Input from external experts and manufacturer on the **2nd draft assessment**
"Wearable cardioverter-defibrillator (WCD) therapy in primary and secondary prevention of sudden cardiac death in patients at risk"
(Project ID: WP4-ACB-CA-1)

eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

Content

[a] "major": the comment points to a highly relevant aspect and a thorough answer is expected from the author(s)
[b] "minor": the comment does not necessarily have to be answered in a detailed manner
[c] "linguistic": grammar, wording, spelling or comprehensibility

EUnetHTA JA3 WP4 - Other technologies
All comments and author´s replies on the 2nd draft assessment "WEARABLE CARDIOVERTER-DEFIBRILLATOR (WCD) THERAPY IN PRIMARY AND SECONDARY PREVENTION OF SUDDEN CARDIAC DEATH IN PATIENTS AT RISK"

November 2016

EXTERNAL EXPERTS

Comments were received from:

Name	Affiliation
Diana Delić-Brkljačić	University hospital Sisters of Mercy, Zagreb, Croatia
Piotr Szymanski (PSZ)	Institute of Cardiology, Warsaw (on behalf of European Society of Cardiology), Poland
Olaf Weingart	Medical Advisory Service of the Statutory Health Insurance Funds North-Rhine, Germany

Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Character of comment • 'major'[a] =1 • 'minor'[b] = 2 • 'linguistic'[c] =3	Author's reply
General					
Diana Delić Brkljačić			No additional comments, comments provided previously are included in the revised text		
PSZ external expert	General		In general appropriate shocks should be re considered as an effectiveness outcome and even if not considered as such should be described in more detail in the text body, also resuscitated cardiac arrest as an outcome is missing and even if not considered as an efectiveness outcome it should be described in more detail in the text body	1	Appropriate shocks are mentioned as an outcome (it falls under the outcome VT/VF incidence in the scope) and extracted in the table which can be found in the appendix. We included the description of appropriate shocks in the text body (summary and discussion of effectiveness). Information on resuscitated cardiac arrest was added to the discussion of effectiveness domain.

[a] "major": the comment points to a highly relevant aspect and a thorough answer is expected from the author(s)
[b] "minor": the comment does not necessarily have to be answered in a detailed manner
[c] "linguistic": grammar, wording, spelling or comprehensibility

PSZ	General		Analyses largely ignores harns specific to comparators and absent in case of WCD use such as infections (incl infective endocarditis), procedure reated complications including deaths, RV perforation etc, this should be mentioned in the analyses	1	The following information was added: "Furthermore it should be kept in mind that comparators do have other specific harms, which the WCD does not have. In case of ICDs these are device infections (pocket infection, deeper infection), procedure related complications including deaths and right ventricular perforation. Pharmacological therapy has side effects especially in elderly patients. Possible complications of catheter ablation are stroke, valve damage, cardiac tamponade, atrio-ventricular block and procedure-related mortality."
PSZ	General		WCD was mentioned as a bridge to optimal pharmacologic therapy but it is supposed to be also used on top of optimal prarmacotherapy	1 (less important that 2 above)	The following stament was added to the Scope section: "As a bridge to optimal pharmacological therapy, or as a protection during pharmacological therapy optimization when a heightened risk of sudden cardiac death (SCD) is present, but possibly resolvable over time or with treatment of left ventricular dysfunction (29, 30) e.g. for patients with:…"

[a] "major": the comment points to a highly relevant aspect and a thorough answer is expected from the author(s)
[b] "minor": the comment does not necessarily have to be answered in a detailed manner
[c] "linguistic": grammar, wording, spelling or comprehensibility

