in equivalent contrast savings in every procedure. As this contrast savings is the foundational mechanism for AKI reduction it is appropriate to assess the DyeVert Power XT System under the totality of the DyeVert System data. Thus, it is appropriate to leverage the DyeVert Plus EZ System data for the DyeVert Power XT System.	
AT RISK POPULATION					
14	3	Company	**4.7-4.8**	***Clinical indicators*** CI-AKI remains a clinically relevant issue for patients undergoing coronary or peripheral angiography when presenting with validated at-risk factors. The at-risk patient population - the subject of this guidance - should not be confused with intravenous procedures or patients not presenting with validated at-risk factors. **Intra-arterial versus Intravenous Contrast Exposure** While contrast agents are of clinical value, iodinated contrast is considered nephrotoxic, regardless of the amount of exposure. The most common causes of AKI in developed countries are decreased renal perfusion, nephrotoxic. medications, and exposure to iodinated contrast (i.e. CI-AKI). Intraarterial exposure to iodinated contrast in procedures like coronary angiography results in increased blood viscosity and vasoconstriction resulting in decreased blood flow and direct cytotoxicity of the renal nephrons. In response to cell death, the remaining functioning cells increase perfusion resulting in a transient resumption of kidney function (maladaptive repair); however, renal cell death is permanent and can result in progressive scarring; overall perfusion capacity of the kidney is impacted. The practice of using variable measures of kidney injury and severity, both practically and in research, has led to cautious consideration when reviewing data. However, the recent decade has seen a significant increase in research regarding patients in catherization laboratories undergoing percutaneous angiography across a broad range of practices and patients. Because of this broad research effort and stronger knowledge of kidney science, the data begins to provide a comprehensive assessment of the impact of contrast on AKI based on real-world evidence after intra-arterial contrast exposure. **It is important to assess Intra-arterial contrast exposure separately from intravenous contrast exposure.**	Thank you for your comment. Section 1.1.6 of the NICE's guideline on acute kidney injury (NG148) states that groups at higher risk of AKI include age, diabetes (with CKD), moderate and severe CKD, heart failure and intraarterial administration of contrast media. Section 2.3 of the guidance has been amended to acknowledge that people having contrast agents for non-emergency imaging should be assessed for their risk of AKI in line with NG148. Clinical experts felt that CKD stage was the most important risk factor for AKI and stated that they would consider using DyeVert in those with CKD stage 4 and over. However they agreed that there are other risk factors which could increase the risk of developing AKI. Section 4.7 of the guidance has been amended to acknowledge all the risk factors which could increase the risk of developing AKI following a contrast procedure. Please see NICE's response to comment 16 on the AKI risk percentage used in the economic modelling and comments 6 to 8 for NICE's response to comments on the association between contrast volume and AKI risk. The committee has amended

				Clinical evidence has demonstrated that intra-arterial injection of contrast media during angiography can be toxic to the kidneys (a different risk profile compared to intravenous contrast exposure), leading to CI-AKI due to first-pass renal exposure when contrast media reaches the renal arteries in a relatively undiluted form. This position is supported under NICE Guideline NG148 (2019) which states contract volume reduction should be considered when “intra-arterial administration of contrast medium with first pass renal exposure” occurs. Likewise, even with limited studies directly comparing intravenous versus intra-arterial contrast administration, the Contrast Media Safety Committee of the European Society of Urogenital Radiology recommends caution and restrictive use of contrast volume when performing intra-arterial procedures. CI-AKI is a leading cause of hospital-acquired renal injury; especially for those undergoing intra-arterial contrast administration. Currently, there is no available treatment for CI-AKI; therefore, prevention measures are critical, especially in at-risk patients. **Validated At-Risk Models** For more than a decade, efforts to determine prognostic factors associated with the post-procedure development of CI-AKI led to the development of numerous published risk models and risk assessment tools for use in the catherization laboratory. Historically analyses were complicated by heterogeneity in the routes and contrast volume administration (intravenous vs intra-arterial), contrast types, and co-morbidities in the patient populations. These factors made it difficult to uniformly identify risk factors, acceptable dosing and define what constitutes clinically acceptable outcomes. However, published risk models for arterial procedures in the catherization laboratory determined age, diabetes, moderate and severe CKD and heart failure on presentation as the leading factors for when to consider renal protection measures such. The overall aim of these models and tools is to facilitate screening or identification of at-risk patients such that prevention strategies may be employed before, during and after a planned procedure involving the use of contrast administration. The resulting comparison of these models highlights consistent areas of concern. See table 6 in company consultation comment document.	section 4.1 of the guidance to acknowledge that accepted practice is to minimise the amount of contrast given, especially for those with an estimated glomerular filtration rate [eGFR] less than 30 ml/min/1.73 m^2 who need complex procedures which are likely to need larger volumes of contrast.

