Input from external experts and manufacturer on the 2nd draft assessment

"TRANSCATHETER AORTIC VALVE IMPLANTATION (TAVI) FOR THE TREATMENT OF PATIENTS AT INTERMEDIATE SURGICAL RISK"

(Project ID: OTCA06)

EUnetHTA JA3 WP4 - Other technologies, OTCA06
Comments by external experts on the 2nd draft rapid assessment on TRANSCATHETER AORTIC VALVE IMPLANTATION (TAVI) FOR THE TREATMENT OF PATIENTS AT INTERMEDIATE SURGICAL RISK

EXTERNAL EXPERTS

Comments were received from:

Name	Affiliation
Reidar Bjørnerheim	Cardiologist, Chief Senior Cosultant, Oslo University Hospital, Norway
Chiara Fraccaro	University Of Padua
Svein Faerestrand	Cardiologist, professor emeritus, Department of Clinical Science, University of Bergen, Norway
Piotr Szymanski	European Society of Cardiology

Comment from	Page number *Insert 'general' if your comment relates to the whole document*	Line/ section number	Comment and suggestion for rewording *Please insert each new comment in a new row.*	Character of comment • 'major'[a] =1 • 'minor'[b] = 2 • 'linguistic'[c] =3	Author's reply
Chiara Fraccaro	7	TABLE (abbreviation list)	In the last row of the table, it's not correct to spell out "TAVR" as "Trans**aortic** valve replacement". In fact, it means "Trans**catheter aortic** valve replacement" (as stated in previous row), whatever the vascular access (femoral, apical, subclavian/axillary or **aortic**).	2	Amended
Reidar Bjørnerheim	3	41	My title: Reidar Bjørnerheim MD, PhD, Cardiologist, Chief Senior Cosultant, Oslo University Hospital, Norway is corrected, see above	2	Amended
Piotr Szymanski	3	41	Piotr Szymanski on behalf of the Regulatory Affairs Committee of the European Society of Cardiology	2	Amended
Summary					
Piotr Szymanski	8	194	when performed from the transfemoral access	2	Amended:" . .., the procedure when performed through transfemoral access is minimally invasive and may be performed with light sedation and without cardiopulmonary bypass."
Piotr	8	198	lower rather than upper	2	Not amended

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Szymanski					
Piotr Szymanski	8	218	in most patients	2	Amended : "...In most patients, SAVR is the first choice of treatment for severe symptomatic aortic valve stenosis."
Piotr Szymanski	9	228	aortic valve (not aortic valve leaflets)	1	Amended: "leaflets" removed
Piotr Szymanski	9	246	single patients have TAVI with EII above 20 so this classification has very little practical relevance and seems to me inappropriate	2	We have checked there is variation in the litterature about high and extreme high. As the ESC/EACTS guidelines only define low and intermediate we removed information about extreme high. Changed to: Surgical risk <4% (STS or EuroSCORE II) is normally defined as low risk, risk 4-8% as intermediate risk, and risk >8% as high.
Description and technical characteristics of the technology					
Piotr Szymanski	30	713	Not "some experts" but CT is routinely performed before the procedure	1	Amended: Computed tomography (CT) is routinely performed for pre-procedural imaging and for long-term post-procedural assessment
Piotr Szymanski	31	722-4	Stroke and need for pacemakers are not specific for TAVI as they occur also after surgery	1	Amended: Specific **concerns** ~~issues~~ related to TAVI compared to SAVR **have been uncertainties regarding** ~~include~~ the risk for stroke, the need for a permanent pacemaker implant, access-related complications and concerns regarding positioning and lifetime of the implant.
Health problem and current use					
Reidar Bjørnerheim	36	877	Aortic stenosis causes impaired outflow, but not regurgitation ("aortic regurgitation" or "Aortic insufficiency"), a separate entity not suitable to be treated with TAVI. Most of line 877 should be removed.	2	Line 877 changed to: Aortic stenosis is the thickening, fibrosis and calcification of aortic leaflets that impair outflow of blood to the system. (delete the rest)