PSZ	General		More a question than a suggestion – in the absece of available data is it in Your opinion reasonable to include in the effectiveness analyses retrospectively/prospetively collected samples with propensity score matching	2	After having discussed the question of propensity score matching with our LBI statistician, we concluded not to do the calculations. The reason is that propensity score matching should be ideally used on the controlled group within the same study if randomisation was not possible. In our case, where no controlled study passed our selection criteria, such cannot be done.
Summary					
PSZ		48-52	Endpoints – resusctitated cardiac arrest and appropriate shocks should be discussed for the effectiveness domain	1	Appropriate shocks are an outcome in our report and respective information was added to the summary and discussion of effectiveness domain. Resusctitated cardiac arrest was only indicated in one study and information was added to discussion of effectiveness: "Furthermore only one study reported on resuscitated cardiac arrest: two patients experienced unsuccessful shocks due to incorrect placement of therapy electrodes, but one of the events was nonfatal since the patient received a successful external defibrillation (18)."

[a] "major": the comment points to a highly relevant aspect and a thorough answer is expected from the author(s)
[b] "minor": the comment does not necessarily have to be answered in a detailed manner
[c] "linguistic": grammar, wording, spelling or comprehensibility

PS		81-97	WCDs role as an add on therapy on top of optimal phatmacotherapy should be mentioned	½	The following sentence was added: "There are four categories of standard treatments, depending on the indication, that are being replaced, postponed, or optimized by the introduction of a WCD for the management of ventricular arrhythmia (VA) and for the prevention of SCA…"
PSZ		112	May be electromechanical dissociation instead of pump failure	½	Accepted and corrected.
PSZ		123-125	definition of utilization is unclear to me – does it mean interventions or number of utilized WCD devices?	2	The sentence was clarified: "The expected annual prescription of WCD is 160 prescriptions per year in Austria when assuming the same prescribing practice as in the US."
PSZ		227-229	"WCD as a placebo that provides security" - does WCD fulfil the definition of placebo which is defined as an inactive intervention	2	Accepted. The term placebo was erased.
PSZ		237	little impact – unclear impact on what?	2	The sentence was clarified via adding "little impact in the treatment of SCA".
PSZ		250-253	appropriate shocks not commented on	2	Information on appropriate shocks was added. "In contrast, there is inhomogeneity in appropriate shocks (1.1% to 43% of patients), which might show that risk stratification of patients is of utmost importance"
Description and technical characteristics of the technology					
PSZ		501-502	delete "recently also" as pacing available from 90s in ICDs	2	Accepted and corrected.
Olaf Weingart (MDK)	29	580	Table you may use the new data from Wäßning 2016 (based on 6043 pts from April 2010 through October 2013, from all states of Germany) relevant data in Table 1 of the publication	1	Data from Klein 2010 will be used for the sake of making a more accurate historical comparison.

[a] "major": the comment points to a highly relevant aspect and a thorough answer is expected from the author(s)
[b] "minor": the comment does not necessarily have to be answered in a detailed manner
[c] "linguistic": grammar, wording, spelling or comprehensibility

Olaf Weingart (MDK)	29	580	The reference 31 (Klein 2013) is a review the data from the 354 pts reported are published first in Klein 2010 (pts 354 patients from Germany hospitalized between 2000 and 2008) or you may change see above. Just fyi the data from Chung are from pts in the U.S. who wore the WCD from August 2002 through December 2006 If you prefer a more "historic comparison" from same prescription time (see comment row above)	1	See comment above.
PSZ		585	Sentence seems irrelevant to the topic – do be deleted?	2	Not accepted. The reason is that the assessment element question [B0003] asks about the phase of development of the WCD and the comparators. The quesiton of ICD compatibility with MRIs is considered to answer this question.
PSZ					
Health problem and current use					
PSZ		726	not described - either natural course of cardiac arrest as in lines 719-733 or natural course of the risk of SCD in various health conditions, for example time related risk of SCD following ICD implantation/primary event - eg myocardial infarcion	2	The assessment question was changed to: "What is the natural course of SCA?". Also, there was a statement added to the methods section that: "Some assessment element questions were answered together i.e. questions were listed below each other and a summarized answer is provided."
PSZ		730	I would rephrase to better "small minority of patients" rather than give precise numbers	2	Accepted and corrected.
PSZ		729-733	describes natural course - should be moved to line 726	2	There was a statement added to the methods section explaining that several questions were answered together stating that: "Some assessment element questions were answered together i.e. questions were listed below each other and a summarized answer is provided."