				More recently, Duan et. al published a risk model that included 5 prognostic factors for CI-AKI following coronary angiography or PCI procedures: age, serum creatinine levels, N-terminal pro b-type natriuretic peptide levels, high-sensitivity C-reactive protein, and primary PCI.6 Today it is widely recognized within these patient populations that the volume of contrast in context of baseline kidney function is directly correlated to CI-AKI risk with a gradient of risk increasing with additional key risk factors and increasing contrast volume. (Please see Figure 3, page 42 company consultation comment document). Limitation of contrast minimization to only those patients at the “greatest” risk, does not provide equitable care across all patient types. The adoption of the draft NICE guidance to limit DyeVert System use to those with stage 4 or 5 CKD only does not account for the severity of an AKI event over the lifetime of a CKD patient nor those exposed to identified co-morbidity factors. Brown et al. (2016) demonstrated an 8-fold increase in CKD in patients after percutaneous coronary intervention if they experienced AKI event (n= 24,405) and this study was inclusive of all patients eGFR<60; not just stage 4 and 5 CKD. The proposed draft guidance does not promote a proactive preventive care pathway that decreases the progression of CKD. These models support the complexity of co-morbidities that amplifies the clinical relationship between contrast volume and AKI outcome. CI-AKI is a clinically relevant issue for patients undergoing coronary or peripheral angiography when presenting with validated at-risk factors. The at-risk patient population the subject of this guidance should not be confused with intravenous procedures or patients not presenting with at-risk factors. And guidance populations should not be subjected to non-validated over-simplification to CKD stages only. The assessment of CKD as baseline consideration for risk factors is reasonable but should not be isolated to just that factor. As such Osprey Medical economic model provided an extremely conservative assessment using CKD as its patient population and still demonstrated an overwhelming cost savings potential for the system. A true baseline risk of an “at-risk” patient with validated risk factors would be much higher than the assumed 8.7% by the NICE committee.	

				Even with moderate consideration of other validated risk factors, the economic model demonstrates a significant cost savings. We have an effect size in the low-risk population (CKD factor only); such that with even a moderate raising of the risk, our device can have significantly less performance and still make a difference. It is of critical consideration that these validated risk factors are part of standard of care assessment, but do not in themselves invalidated the influence of contrast volume has on the resulting AKI outcomes. Meta-analysis and large registry databases such as the National Cardiovascular Data Registry (NCDR), Cath-PCI Registry - USA – which covers more than 1000 sites across the United States – has determined through a validated model of over 1 million consecutive PCI patients that increased of contrast volume by itself may be predictive of an increased occurrence of CI-AKI. As such, a decrease in contrast volume may be predictive of a reduction in the occurrence of CI-AKI for all moderate and severe CKD patients (Amin, 2017). In addition, recognizing identification of at-risk patients is confounded by multi-factors and validated models are clinically complicated to implement, professional guidelines attempt to simplify standard of care by recommending contrast minimization is applied to all patients and when identifying patients with pre-existing renal dysfunction, guidelines have identified broader eGFR measurement as state-of-the-art. Specifically, the American College of Cardiology Foundation, American Heart Association Task Force on Practice Guidelines, The society for Cardiovascular Angiography and Interventions Guidelines recommend, "In patients with CKD (*creatinine clearance <60 ml/min*), the volume of contrast media should be minimized (Class I, B)." And NICE ***current*** guidelines state to '*consider delay of imaging of eGFR <40* and strong consideration for AKI risks *when giving intra-arterial administration of contrast*' along with other various CI-AKI prevention strategies. Both NICE and UK Renal Association state CI-AKI risks should be identified, and contrast volume reduced for purposes of reducing CI-AKI. As such, the current draft guidance at a minimum does not align with current guidelines and is not taking into consideration the higher risk patient population as identified by the validated risk models.	
CLINICAL EVIDENCE BASE					
15	3	Company	4.4, 4.11, 4.12 and 1.2	***RCTs in the topic*** Randomized controlled trials in themselves or as part of systematic review or	Thank you for your comment.