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Svein Faerestrand	36	876, 877	Aortic stenosis is the thickening, fibrosis and calcification of aortic leaflets that impair outflow of blood to the system and **can also** cause regurgitation (backward flowing of blood to the left ventricle). The	2	As above
Svein Faerestrand	37	896-898	together with age, symptoms, and comorbidities. Doppler**, two-dimensional and M-mode** echocardiography **is the preferred tool** for assessing major indicators of severity such as valve area, transvalvular pressure gradients, flow rate, ventricular function, size and wall thickness, degree of valve calcification and blood pressure (20).	2	Amended There are 3 types of **echocardiography** used clinically: **M-mode**, **two-dimensional** (**2**-D, B-**mode** or real time), and **Doppler echocardiography.**
Piotr Szymanski	37	Table 8	Check risk grading for Euroscore II – the thresholds seem to high – very few people undergo TAVI with Euroscore above 20		We have re-checked and find variations (in various not referenced sources) for cut-off values. To not introduce a new reference we suggest thefollowing as The ESC/EACTS guidelines (only) defines low and medium risk we: 1. Inserted the line revealed in yellow: …The latest version of the model – EuroSCORE II was launched in 2011 is an on-line tool, constantly updated and enhanced. The exact cut-off values for risk scores vary across the litterature and may be arbitrary. However, for STS-Prom and EuroSCORE II intermediate and low risk are defined by the ESC/EACTS (insert ref) as shown in Table 8. 2. Delete the two upper lines in the table 8 (deletet high and extreme high risk)

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Piotr Szymanski	38	969-71	≥ not > for both	1	Amended
Piotr Szymanski	39	1009	recent summary suggests that less than 70% is symptomatic - but numbers vary		No reference given, we can not change this as this is based on a reference
Clinical effectiveness					
Piotr Szymanski	42	1082 and 1085	Valves used in both pivotal trials are not CE marked for intermediate risk	1	Not clear
Piotr Szymanski	43	1128	Mortality NOT analysed according to access site (same for morbidity and safety)	1	Added: "The choice of access route depends on the patients anatomy and transfemoral access is less invasive than the transapical approach. Neither the NICE guidelines nor the ECT/EASCT guidelines provide recommendations with regard to access route or choice of system. The systematic review of Siemieniuk 2016 (ref) included four RCTs for which only two fulfilled our inclusion criteria. Analysis of data were performed based on access routes, and the authors concluded that patients at low and intermediate surgical risk are likely to perceive net benefit with transfemoral TAVI compared to SAVR, but that SAVR performs better than transapical TAVI. These analysis were mainly based on data from the PARTNER trial."
Reidar Bjørnerheim	44	1153	"..while 7.9%.7% died.." seems to be a printing error	2	Now the sentence "At two years follow-up 8.2% of participants died in the TAVI group while 7.9% .7% died in the control group." Is replaced with "At two years follow-up 7.9% of participants died in the TAVI group while 8.2% died in the control group."

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Reidar Bjørnerheim	46	1190	The threshold for reintervention after valve intervention is higher for SAVR than for TAVI, since reoperation is more difficult and carrying higher risk than the primary procedure, while the increase in operational risk is lower in a percutaneous procedure. Thus, the higher incidense or reintervention with TAVI may be operator bias, more than more frequent indication for reintervention.		We think that this reflection could hypothetically be possible but it is difficult to substantiate it with evidence as we do not have more information from the two trials. However, we think that despite the statistically significant difference between the two groups in terms of aortic intervention, the quality judgement reflects better the situation: the evidence behind this difference is very low as the events rates are very low.
Piotr Szymanski	48	Table 10	conclusions that are very different from the conclusions of professional organizations	1	Added: "Most importantly, the evidence evaluations supporting the guidelines preclude the publication of results from the SURTAVI trial. Furthermore, neither the NICE guidelines nor the ECT/EACST guidelines are based on the GRADE approach to evaluate confidence in each outcome. In our assessment, we have included data from the SURTAVI trial and we have used the GRADE approach for the most important outcomes. Our confidence in TAVI being non-inferior to SAVR with regard to 30 days mortality across the two trials is moderate. However, we report substantial uncertainty (low and very low quality of evidence) for several important outcomes making us unable to provide a firm conclusion with regard to benefits of TAVI versus SAVR for patients at intermediate surgical risk. "
Piotr Szymanski	53	1333	conclusions that are very different from the conclusions of professional organizations	1	See above