[a] "major": the comment points to a highly relevant aspect and a thorough answer is expected from the author(s)
[b] "minor": the comment does not necessarily have to be answered in a detailed manner
[c] "linguistic": grammar, wording, spelling or comprehensibility

PSZ		733-738	as a burden of the disease I would describe death (burden to the family – especially frustrating in the case of SCD) and consequences of delayed intervention - mainly permanent neurologic deficit	2	The following sentence was added: "The burden of disease for the patient is death and the consequences that follow a delayed intervention, mainly a permanent neurological deficit."
PSZ		761-762	This refers to competiitive sports and competitive athlets only	1	Accepted and corrected.
PSZ		773	Unclear to me - "on patients requiring AED help" –to be explained – it seems to suggest that AED can be used by SCD victims themselves ?	2	The term "timely defibrillation by AEDs" was added.
Olaf Weingart (MDK)	34	783	(12) Reference Link ?? may be wrong	3	Accepted. The reference was changed to: Committee on the Treatment of Cardiac Arrest, Current Status and Future Directions, Board on Health Sciences Policy, Medicine. Io. Strategies to Improve Cardiac Arrest Survival: A Time to Act. Graham R., McCoy M.A., Schultz A.M., editors. Washington (DC): National Academies Press (US); 2015.
PSZ		799-800	utilization – unclear as in line 123-125 – to be more precisely defined	2	The sentence was clarified: "The expected annual prescription of WCD is 160 prescriptions per year in Austria when assuming the same prescribing practice as in the US."
PSZ		814-15	Placebo definition unclear as in line 123-125	2	Accepted. The term placebo was erased.
PSZ		816	Perhaps a number of appropriate shocks should be described in more detail	2	The following statement was added "…appropriate shocks to less than 2% of the patients (described in further detail in the effectiveness domain discussion)"

[a] "major": the comment points to a highly relevant aspect and a thorough answer is expected from the author(s)
[b] "minor": the comment does not necessarily have to be answered in a detailed manner
[c] "linguistic": grammar, wording, spelling or comprehensibility

Olaf Weingart (MDK)	35	816-818 FF	Up to 2 % events in a short treatment period of 3 month are high May be you extend the discussion here, that these data esp. for pts in high risk subgroups are not reported but still available. In recent publications I see a publication policy which is good for business but not for pts and health systems. For example in prospective register Kutyfifa 2015.in they reported outcome and safety data in a mixed group: DCM 927 pts of these 67 pts in secondary prevention (after SCD) 116 pts with previous syncope which qualified in most guidelines for ICD. ICPM 805 pts are 85 with SCD and 182 pts with previous syncope also. Due to these publication policy with published data of e.g. 0,616% pts / month in relevant event rate for ICPM suggest there is a need for all (including the low risk pts) which result in higher WCD prescription. On other side there is waist of research because I think they record more pts. data, which may allow to identify relevant risk factors for VT /VF.	2	Accepted. The following sentence was added: "In particular, more data is needed for specific risk stratification of high risk patients whose data is available, yet reported as part of larger subgroups. That skews the results and presents the WCD as the treatment of choice for the whole subgroup, even though it is most needed for the high risk patient groups as it is the case in (22), where previous SCA and syncope patients at highest risk fall under the general subgroup of non-ischaemic cardiomyopathy."
Olaf Weingart (MDK)	35	843	"see above and below" an RCT without "risk stratified " subgroup data may be also not useful.	1	Accepted. The following statement was added: "…but more comparative data for risk stratified subgroups is needed to establish the WCD's effectiveness.."
Clinical effectiveness					
PSZ		848	As mentioned above - number of appropriate shocks as a measure of clinical effectiveness missing?	½	Appropriate shocks now mentioned in discussion section of effectiveness
PSZ		875, 879 and 883	higher incidence of ineffective high voltage therapies compared to classic ICDs; should not it be considered here?	2	Since no evidence seems to be available, we did not include this statement.
PSZ		906-909	these outcomes not included in the effectiveness analysis – perhaps to be considered – appropriate shocks (as mentioned above)?	2	Information on appropriate shocks was added to discussion section of effectiveness: "Appropriate shocks ranged from 1.1 to 8% (18, 20, 22) up to 43% (19), whereas one registry study did not report on this outcome (21)."

[a] "major": the comment points to a highly relevant aspect and a thorough answer is expected from the author(s)
[b] "minor": the comment does not necessarily have to be answered in a detailed manner
[c] "linguistic": grammar, wording, spelling or comprehensibility

PSZ		911-923	appropriate shocks not discussed (see above)	2	See above
Safety					
PSZ		1037-1060	safety of WCD in relation to comparators – perhaps harms specific to comparators should be discussed here – for example local infections, infectious endocarditis (lead infections), other procedure-related complications including deaths, right ventricle perforation, tamponade, tricuspid regurgitation – this is an important aspect given their zero prevalence in WCD patients	1	The following information was added: "Furthermore it should be kept in mind that comparators do have other specific harms, which the WCD does not have. In case of ICDs these are device infections (pocket infection, deeper infection), procedure related complications including deaths and right ventricular perforation. Pharmacological therapy has side effects especially in elderly patients. Possible complications of catheter ablation are stroke, valve damage, cardiac tamponade, atrio-ventricular block and procedure-related mortality."
Potential Ethical / Organisational					
Olaf Weingart (MDK)	46	1226ff	In addition to point of misleading "publication policy" (see above page 35 /line 816ff) is also an ethical question I suggest to add also some remarks to the responsibly of authors / scientists and the company in context with discussion of F0010.	1	Accepted. The legal question I0026 was extended in the following way: "Also, in the absence of comparative data and hence the promise of false security (as outlined in F0010), there is a potential issue with liability for harms inflicted on the side of authors, scientists, and the manufacturer."
Appendix					
PSZ			There is a Polish Expert Consensus approved in 09.2016 by Polish Cardiac Society	2	Since this document is not available in English and none of the authors/co-authors is speaking Polish we were not able to include it.

[a] "major": the comment points to a highly relevant aspect and a thorough answer is expected from the author(s)
[b] "minor": the comment does not necessarily have to be answered in a detailed manner
[c] "linguistic": grammar, wording, spelling or comprehensibility

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
Part I: Methods				
1. Are inclusion/exclusion criteria for selection of the studies described in appropriate detail?	3x			
2. Are the quality appraisal tools appropriate?	3x			
3. Is the type/presentation of evidence (e.g. Meta analysis, qualitative synthesis, GRADE) appropriate for this analysis?	3x			
4. Is the risk of bias sufficiently assessed, both on study level and on an outcome level?	3x			
5. Is the choice of study types appropriate to the population, intervention(s), comparison(s) and outcome(s)?	3x	Comment PSZ: (see comment/question on retrospective studies with propensity score matching)		
6. Are the types of studies to be included (randomised trials, quasi-randomised trials or other designs) described?	3x			
7. If it was relevant to include data from indirect comparisons, is this step justified and the methods of indirect comparisons sufficiently described?	3x			
8. Are appropriate methods of measuring each outcome and appropriate time points for measurement identified?	3x			
Comments:				

9. Are details on sources of information and literature search strategies provided?					
Search strategy	Databases	Year range	Language restriction	Primary data	Other kind of information resources
O	O	O	O	O	O
Comment Olaf Weingart: all ok					
10. Information on basis for the assessment and interpretation of selected data and information:					
Method of data extraction described?	Critical appraisal method (for quality assessment of the literature) described?	Method of data synthesis described?			

[a] "major": the comment points to a highly relevant aspect and a thorough answer is expected from the author(s)
[b] "minor": the comment does not necessarily have to be answered in a detailed manner
[c] "linguistic": grammar, wording, spelling or comprehensibility

O	O	O
Comment Olaf Weingart: all ok		

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
Part II: Results (See Domain Reports)				
Description and technical characteristics of the technology				
1. Does the section describe the intervention under review including how it works and how it may have an impact on potential recipients?	3x			
2. Does the section describe the comparator(s) under review including how it works and how it may have an impact on potential recipients?	3x			
3. Are the supporting references current and do they provide an international picture of the problem?	3x			
Comment Diana Delić-Brkljačić: very well written				
Health problem and current use of the technology				
4. Does the section describe the health issue including incidence and prevalence, how it occurs, who is affected (including high-risk groups, vulnerable/disadvantaged populations, where it occurs, how it is diagnosed, symptoms and consequences)?	3x			
5. Are the supporting references current and do they provide an international picture of the problem?	3x			
Comment Diana Delić-Brkljačić: very well written				
Safety and effectiveness				
6. Is the risk of bias clearly reported?	3x			
7. Is quality of data sufficiently evaluated?	3x			
8. Are both relative and absolute effect measures presented for each dichotomous outcome?	2x			
9. Are continuous data reported according to appropriate statistics (e.g. 'standardised mean difference' or 'weighted mean difference')?	2x, 1xNA,			
10. In case of time-to event analysis, are hazard ratios (HR) and ratios of medians presented?	2x, 1xNA			
11. Are measures of the precision of the effect estimates presented or, in case of absence of this essential information, is this fact reported?	2x	1x		
12. Is frequency of adverse events, frequency of occurrence, relative risk or number needed to harm (NNH) presented for the safety data?	3x			
13. In cases where adverse events are incorporated in utility values of quality of life, is the source of quantification accessible?	2x, 1xNA			

[a] "major": the comment points to a highly relevant aspect and a thorough answer is expected from the author(s)
[b] "minor": the comment does not necessarily have to be answered in a detailed manner
[c] "linguistic": grammar, wording, spelling or comprehensibility

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
14. Was the transformation of the surrogate outcomes into patient-relevant final outcomes considered (if relevant)?	2x, 1xNA			
Comments Olaf Weingart: • NA not applicable • (11) As I stated above, due to the "publication policy" essential information of known results of risk stratified subgroups is missing in all WCD publications.				
General				
15. Do you agree that the data extracted are relevant to the research questions formulated in the beginning and that analysed and synthesised data still answer the question?	3x			
16. Can the results be applied to the intended population?	3x			
17. Is the assessment sufficiently transparent and evidence ('facts') distinguished from judgements (including values and preferences)?	3x			
Comments:				
Part III: Summary of Relative Effectiveness				
18. Does the summary present a balanced representation of the content of the report?	3x			
19. Does the discussion of the summary clearly address the uncertainty in the available evidence, the evidence gaps and the applicability of the evidence?	2x	1x		
Comment Olaf Weingart: • As I stated above, due to the "publication policy" essential information of known results of risk stratified subgroups is missing in all WCD publication.				
Part IV: Other Considerations				
20. Have all relevant ethical, organisational, social and legal aspects been considered? (See Appendix 3 of the Pilot assessment)	3x			
Comments Diana Delić-Brkljačić: very well written				

[a] "major": the comment points to a highly relevant aspect and a thorough answer is expected from the author(s)
[b] "minor": the comment does not necessarily have to be answered in a detailed manner
[c] "linguistic": grammar, wording, spelling or comprehensibility

November 2016

MANUFACTURER

Comments were received from:

Name	Affiliation
Carla Zema et al.	ZOLL Medical Corporation (factual accuracy check)

Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Character of comment • 'major'[a] =1 • 'minor'[b] = 2 • 'linguistic'[c] =3	Author's reply
Description and technical characteristics of the technology					
ZOLL	9, 25	69-73, 439-442	Replace with "The WCD consists of two main components: (1) an electrode belt and garment that surrounds the patient's chest, and (2) a monitor that that patient wears around the waist or from a shoulder strap."	2	Accepted.

[a] "major": the comment points to a highly relevant aspect and a thorough answer is expected from the author(s)
[b] "minor": the comment does not necessarily have to be answered in a detailed manner
[c] "linguistic": grammar, wording, spelling or comprehensibility

ZOLL	9	82-97	The WCD is not used to "replace or postpone" the therapies listed. The WCD is used when ICDs are not indicated (e.g., guideline recommended waiting periods) or cannot be used (e.g., infection prevents implantation). The WCD can be comcommitently used with GL pharmacological therapy as described in the document. Cather ablation is typically used for patients after they have received an ICD, therefore, would not be WCD patients. AEDs are not recommended as effective for patients at high risk for SCD and are used when SCA occurs in a general population that is not at high risk for SCD.	1	The statement will be adjusted as follows: "There are four categories of standard treatments, depending on the indication, that are being replaced, postponed, bridged, or optimized by the introduction of a WCD for the management of ventricular arrhythmia (VA) and for the prevention of SCA…" As outlined in answers to previous comments, that is the case because, for example: - WCD attempts to replace ICDs immediately post MI, - WCD attempts to postpone other treatments as part of the watch and wait strategy during diagnosis, - WCD attempts to provide a bridge to an ICD replacement, WCD claims to protect the patient during the optimization of pharmacological therapy.

[a] "major": the comment points to a highly relevant aspect and a thorough answer is expected from the author(s)
[b] "minor": the comment does not necessarily have to be answered in a detailed manner
[c] "linguistic": grammar, wording, spelling or comprehensibility

ZOLL	9	101-103	This statement is inaccurate. The WCD "claims" to protect patients at high risk of SCD during their changing condition while permanent SCA risk has not been established.	1	As the two statement convey almost the same meaning, the statement will not be changed as suggested. The statement will be changed as follows: "WCD claims to offer temporary protection from SCA in **high risk** periods between diagnosis, or an experience of VT/VF, and the appropriate treatment (**or optimization of it**)".
ZOLL	25	444-445	Replace with "The garment comes in various sizes and is worn under the patient's clothing to hold four dry, non-adhesive sensing electrodes and three therapy pads on the electrode belt..."	2	Accepted.
ZOLL	25	449	Replace "take two hours" with "can take up to 16 hours"	2	Accepted.
ZOLL	25	449	Replace "two additional" with "a total of two"	2	Accepted.
ZOLL	26	455-456	Replace "and in case it detects a life-threatening heart rhythm it can restore, such as" with "for"	2	As both alternatives convey the same meaning, the original will not be changed.
ZOLL	26	466-468	Replace "seek medical attention, where..." with "call their doctor". Also, please note that ZOLL services the WCD and provides any necessary replacements, not the physician.	2	Partially accepted. The sentence will be changed as follows: "...call their doctor or seek medical attention". That is the case because it is assumed that if the respective cardiologist is unavailable, further medical attention is required nonetheless.
ZOLL	26	472	Replace "records and transmits the data on VT and VD via a modem" with "monitors for VT and VF and can transmit event recordings"	2	Accepted.
ZOLL	26	481	Only the WCD 4000 are currently offered in Europe.	2	Accepted.

[a] "major": the comment points to a highly relevant aspect and a thorough answer is expected from the author(s)
[b] "minor": the comment does not necessarily have to be answered in a detailed manner
[c] "linguistic": grammar, wording, spelling or comprehensibility

ZOLL	26-27	482-491	Please remove this description and figure as this confidential information was provided upon request for reviewer information only and not intended to be part of a publicly-disseminated document.	1	Accepted.

[a] "major": the comment points to a highly relevant aspect and a thorough answer is expected from the author(s)
[b] "minor": the comment does not necessarily have to be answered in a detailed manner
[c] "linguistic": grammar, wording, spelling or comprehensibility