				meta-analysis provide the strongest level of evidence, however, RCTs may not always be the preferred study method for various reasons. In the case of CI-AKI for angiographic procedures, the following eliminates RCTs as the preferred study design: - Ethical consideration of randomizing patients away from state-of-the-art professional society guidelines. - Ethical consideration of randomizing patients away from care that provides the patient less exposure to a recognized pharmaceutical ***with no additional patient risk***. - RCT would not be clinically feasible unless it included patients with multi-factors as defined by validated risk models, and the feasibility of statistically performing randomization to account for all factors would be unrealistic. The recommended draft NICE guidance research by stratification (in context of validated risk model co-morbidities (eGFR, diabetes, HF, etc. and required matching) would require over 10, 000 patients to be statistically relevant in all subsets, and is simply not feasible for the proposed low-cost disposable, that introduces no new or different risks to the patient. Osprey Medical recognizes the challenge of defining standard of care or recommended care based on totality of data versus an overwhelming single RCT. To that, the presentation of the subject devices relied on *numerous* data sets and not just retrospective study information. Rather 19 different studies were presented demonstrating consistent and reliable information. Of the studies provided, full text studies included 1 RCT, 3 prospective studies (2 of which were feasibility studies) and 4 retrospective studies (2 of which were comparative). In addition, additional posters and abstracts were presented representing 1 RCT and 8 retrospective studies (4 of which were comparative); and two unpublished studies (1 retrospective comparative and 1 prospective comparative). • 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)	The EAC's assessment of the evidence reviewed the 19 studies submitted by the company and this evidence was presented to the committee. The EAC concluded that Desch et al (2018) was the best source of evidence with a low risk of bias. However, this RCT was limited by not reporting longer term outcomes. The EAC's assessment report also critiqued the validity of the meta-analyses. They considered them to be fairly robust but noted that some of the analyses included a small number of studies, where some studies were judged to be of moderate to low quality. Further, the sample size in some of the included studies is much greater than others, such that they dominate the results. The EAC stated that an RCT would be the best option. However, they acknowledged that there are difficulties associated with performing such research. The EAC did not believe that randomisation would be an ethical barrier since RCTs are reported in the literature and there are ongoing RCTs for this device (REMEDIALIV; NCT04714736; trial that aims to recruit around 350 people). The EAC further noted that they were uncertain about the necessity for large sample sizes over 10,000 patients due to the size of the ongoing RCT which is looking to collect longer term outcome data. The committee decided the recommendations should remain unchanged. It felt that the evidence base for AKI incidence reduction as a result of DyeVert use was not strong enough to support the case for adoption. The

				• 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). Meta analysis was presented based on these studies and demonstrated a pooled reduction in the rate of CI-AKI within the subject patient population. Meta analysis was based on real world use across different countries (UK, USA, Germany, Netherlands, Italy and Australia). The data demonstrates consistent and clinically relevant reduction in contrast volume to patients while maintaining image quality; as well as better reflects real world reduction of CI-AKI rates arguably in circumstance of low detection practices of AKI due to lack of long-term follow up and lack of post-procedural serum creatinine. It is important to note, the subject devices are extremely low risk. And consideration for extensive RCT (in both cost and time/size), does not align with most clinical site resource allocation decisions. The subject systems pose essentially no additional risk to the patient while minimizing exposure to total contrast agent volumes during contrast injections; all while achieving the desired level of image opacification. • The device introduces no new or potential increase in user error: The physician user interface, injection practice and user performance feedback (image quality) remains unchanged. • The device introduces no new patient exposure or additional exposure risk from contrast agents. The device does not have the capability nor is designed to control or administer contrast to the patient. The contrast agent volume injected is *physician-determined* and *physician-administered* as it is today. • There is no new or increased risk that physician's would under inject contrast media. The device is designed to deliver a minimum patient flow rate for image adequacy. Image adequacy of this flow rate is supported by the company's clinical data reviewed and approved by regulatory authorities. • The disposables make no direct contact with the patient (indirect patient contacting only).	committee agreed that an RCT was the most appropriate trial design needed to address the uncertainty. The committee and clinical experts agreed that there were no ethical concerns around doing an RCT.