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Piotr Szymanski	55	1377	conclusions that are very different from the conclusions of professional organizations	1	See above
Safety					
Piotr Szymanski	57	1429	conclusions that are very different from the conclusions of professional organizations	1	See above
Piotr Szymanski	61	1505	conclusions that are very different from the conclusions of professional organizations	1	See above
Piotr Szymanski	68	1628	The – spelling	3	Amended
Appendix					
Reidar Bjørnerheim	General		The manuscript is good, based on the limited number of studies available. However, there are some questions that are not answered because of the limited studies. There are a couple of observations in favour of TAVI: - The types of valves that are evaluated are not the ones most highly rated in current clinical practice. In our institution, we mostly use Evolute R or Evolute Pro. The hemodynamic improvement after 2 days and 3 months (and one year) is striking (Vmax 1.5-1.8 m/s, compared to 2.8-3.5 m/s for the most widely used biological valves) - The convalescence phase is much shorter for TAVI than SAVR, since there is no sternal split to heal. This is particularly important for the octogenerians with slower healing process and shorter life expectancy, but also for younger people still at work. It is not just the length of the hospital stay that matters.	2	The following sentences have been added at the end of the discussion: *"As emerged by the comments from clinical experts, some issues at the moment remain uncovered and hardly can be incorporated within a health technology assessment. It's very difficult to reach conclusions on the diffusion of the different models of TAVI in the different settings or to assess whether the diffusion of a specific model is related to the availability of (good quality) supporting evidence. In fact, some centres have preferences towards a specific model or a specific manufacturer but the analysis of these variations were not within the scope of the present assessment. We acknowledge that convalescence phase can be another key-element for the choice of TAVI. However, only length of hospital stay is commonly reported*

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			An important question for extending the use of TAVI into younger age is the expected durability of the valves. Will they last eaqually long as surgical biological valves? Based on their manufactured structure, there is no reason to believe that they will be more short lived. However, this has not been clarified. Another important question is whether SAVI is more susceptible to endocarditis than current biological SAVR. This remains to be demonstrated. Patients younger than the current age-recommendations are increasingly demanding TAVI. This developement is hard to stop. One reason to try so, is as that currently the cost of TAVI is higher than SAVR. Since the procedure requires less resources, the cost should be lower. I do realise that these issues are difficult to incorporate in this manuscript, since there are no RCTs to clarify them.		*within the studies. Equal durability of the prosthetic valves used for TAVI and SAVR is another very important issue but, at the moment, since long-term data are not available for TAVI, it remains theoretical. Moreover, the high number of ongoing studies on low surgical risk patients could predict an increasing trend in the use of TAVI in future years."*
Piotr Szymanski			Initial analyses of SURTAVI outcomes were published and presented in 2017 – the text variably asserts that completion is anticipated in 2018/2026.		https://clinicaltrials.gov/ct2/show/NCT01586910 Notably new reference added October 30th. 2018: Durko AP, Reardon MJ, Kleiman NS, Popma JJ, Van Mieghem NM, Gleason TG, Bajwa T, O'Hair D, Brown DL, Ryan WH, Chang Y, De Leon SD, Kappetein AP. Neurological Complications After Transcatheter Versus Surgical Aortic Valve

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					Replacement in Intermediate-Risk Patients. J Am Coll Cardiol. 2018 Oct 30;72(18):2109-2119. doi: 10.1016/j.jacc.2018.07.093. Primary Completion Date : July 2018 Study Completion Date : November 2026

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MANUFACTURERS

Comments were received from:

Edwards Lifesciences
Medtronic Italia

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Description and technical characteristics of the technology					
Edwards Lifesciences	30	697-698	*"...with a prosthesis delivered through the blood vessels"*: TAVI can be implanted also through the apex of the heart (though mentioned later in the document).	2	Changed to "TAVI is the replacement of the aortic valve of the heart with a prosthesis delivered through the blood vessels using a catheter (transluminal via a large artery or vein) or alternatively via a small incision through the heart wall (apex of the left ventricle).
Edwards Lifesciences	30	703	***Suggestion: be more precise on the definition of the transapical access: it is made through the apex of the left ventricle and not "through the wall of the heart"***	1	Amended: wall is not wrong (see above), but to be precise changed (through the wall of the heart) to *(through the apex of the left ventricle)*
Medtronic Italia	30	710	"TAVI may be carried out either with general anaesthesia, **but in most of cases**, it is performed with local anaesthesia with sedation". REFERENCE: RISPEVA trial: Giordano A et al. Journal of Cardiovascular Medicine 2017, Vol 18 No 2. FORWARD trial. Grube E at al. Journal of American College of Cardiology 2017, Vol 70 No 7	2	Amended
Edwards Lifesciences	30	712-714	Angiography is mandatory, echo guided implants are limited, anecdotal experiences, so it should read: *"is assured by intra-procedural fluoroscopic guidance"*. Echo may be used to complement angiographic imaging. CT is the primary screening method to plan TAVI procedures and choose correct size. This is the consensus and gold standard in 2018.	2	Amended by changing the senetence as indicated: Correct placement of the implant is assured by *intra-procedural* radiographic imaging using fluoroscopy (angiography). Echocardiography may be used to complement angiographic imaging. CT Amended based on changes coverd after input from PS.

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Medtronic Italia	31	722	"TAVI may be carried out either with general anaesthesia, **but in most of cases**, it is performed with local anaesthesia with sedation". REFERENCE: RISPEVA trial: Giordano A et al. Journal of Cardiovascular Medicine 2017, Vol 18 No 2. FORWARD trial. Grube E at al. Journal of American College of Cardiology 2017, Vol 70 No 7	2	Amended
Medtronic Italia	31	723	Statement "specific issues related to TAVI compared to SAVR includes the risk for stroke." is not correct. SURTAVI trials reported statistically significant lower stroke rates in TAVI (2.6%) compared to SAVR (4.8%) at 30 days. REFERENCE: SURTAVI trial. Reardon MJ et al. The New England Journal of Medicine 2017, Apr 6;376(14):1321-1331; Durko et al. J Am Coll Cardiol. 2018 Oct 30;72(18):2109-2119. doi: 10.1016/j.jacc.2018.07.093.	1	See comment to Piotr Szymanski line 31
Medtronic Italia	31	727	"The latest TAVI devices in addition to being easier to handle, aim to reduce the introducer sheath diameter, minimize or avoid "**perivalvular**" aortic valve leakage"	2	Amended
Edwards Lifesciences	31	727	*"Aortic valve leakage"* is uncorrect. ***Suggestion: correct with "Paravalvular leakage (PVL)".***	3	Amended
Edwards Lifesciences	31	727-728	*"..offer reposition the valve prosthesis before final deployment"*: Repositioning has not been demonstrated to enhance procedural results, it is also specific to self-expandable products.	2	Not a factual mistake no need to change
Medtronic Italia	31	728	"**With reduced introducers diameters, vascular complications were reduced as well. New valves design and implant technique improvement reported lower pace-maker rates**". REFERENCE: FORWARD trial. Grube E at al. Journal of American College of Cardiology 2017, Vol 70 No 7. TVT registry. Forrest et al "30-day outcomes following transcatheter aortic valve replacement with the evolut pro valve in commercial use: a report from the sts/acc tvt registry™". TCT 2018.	2	This is new information which needs to be assessed. The assessment of registry data not being part of national registries was out of the scope of this report. However we aknowledge the information. Please add the following without inserting a new reference: Other improvements such as reduction of complications and the need for permanent pacemaker implantations are also aimed at with new designs and techniques.

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Medtronic Italia	31	739-741	The sentence "Even if involved... this new TAVI system" should be deleted as it is not relevant to the description of TAVI systems.	2	Sentence removed
Edwards Lifesciences	31	749	*"The Edwards SAPIENS prosthesis"* is formally wrong. ***The correct form is "The Edwards SAPIEN prostheses".***	3	Amended: SAPIEN (no S), check spelling prosthesis/prostheses throughout the manuscript – I think we should only use one spelling (UK english =prosthesis) as this is not obviously part of the name. SAPIENS all changed to SAPIEN UK english =prosthesis used throughout the document
Edwards Lifesciences	31	755-757	Edwards XT 20mm is available for TF only. Edwards SAPIEN 3 all sizes and Edwards SAPIEN XT 23 mm, 26 mm and 29 mm can be delivered through the transaortic access.	1	Replaced: "Both systems can be delivered transfemorally or transapically. S-XT may, due to its wider range of annulus sizes, also be delivered via the direct aortic access route. Both S-XT and S3 are available in four sizes: 20 mm, 23 mm, 26 mm and 29 mm in diameter." With: "Both S-XT and S3 are available in four sizes: 20 mm, 23 mm, 26 mm and 29 mm in diameter. S-XT 20 mm is only available for transfemoral use."
Medtronic Italia	31	760-761	Suggestion for rewording: The CoreValve and Evolut systems are delivered by Medtronic (www.medtronic.com) and are available in both USA and Europe for use outside clinical trials	2	Removed: www.corevalve.com
Medtronic Italia	32	763-764	Suggestion for rewording: The second generation CoreValve(TM) Evolut(TM) R System received CE mark in 2014 and FDA approval for treating patients who are at high or extreme risk for surgery in 2015. In Europe this indication was extended to treat aortic stenosis patients who are at intermediate risk for open-heart surgery as determined by a heart team in 2016. At that time Evolut(TM) R was the first transcatheter aortic valve implantation (TAVI) therapy to obtain an expanded indication in Europe for this patient population. In USA the FDA approved the treatment	1	Replaced sentence (763) "Evolut received a CE mark for patients at intermediate surgical…….. 2017." With this: "The second generation CoreValve(TM) Evolut(TM) R System received CE mark in 2014 and FDA approval for treating patients who are at high or extreme risk for surgery in 2015. In Europe this indication was extended to treat aortic

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			of intermediate surgical risk patients with Evolut(TM) R in 2017. Furthermore, the new Evolut R 34mm valve was approved in Europe for severe aortic stenosis patients who are at intermediate, high or extreme risk for surgery with an annulus size ranging from 26mm to 30mm in 2017. Previously, some of these patients were unable to receive a TAVI due to the larger size of their native diseased aortic valve.		stenosis patients who are at intermediate risk for open-heart surgery as determined by a heart team in 2016. In USA the FDA approved the treatment of intermediate surgical risk patients with Evolut(TM) R in 2017. Furthermore, a new Evolut R 34mm valve was approved in Europe for severe aortic stenosis patients who are at intermediate, high or extreme risk for surgery with an annulus size ranging from 26mm to 30mm in 2017."
Medtronic Italia	32	769-772	Suggestion for rewording: Both systems can be delivered via the transfemoral or alternative access routes, such as transsubclavia or transaorta. The InLine(TM) Sheath significantly reduced the delivery profile (14 Fr equivalent). Evolut R Valves have a supraannular design, consistent radial force and the possibility of recapture and repositioning, if needed. Furthermore, the valves are treated with a specific anticalcification treatment and are available in the following sizes: 23, 26, 29, 34 mm and can therefore treat a range of annulus size from 18-30 mm.	1	Ammended but shorten down as reveled Replaced sentence 769 "Both systems...route." With this: Both systems can be delivered via the transfemoral or alternative access routes, such as transsubclavial and transaorta. Replaced sentence: 769 "Evolut R is the third generation technology …. to 30 mm diameters." with these: "Evolut R valves are provided with a specific anticalcification treatment, they may be recaptured and repositioned if needed, and are available in different sizes to treat a range of aortic annulus dimaters from 18mm to 30 mm diameters."
Medtronic Italia	32	773	Suggestion for rewording: In 2017 the CoreValve(TM)Evolut(TM) PRO valve received CE mark and FDA approval for the treatment of severe aortic stenosis for symptomatic patients who are at intermediate, high or extreme risk for open heart surgery. The Evolut PRO valve has an outer wrap that adds surface area contact between the valve and the native	2	Amended

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			aortic annulus to further advance valve sealing performance.		
Medtronic Italia	32	775	Table 5: Features of identified TAVI systems in June 2017. Engager valve was not designed for TF approach.	1	We kept in table 5 only the devices for intermediate risk, all the others have been deleted from the table and related text.
Edwards Lifesciences	32	775 Table 5	Edwards SAPIEN XT and SAPIEN 3 have a chobalt Chromium alloy stent frame. ***Suggestion: remove "Stainless Steel" from table 5, first line***	1	amended
Edwards Lifesciences	32	775 Table 5	Since several TAVI systems are CE marked for Inoperable and high surgical risk patients, as the report explains, Table 5 should be updated to 2018: in fact, in February 2018 Edwards CENTERA (the first Edwards Self-exandable percutaneous aortic valve). received CE mark for Inoperable and High Risk patients. ***Suggestion: Add Edwards CENTERA to the table***	1	All devices out of our scope (intermediate risk) have been deleted and related text has been amended. Under the table the sentences "*Systems available for general use in Europe outside clinical trials as of June 2017. An additional system (Medtronic Evolute Pro) was launced in Europe in July 2017 for intermediate, high risk patients and extyremely high risk patients. Note: At the top of the table, the TAVI systems into the grey rows (Sapien 3 and Evolut R) are those with indication for patients at intermediate surgical risk." Can be replaced by this sentences: "*TAVI systems available for general use in Europe outside clinical trials as of June 2017.

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					Sapien 3 and Evolut R are those with indication for patients at intermediate surgical risk. Since June 2017 additional systems have been launched in Europe. This includes the Medtronic Evolute Pro system, with a CE mark from July 2017 for intermediate, high as well as extyremely high risk patients and the Edwards Centera selfexpandable system with a CE mark from February 2018. We can not exclude that additional TAVI systems have been launched."
Edwards Lifesciences	35	775 Table 5	Edwards SAPIEN 3 valve isn't CE marked for subclavian access. ***Suggestion: Delete "SC" from the list of delivering approaches.***		Amended
Edwards Lifesciences	33	794	*"More recent approaches to SAVR include sutureless valves"*: new generation of surgical valves includes also the rapid deployment valves. Sutureless and rapid deployment aortic valves are biological, pericardial prostheses that anchor within the aortic annulus, respectively by no sutures, or no more than three sutures. ***Suggestion: Add "and rapid deployment valves" to the sentence.***	1	Amended
Medtronic Italia	33	800	The sentence from line 852 should be added here "However SAVR with sutureless valves is less documented and not considered an established treatment"	2	Not amended as mentioned below Not a comment from the fact check. But deleted: *which may be of benefits.*
Edwards Lifesciences	34	813-819	References on claimed benefit on TAVI are missing. ***Suggestion: Add references.***	2	These are the same as the references under B0001 what is TAVI...TAVI systems: that is ((16), (53), (3); manufacturers web sites; submission files from manu facturers)).

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EUnetHTA JA3 WP4 - Other technologies, OTCA06
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Medtronic Italia	34	819	"Other claimed benefits are related to length of hospital stay, recovery time and **the recurrence of rehabilitation post discharge (as for clinical practice post SAVR in Italy). These consideration have an impact on the total cost of care of aortic stenosis in the regional/national perspective**". REFERENCE: euroPCR 2018 and ISPOR Baltimore 2018. "*Determinants and pathways of rehabilitation after surgical aortic valve replacement: a population-based, retrospective study with administrative data*". Callea G et al. Paper in submission.	1	Added hospital stay, ~~and~~ recovery time **and post discharge rehabilitation.**
Edwards Lifescience	34	825 830	There are 2 misspellings of Edwards "Life Sciences" to be corrected. ***Suggestion: Correct with "Edwards Lifesciences".***	3	Amended
Medtronic Italia	34	838-843	"Lack of evidence on improved effectiveness", uncertainty with regard to prosthesis lifetime and uncertainty with regard to risks of early complications and long-term outcomes, as well as higher device costs and need for organizational changes influences the use of TAVI, and has restricted its use in particular for younger patients and those at lower surgical risk. However, at least in some countries there has been a shift towards the use of TAVI also for patients at intermediate and low risk". **1.** "Lack of evidence": there are 2 randomized clinical studies (PARTNER IIa, SURTAVI) that studied TAVI use in intermediate risk patients. For higher risk there is a lot of evidence that confirms effectiveness of the procedure. **2.** The main reason of the heterogeneous use of TAVI in the different European countries should be found in the barriers created from decision makers (funding and reimbursement issues, limitation in terms of volume and # of patients elegible to the treatment, etc). Regarding that, the exiting literature show that main drivers of TAVI adoption and diffusion in Italy seem to be hospital type & ownership and reimbursement schemes. REFERENCE: "Reimbursement policies, hospital features and innovation in healthcare. The case of transcatheter aortic valve implantation in Italy". G. Callea, M. Cavallo, R. Tarricone, A. Torbica, N. Piazza, MD, F Maisano. EHJ 2014. **3.** Suggestion for rewording: delete ""Lack of evidence on improved effectiveness" in line 838	1	"The manufacturer/ MAH was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check". Notably, questions regarding effectiveness is assessed in the EFF and SAF domains. Lack of evidence on improved effectiveness has restricted its use. We have not read the suggested reference.

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Edwards Lifesciences	34	838-843	The shift towards intermediate risk with Edwards SAPIEN 3 is supported by clinical study evidence of superiority over SAVR (Partner II S3i study – Thourani VH, Kodali S, Makkar RR et al. Lancet 2016) ***Suggestion: Add reference.***	1	"The manufacturer/MAH was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy of the TEC domain – belongs to the EFF and SAF domain".
Medtronic Italia	35	857	Table 7: payment models in 2013. The Italian regions have 3 different reimbursement types for TAVI: add-on reimbursement, lump-sum reimbursement and ad hoc funding for device use). REFERENCE:"Il governo dell'innovazione tecnologica in sanità. Il caso dell'impianto di valvola aortica transcatetere: stato dell'arte delle indicazioni e della rimborsabilità nelle regioni italiane", Callea G et al. Mecosan, 2015	1	We have not read this reference. This is based on the cited refernce from 2013. Will be considered in the italian national report on TAVI
Edwards Lifesciences	35	857 Table 7	Payment models in Italy diffentiate between public and private hospitals: • Private hospitals provide their services and requests for a reimbursement to the Region where they belong, based on DRG Tariff and/or specific add-on reimbursements.	2	Will be considered in the Italian national report -
			• Public hospital are funded by Regional budgets, defined and spread overall the Italian Region by the Central Government. ***Suggestion: Add "Hospital Budget" to Italy line in the table***		
Health problem and current use					
Edwards Lifesciences	39	978-997	The list of aspects favoring either TAVI or SAVR is not exhaustive, as in the 2017 ESC/EACTS Guidelines several other aspects are mentioned.There is no explicit rationale why some of them are includes are some other aren't. ***Suggestion: add all the aspects mentioned in the guidelines (table 7 p. 19 of ESC/EACTS Guidelines – Eur Heart J 2017).***	1	This is a selection of aspects. The selection does not aim for completion. A reference for more detailed aspects is given.

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Edwards Lifesciences	40	1024-1025	The reference to the intermediate risk indication should be removed from this sentence, since TAVI is indeed recommended for IR patients in the European guidelines (as mentioned elsewhere in this chapter). ***Suggested new wording: "However, in many countries the use has extended to patients at low-risk not included by guideline recommendations (65), (12").***	1	This referers to the 2012 guidelines: changed ..." the use has extended to patients at intermediate and low-risk not included by guideline recommendations (). the use in June 2017 had extended …. Not included by the 2012 guideline rec… (ref)
Edwards Lifesciences	40	1036-1037	The phrase: *"with additional patients treated beyond those who would be eligible for open heart surgery"* gives the impression that patients are treated, even though they should not be treated. ***Suggested new wording: "with elderly patients treated with AVR who otherwise would not have been able to have a heart valve replacement"***	2	Amended
Edwards Lifesciences	40	1039-1040	The report offers no evidence to support the conclusion that costs and reimbursement systems are important factors in adoption rates. ***Suggestion: remove phrase entirely.***	1	References are given
Medtronic Italia	40	1053	Table 9: Reimbursement status of TAVI among EUnetHTA partners. GISE database includes also the n° of procedures related to 2017: Number of procedures 2017 = 5.528 TAVI (91 per million inhabitants)	2	Will be considered in the italian national report on TAVI as we do not up-date for other countries)
Edwards Lifesciences	40	1053 Table 9	The reported number of procedures for Belgium represents the annual number of reimbursed procedures and doesn't correspond to actual number of procedures performed/patients treated with TAVI per annum. ***Suggestion: clarify that this number pertains to capped reimbursed volume per annum***	2	

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Edwards Lifesciences	41	1053 Table 9	Scotland, UK: According to the NICOR audit of TAVI in the UK, there were 157 TAVI performed in 2016. Since Scotland data is specified in the report, this should specifically refer to either England Wales or Northern Ireland, too. In 2016 the total volume of TAVI (England, Wales; Scotland and Northern Ireland) is 3.250. ***Suggestion: include this data.***		This was based on our survey, we did not receive separate data for England, Wales and NI
Edwards Lifesciences	41	1053 Table 9	The number of TAVI procedures in Italy shall be updated with new data from GISE (The Italian Scientific Society of Interventional Cardiology) Registry. In 2017 5.528 TAVI were implanted in Italy. In addition, also the number of procedures per million inhabitants (ppm) shall be changed, explaining that it refers to 2017 data. Now it amounts to 91 ppm. ***Suggestion: include new data of implants.***	1	Will be considered in the Italian national report on TAVI
Edwards Lifesciences	41	1053 Table 9	Add the endnotes that are still missing below Table 9: • Italy (60.7***) • 3 466 (2015)# • 4.592 (2016)#	2	Amended
Summary of relative effectiveness					
Medtronic Italia	11	L341-342	Author concluded uncertain whether TAVI is non-inferior to SAVR in terms of mortality at two years follow-up. Evidence was downgraded due to study withdrawals prior to procedure mainly in SAVR group and incomplete two year follow-up. We think evidence should not be downgraded for SURTAVI study., SURTAVI compared SAVR subjects who didn't undergo the procedure with those who did and identified no differences in baseline demogrpahics, surgial fraility, disablity or coexisitng illness., there were not 30% or 50% participants who were lost to follow-up in the SURTAVI trial. Most of those haven't reach 24 months follow-up yet and the 24 months outcomes were imputed using sound Bayesian methodology.	1	The quality assessment is provided for the overall evidence and not usingle single trial. In addition, the fact that authors used an imputation method does is not sufficient to avoid downgrading as people as more than 50% of subjects were lost to follow up
Clinical effectiveness					
Medtronic Italia	43	1119-1120	There were 280 patients in the TAVR group and 249 in the SAVR group who were alive at 24 months defined as 730 days post procedure. Patients who died prior to 24 months were counted in the mortality analysis and no imputation was done for this patient. Suggest deleteting wording of 'As an example, for the outcome mortality at 24 months 280	1	We disagree. Figure 1 in the paper shows that at 24 months follow-up there were 280 and 249 at risk for the outcome total mortality

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			patients were available for outcome measures in the TAVI group and 249 in the SAVR group'.		
Medtronic Italia	45	1182	Please add 'SURTAVI trial assessed aortic valve re-hospitalizations at 30 days, 1 year and 2 years showing no evidence of differences between TAVI and open surgery'.	1	Agreed. Sentence added: 'In addition, SURTAVI trial assessed aortic valve re-hospitalizations at 30 days, 1 year and 2 years showing no evidence of differences between TAVI and open surgery' at the end of the paragraph *Aortic valve reintervention*
Medtronic Italia	47	1245	This sentence is incorrect: SURTAVI trials reported KCCQ, SF-36 and EQ-5D change from baseline data.	2	The reported data on quality of life in the SURTAVI trial is from KCCQ assessment. Added in braket (KCCQ) in line 1239 (after the words "class III or higher""
Medtronic Italia	51	1267-1268 1272-1273 1285-1286	'(b) at two years follow-up more than 30% and 50% of participants were lost to follow-up in each trial respectively'. This sentence is incorrect for SURTAVI as many patient were still followed but just haven't reached 24 months follow-up yet. Suggest rewordinig '(b) at two years follow-up more than 30% and 50% of particpants were lost to follow-up in one trial and haven't reached 24 months follow-up or were lost to follow-up in another trial'.	1	The sense of the sentence is the same.

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