				Support for innovative technology in context *of the totality of the data must be considered* (and is normal in innovation adoption) and is appropriate for simple/low-cost devices that are adaptable to current care pathway prevention with no introduction of a greater risk profile.	
COST MODEL AND COST IMPACT OF CI-AKI					
16	3	Company	General	Baseline Risk restricted to CKD only is not aligned with validated models. Baseline At-Risk to be defined as Stage 4 or 5 CKD (risk rate of 8.7%) These models support the complexity of co-morbidities that amplifies the clinical relationship between contrast volume and AKI outcome. Limitation of contrast minimization to only those patients at the "greatest" risk, does not provide equitable care across all patient types. The adoption of the draft NICE guidance to limit DyeVert System use to those with stage 4 or 5 CKD only does not account for the severity of an AKI event over the lifetime of a CKD patient nor those exposed to identified co-morbidity factors. CI-AKI is a clinically relevant issue for patients undergoing coronary or peripheral angiography when presenting with validated at-risk factors. The at-risk patient population the subject of this guidance should not be confused with intravenous contrast administration procedures or patients not presenting with at-risk factors. And guidance populations should not be subjected to non-validated over-simplification to CKD stages only. The assessment of CKD as baseline consideration for risk factors is reasonable but should not be isolated to just that factor. As such Osprey Medical economic model provided an extremely conservative assessment using CKD as its patient population and still demonstrated an overwhelming cost savings potential for the system. A true baseline risk of an "at-risk" patient with validated risk factors would be much higher than the assumed 8.7% by the NICE committee. Even with moderate consideration of other validated risk factors, the economic model demonstrates a significant cost savings. We have an effect size in the low-risk population (CKD factor only); such that with even a moderate raising of the risk, our device can have significantly less performance and still make a difference.	Thank you for your comment. Clinical experts stated that people with CKD stage 4 and 5 were the groups who would most benefit from using DyeVert. They felt that the risk of CI-AKI in those with better kidney function was relatively low. Section 4.7 of the guidance states where DyeVert is best used based on clinical expert opinion and was amended to acknowledge the risk factors associated with developing AKI. The committee were advised that the EAC used a risk of AKI of 8.72% based on NG148 evidence. The studies which make up this risk value are on those having PCI or coronary angiography who have been given oral fluids and does not include those having intravenous administration of contrast. The EAC stated that a 30% baseline risk is unlikely, as it seems to be too high for patients appropriately hydrated. The committee decided the recommendations should remain unchanged.

				as contrast minimization tools and processes. Table 06 summarizes key publications citing patient risk factors to consider when considering the use of strategies to reduce contrast use.	
17	3	Company	3.11	***If the baseline risk of contrast-induced AKI is below 8.2% DyeVert Systems are no longer cost saving*** Published literature identifies CI-AKI as a leading cause of hospital acquired acure renal failure and is associated with prolonged length of stay, accelerated onset of end stage renal disease, need for dialysis, increased health care costs and higher morbidity/mortality rates. Intra arterial contrast induced kidney injury is the result of renal impairment within a short period of time, two to seven days, after administration of iodinated contrast media. Although these conditions can be mistakenly reported as self resolved, CI AKI events carry significant risk of more permanent renal insufficienct, dialysis or death. Unfortunately, most patients are asymptomatic, so CI AKI can go undetected unless patients are tracked and evaluated as such most reported rates are under reported. Oliguria and rise is SCr have been the primary means for diagnosing CI-AKI. And initiatives and classification systems such as RIFLE, AKIN and KDIGO have provided some clarity on diagnosis and severity of CI-AKI incidence. The course of CI-AKI occurs within 24 hours and peaks within 3-5 days. Patients that experience CI-AKI are severely impacted by the event. CI-AKI is associated with prolonged length of stay, accelerated onset of end-stage renal disease, need for dialysis, increased health care costs and higher morbidity and mortality rates. Sick patients with complex clinical presentations are more likely to undergo procedures requiring higher volumes of contrast media thereby increasing their risk of CI-AKI based on presentation. In-hospital mortality for patients with CI-AKI ranged from 6% to 31% compared to 0.5% to 7% for non-CI-AKI patients (references seen on page 30 company consultation response document). In addition, long-term mortality was also higher for CI-AKI patients. In one study, the 1-year and 5-year mortality rates were 12.1% and 44.6%, respectively for CI-AKI patients compared to 3.7% and 14.5% for non-CI-AKI injury patients. A recent systematic review and meta-analysis by See et. al found that AKI after angiography with contrast increased risks of new or progressive CKD (HR 23) Clinical data also exists to suggest that mortality is directly related to the ratio of CV/BKF. Patients who require dialysis as a result of CI-AKI have even worse outcomes. McCullough, et al. reported that the in-hospital death rate was	Thank you for your comment. The committee acknowledges the potential adverse outcomes of having CI-AKI. Section 4.5 of the guidance states that according to expert opinion most AKI events happen 4 to 5 days after the contrast exposure, and sometimes as late as 7 to 10 days afterwards. It also acknowledges that incidence of AKI may be difficult to track because serum creatinine measurements may not be done routinely. Please see NICE's response to comment 16 on the baseline AKI risk. The committee and the EAC accepted the company's economic model, based on NICE's guidelines on acute kidney injury, which captured the long-term outcomes of an AKI event. The committee considered the additional information provided and concluded it does not answer the uncertainties which led to their recommendation for further research. The committee decided the recommendations should remain unchanged.

				35.7% for CI-AKI patients requiring dialysis compared to 7.1% and 1.1% for non-dialysis CI-AKI patients and non-CI-AKI, respectively. By two years, the mortality rate for CI-AKI patients requiring dialysis was 81.2%. Similarly, Tsai et al demonstrated an in-hospital mortality rate of 9.7% for acute kidney injury patients and 34% for those patients on dialysis compared to 0.5% for non-AKI patients ($p<0.001$) out of 957,548 patients at 1,253 sites. In addition to increased mortality, patients with CI-AKI have relatively higher incidences of other adverse outcomes including myocardial infarction, target vessel revascularization, bleeding requiring transfuction, and vascular complications compared to non CI-AKI patients. Along with increased morbidity and mortality, CI-AKI significantly increases long-term costs associated with angiography. A single-center retrospective study by Koulouridis et al. of 22,001 patients over 7 years (October 2000 to September 2007) demonstrated that compared to non-AKI patients, the AKI group had a significantly higher 30-day hospital readmission rate (11% vs. 15%; OR 1.21; 95% CI 1.02-1.25; $p<0.001$) which persisted out to 60 and 90 days. Events triggering readmissions in the AKI group were cardiovascular-related conditions, primarily heart failure ($p<0.001$) and acute myocardial infarction ($p=0.01$)	
GENERAL COMMENTS					
18	2	Health care profes sional	4	Agree with the evidence.	Thank you for your comment.
19	2	Health care profes sional	Equality considera tions	Are there any equality issues that need special consideration and are not covered in the medical technology consultation document? None	Thank you for your comment.
20	3.	Comp any	General	Based on the information provided above, those data provided in the clinical and economic submissions and interactively, Osprey Medial believes the draft guidance requires significant modification prior to finalization. Modifications should include the ongoing recognition of the clinical validity of CI-AKI, the ongoing association of contrast volume on C-AKI rates in at-risk patients, and recommendation of using DyeVert Systems for at-risk patients based on robust cost reduction demonstrated within conservative modelling and the strong demonstration of contrast volume reduction.	Thank you for your comment. Please see NICE's response to comments 6 to 8 on the association between contrast volume and AKI as well as comments on existing AKI guidelines. Please see NICE's response to comment 14 on risk factors for AKI development.

				These modifications will better align with current state-of-the-art globally recognized guidelines and ensures that the guidance is addressing the initial scope of the assessment. For example, the proposed NICE Draft Guidance "DyeVert Systems for reducing the risk of acute kidney injury in coronary and peripheral angiography", GID-MT550, supports the cost effectiveness and contrast reduction in the conservative assessment under the device MedTech Innovation Briefing (MIB) and was a driving consideration for NICE Guidance selection under the Medical Technologies Guidance program. *The recommendations for the DyeVert Systems should not be considered in exclusion of the current NICE guidelines* that recognize contrast volume as a critical risk factor for AKI in angiographic procedures (refer to NICE Guidance "Acute kidney injury: prevention, detection and management" Issued 18 Dec 2019; and the clinical relevance of an AKI event (i.e. morbidity and mortality rates, system cost exposures) as stated in the project SCOPE document: "prolonged hospital stay, increased mortality and increased health care costs". In addition, Osprey Medical raises concern over what appears to be inconsistent expressed opinion of Expert #6 (MD) and other committee members (as noted in the published supporting documentation). Expert #6 appears to differ in the opinion of CI-AKI clinical validity within the different forums and does not appear to delineate their concern of scope (e.g., intravenous versus intraarterial, angiography/interventional procedures versus CT) nor does the opinion provide data that would support the total exclusion and contradiction with current NICE guidelines. Osprey Medical believes that modifications to the proposed guidance to recommend use of the DyeVert Systems for at-risk patients (as defined in validated models) in preventative measures for an area of high burden on the health system while encouraging ongoing real-world evidence data.	

"Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees."