Input from external experts and manufacturer on the **project plan** “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 draft project plan "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
Olaf Weingart (MDK)	4	Table 1 #7	I know that there is no official translation. those who publish international way use similar like I do, to distinguish form private insurances (advisory) services: *"Medical Advisory Service of the Statutory Health Insurance Funds North-Rhine" (MDK-Nordrhein)* Please rename may be without the translated title (in brackets)	3	OK
Olaf Weingart (MDK)	5	3.0 line 2.)	The WCD/LifeVest ® received CE mark in 2015; please add "the current model WCD 4000" in studies you will find published data from older models like WCD 3000 or older with provide monophasic shock (LifeCor)	2	We contacted the manufacturer ZOLL for clarification: The most recent CE mark certificate (issued on 15.09.2015) only included the WCD 4000 model. We will update this accordingly.

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Olaf Weingart (MDK)	6 / general		As the authors wrote the discussion of indications are very difficult because there are no established risk factors and prognostic value for treatment (see below) in general in may be the possibility reduce the main groups to strategies for patients at general risk for SCD (also primarily independent from LVEF), like these; 1. pts. with indication for ICD, WCD used for "standby" if ICD is not available for medical reason (contraindication) or personal reasons 2. pts. with indication for ICD, WCD used as "watch" and weight strategy (e.g. "prolonged risk stratification" in secondary prevention). 3. pts. with no indication for ICD, WCD used as additional tool to reduce the temporary risk of SCD <u>outside hospital</u> a. MI and LVEF of ≤ 35%, b. DCM and oher with LVEF of ≤ 35%, c. During phase of for detection of unclear syncope 4. pts. with no indication for ICD, WCD used as additional tool to reduce the temporary risk of SCD inside / during hospital 5. NN The use of syncope diagnostic and other risk stratification outside of secondary prevention indications for ICD may be new option (1, 2) Which focus on other treatment goals.	2	We are aware that there exist a lot of options on how to split the data. "Watch and wait" strategy for patients at risk for SCA during diagnostics will be added as a separate indication. We contacted the manufacturer ZOLL for clarification with regard to "hospital wearable defibrillator": they told us that it is a different device. Therefore we decided not to include it in the assessment. But thank you for making us aware of it.

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Olaf Weingart (MDK)	6 / general		Beside the point above, the authors may **add additional patient group** which are in accordance with existing evidence based **guidelines** clear candidates for an ICD. The published Data for WEARITT II (3) in 170 (8,5%) of the 2000 patients in **secondary prevention (precious SCD**) and still 348 (17.4%) patients with **previous syncope**. In current guidelines many of them qualified for ICD but have no clear documented transistent contraindication for ICD. May be rewording and separate these group for, the point of *"1.b).2 ...but not possible"* of contraindication may study results are relevant for clinical and research consequences: • In case of contraindication for ICD the WCD may be an option for those who have no need longer hospital treatment beside the monitoring (generally accepted / guidelines IIa recommendation). • In case to change the treatment in these patients with clear indication as "ICD-standard" to a previous planned "watch" and weight strategy, there is a need for RCT results which show non inferiority to SCD and safety of these de-escalation strategy and may be than in later discussion about saved unnecessary ICD implantations and costs for this treatment combination. I recommend to give these intervention strategy of watch and weight an own major group, because the company "sells" these to decision makers so these might be more relevant in near future and still established for "prolonged risk stratification" in some guidelines (4).	1	

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University hospital center Sisters of mercy, Zagreb	6-7	1/1	Why are reversible extracardiac conditions (hypothermia, severe electrolyte disturbances, iatrogenic QT prolongation) excluded from the list of indications for WCD	2	After asking for clarification we received the following answer: "the aforementioned conditions usually do not lead to LV systolic function impairment but may provoke malignant arrhythmias even in a perfectly healthy heart. Patients with those conditions are usually monitored specifically because of the risk of malignant arrhythmias. I suggest that criterion 2c be amended to incorporate these conditions. It may then be written like: secondary cardiomyopathy (tachycardia mediated, thyroid mediated, etc.), **induced arrhythmias (secondary to hypothermia, electrolyte imbalance, iatrogenic prolongation of the QT interval, etc) in which the underlying cause is potentially treatable**". We will amend this indication accordingly.

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Olaf Weingart (MDK)	8	Comparison	There are two other comparators, the main issue is the "complete" standard treatment under rhythm monitoring in hospital, these include acute intervention (e.g. like PTCA) but also mobilisation and first training (e.g. rehabilitation-clinic). The other point might be to extend this standard to other method to identify the individual risk for SCD to additional methods, which are in most patients groups not evidence based standard (e.g. elektrophysiologic testing after MI, genetic analysis). The use of external defibrillators are two possibilities; • the public health aspect (in context with emergency services) • and the individual prescription by doctor for home use (These is used in special cases e.g. children cardiology, when WCD and ICD is not possible). The "public health services" comparator guide in a need for methodical discussion about "all or none" evidence (see below).	2	We will add home-use defibrillators: External defibrillators to be used in 3 settings (home, public places, emergency services).
PSZ	8	Comparison	cardiac surgery or more broadly cardiac procedure either surgical or interventional		As suggested, Guideline directed medical surgery will be changed to guideline directed cardiac surgery.

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Olaf Weingart (MDK)	general		The long time treatment in hospital only for monitoring is in developed countries still available, but very difficult to communicate to patients, doctors and also decision makers! The treatment is with shock due to VT / is obviously effective, there is no clinical uncertainty, and there is a big discussion in the clinical world, withhold of the WCD treatment from one group in a trial would be unethical or impractical (but notwithstanding done in ICD trials). Those dramatic effects may occur in the most cases like "some patients dies due to SCD from tachycard-heart rhythm abnormalities (**the only reason of SCD, which WCD´s can treat**). In this "parachute" discussion they made no difference between SCD on VT and the observation period during wearing a WCD as treatment. Dealing with studies of "all or none" evidence which met when all patients died before the WCD became available, **but some now survive on it**; or when some patients died before the Rx became available, but none now die on it. This might be result in high level evidence for effectiveness: http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/	1	Following the 2015 EUnetHTA Core Model Application for Rapid Relative Effectiveness (REA) Assessments (4.2): "Although RCTs provide the most robust evidence, other types of studies may provide additional information on the relative efficacy or effectiveness. Non-randomised intervention studies or observational studies can be considered where an RCT has not been conducted, published yet or is not feasible…". In our situation, even though we agree that an RCT is possible and it would be ideal for assessing effectiveness, in the absence of an RCT, we suggest including controlled non-randomized studies in the attempt of providing the 'best guess', rather than no answer at all, for the relatively new technology of WCD regardless of its "not-very-large" effect.
PSZ	9	Outcomes	inappropriate WCD shocks as either a secondary endpoint or safety		Inappropriate WCD shocks will be part of safety ourcomes in the section SAEs.

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PSZ	9	Study design	no registries/case series for the assessment of effectiveness? might be useful for some subsets ?		Following the 2015 EUnetHTA Core Model Application for Rapid Relative Effectiveness (REA) Assessments (4.2): "Although RCTs provide the most robust evidence, other types of studies may provide additional information on the relative efficacy or effectiveness. Non-randomised intervention studies or observational studies can be considered where an RCT has not been conducted, published yet or is not feasible…". In our situation, even though we agree that an RCT is possible and it would be ideal for assessing effectiveness, in the absence of an RCT, we suggest including controlled non-randomized studies in the attempt of providing the 'best guess', rather than no answer at all, for the relatively new technology of WCD regardless of its "not-very-large" effect.
Olaf Weingart (MDK)	9	Study	There are only results from prospective register studies without control group like the WEARITT II (3) as best available evidence published. (RCT ongoing). In conclusion you might discuss in context with possible dramatic effects (see above), why you exclude (prospective) registers, cases series and low evidence for effectiveness but you include these for safety outcomes. In other point these studies (esp. registers) may help to identify further prognostic factors, these may relevant for clinical decision but also for interpreting results from RCT in future.	2	

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Olaf Weingart (MDK)	General To 10 /11		Major point for information, and discussion about use of the correct use of the risk of bias tools and in / exclusion of trial results (in a protocol?), but I cannot provide a practical solution: Observational studies are at risk of bias because of differences in prognosis; nevertheless, prognostic imbalance threatens the validity of all studies without control group. In addition in all known WCD publications ((3)(5) and more) the risk of SCD differs across clinical subgroups, and also in the reported "subgroups". The assessment of different baseline risk is relevant for the WCD outcome. Therefore the description how to deal with this data it is a part of methods section in the protocol, but beside an individual patient data analysis I know no way out to solve this problem.	1	Following the 2015 EUnetHTA guideline on Internal validity of non-randomized studies (NRS) on interventions, we choose to use the ACROBAT-NRSI and RoBANS.
PSZ	12	Preliminary evidence table	appropriate/inappropriate WCD shocks?		Inappropriate WCD shocks will be part of safety ourcomes in the section SAEs.
Olaf Weingart (MDK)	General Page 14 A003		There are only few established and evidence based prognostic factors for SCD, the LVEF used often in guidelines are based on the consensus decision of inclusion criteria for ICD trials in the nineteen's. The comorbid diseases like diabetes, obstructive sleep apnoea, clinical finding´s like short VT´s / sustained VT´s in holter ECG and also additional methods like electrophysiological or genetic testing is in most cases unclear and have only weak evidence. My question is it necessary to describe the available evidence (or the uncertainty) of these for WCD outcome relevant factors in an own systematic review?	1	Certainly, there is a need for future review in WCD outcome relevant factors.
Olaf Weingart (MDK)	17 F0017		Only for HOCM an evidence based guideline recommend the use of risk stratification tool for decision making (6). Beside these there in the relevant medical guidelines there is no established value of acceptance remaining risk for SCD.	2	

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Olaf Weingart (MDK)			Literature 1. Meyer C, Carvalho P, Brinkmeyer C, Kelm M, Couceiro R, Muhlsteff J. Wearable sensors in syncope management. Med Sci Monit. 2015;21:276-82. 2. Klein HU, Goldenberg I, Moss AJ. Risk stratification for implantable cardioverter defibrillator therapy: the role of the wearable cardioverter-defibrillator. Eur Heart J. 2013;34(29):2230-42. 3. Kutyifa V, Moss AJ, Klein H, Biton Y, McNitt S, MacKecknie B, et al. Use of the Wearable Cardioverter Defibrillator in High-Risk Cardiac Patients: Data From the Prospective Registry of Patients Using the Wearable Cardioverter Defibrillator (WEARIT-II Registry). Circulation. 2015;132(17):1613-9. 4. Schwab JO, Bänsch D, Israel C, Nowak B. Stellungnahme zum Einsatz des tragbaren Kardioverter/Defibrillators. Kardiologe. 2015;9(2):165-70. 5. Chung MK, Szymkiewicz SJ, Shao M, Zishiri E, Niebauer MJ, Lindsay BD, et al. Aggregate national experience with the wearable cardioverter-defibrillator: event rates, compliance, and survival. J Am Coll Cardiol. 2010;56(3):194-203. 6. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014;35(39):2733-79.		
PSZ	19	Ethical (1.1)	quality of evidence is different		It is unclear to us how is the difference in quality of evidence an ethical issue? In our view, the discrepancy is surely ethically relevant, as it gives rise to uncertainty in the evaluation of consequences and rights/duties, but it does not seem to us to be an ethical issue in and of itself.

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PSZ	19	Ethical (1.2)	but protection may be less - it is voluntary - one may not wear WCD 100% of time		Good point. The last sentence will be changed to the following: "Further issues may arise by comparing ICD to WCD due to the ICD's intrusion on bodily integrity that brings along more mortality related harms at the expense of the ICD's better protection."
PSZ	20	Organisational (2.2)	why less emergency calls - less inappropriate shocks? the number of appropriate shocks should be the same?		The difference in the number of emergency ambulance calls needed is not supposed to apply when compared to an ICD, but rather when compared to an ACD or medical therapy.
PSZ	20	Legal (4.)	in general the restriction to drivie with WCD will vary depending on an indication		Good point. The first sentence will be changed to the following: "Introduction of the new technology gives rise to legal issue concerning person's rights and state's duties that will presumably vary upon particular indications."
PSZ	21	Legal (4.2)	legal responsibility of the patient to wear WCD		Good point. The last sentence will be changed to the following: "Also, in particular settings with an elevated cultural perception of the notion of liability, patients may be themselves required to be legally responsible for wearing the WCD."

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November 2016

MANUFACTURER

Comments were received from:

Name	Affiliation
Carla Zema et al.	ZOLL Medical Corporation

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
Carla Zema, ZOLL	6	Table 3, Row 1- Population	Patients according to CE mark indicates "patients who are 16 years of age and above…" This should be 18 years of age and above in accordance with the CE mark.	1	Accepted.
Carla Zema, ZOLL	6	Table 3, Row 1- Population	2. "As a bridge to pharmacological therapy when a heightened risk of SCD is present…" Recommending adding 'optimal' so that the revised wording is "As a bridge to optimal pharmacological therapy when…."	2	Accepted.
Carla Zema, ZOLL	7	Table 3, Row 1- Population	3. "Post-MI…such as within 40 d of MI" The following should be added to make it accurate with the guidelines cited: "…such as within 40 d of MI or 90 d of MI with revascularization."	1	Partially accepted. The post MI statement will stay as it is, but the indication concerning revascularization will include the statement from AHA 2016 guideline saying, 90-day waiting period post revascularization with either CABG or PCI.
Carla Zema, ZOLL	8	Table 3, Row 2- Intervention	"- a monitor and alarm that the patient wears around the waist" Remove "and alarm" as the alarm is now integrated into the monitor.	2	Accepted.

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Carla Zema, ZOLL	8	Table 3, Row 3- Comparison	ICD as a comparator: ICD is not an appropriate comparator for the WCD. The WCD is used specifically when use of an ICD is not possible (e.g., infection, patient condition prohibits implantation, etc) or when long-term risk of SCD and need for an ICD is being determined (e.g., during medical optimization, waiting periods, etc.) Patients for whom an ICD is indicated	1	WCD is not only used in situations when the use of an ICD is not possible or as a bridge to an ICD, but also in situations where the two can be compared. Even though MADIT II and VALIANT suggest that there is no mortality benefit from an ICD implantation immediately post MI, it does not automatically mean that there is therefore mortality benefit in that time period from a WCD – that needs to be established by a controlled trial to see if WCD has an "added therapeutic benefit (including clinical as well as quality of life benefits)" (EUnetHTA guideline on comparators). WCD is also used in patients who refuse ICD therapy, so it is important to see relative effectiveness of a WCD in comparison to an ICD. Hence, an ICD is a comparator to a WCD – just as the ongoing, Zoll funded, VEST trial compares WCD and conventional treatment immediately post MI.

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Carla Zema, ZOLL	8	Table 3, Row 3- Comparison	Guideline directed pharmacological therapy as a comparator: The WCD should be used with guideline directed pharmacological therapy not as a replacement. From Section 4.2.1 of the ESC Guidelines (that are cited for this recommendation in the project plan), "With the exception of beta-blockers, currently available anti-arrhythmic drugs have not been shown in randomized clinical trials (RCTs) to be effective in the primary management of patients with life-threatening VAs or in the prevention of SCD." Since beta-blockers are part of optimal medical therapy (OMT) and the WCD is recommended for use during OMT, pharmacological therapy is not considered a comparator to the WCD. Additionally, Section 4.2.2 states "The use of drugs for inherited primary arrhythmia syndromes (LQTS, SQTS, Brugada syndrome) and cardiomyopathies is an off-label indication.", which provides further evidence that pharmacological therapy is not a replacement/comparator for the WCD.	1	The list of comparators is simply a detailed list of standard therapies that were/are common practice when WCD was/is not available. Even though the AHA and ESC guidelines incorporate WCD in their list of standard therapies, it does not follow that standard pharmacological therapy cannot be a comparator. According to the literature data, guideline directed pharmacological therapy could be a comparator for patients who refuse WCD (as for patients who refuse ICD therapy).
Carla Zema, ZOLL	8	Table 3, Row 3- Comparison	Guideline directed medical surgery as a comparator: Per the ESC Guidelines, Section 4.5, "Catheter ablation has evolved into an important treatment option for patients with scar-related heart disease presenting with VT or VF…[and] is often used to control incessant VT or electrical storms (i.e. recurrent VT/VF with frequent appropriate ICD firing) and to reduce or prevent recurrent episodes of sustained VT." The WCD is used to protect patients when use of an ICD is not possible or when long-term SCD risk and the need for an ICD is being determined. Patients with highly recurrent VT or VF would be indicated for an ICD; therefore, patients who are indicated for ablation are typically ICD candidates (or already have an ICD) and are not appropriate for the WCD (unless there is a clinical reason why the patient cannot have an ICD implanted, such as an infection). Moreover, surgical ablation is indicated following failure of catheter ablation. Therefore, medical surgery is not an alternative/comparator to the WCD since patients that are indicated for surgery are not typically WCD patients.	1	The same as above applies to this point on medical surgery (Catheter ablation or Radiofrequency ablation) as a comparator as well. Additionally, the EUnetHTA guideline on comparators suggests that "a comparator is commonly defined as current routine care in the individual health care system, the most used, or what would be replaced by the introduction of that new pharmaceutical." Since WCD attempts to replace medical surgery (Catheter ablation or Radiofrequency ablation) at some instances, it can be considered a comparator that helps through the bridging stage leading either to ICD implantation, optimal pharmacological therapy, or heart transplantation.

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Carla Zema, ZOLL	8	Table 3, Row 3-Comparison	External defibrillators available at public places and/or used by medical emergency staff during resuscitation: Per the ESC Guidelines, Section 4.3.4, "Out-of-hospital cardiac arrests occur most commonly (≈70%) in the home, even in younger patients, but these are infrequently witnessed and therefore cannot be prevented by home-based defibrillators." Use of automated external defibrillators (AEDs) whether in public places or by emergency medical staff is not a viable option to protect patients at high risk of SCD given that most events occur at home and are unwitnessed. Therefore, AEDs are not a viable comparator to the WCD.	1	The same as above applies to this point on external defibrillators as a comparator as well. In the absence of a WCD, external defibrillators would need to be the therapeutic option. To establish the WCD's effectiveness, comparing it to AEDs is another option.
Carla Zema, ZOLL	12	Table 4b	"Incidence of VT/CF" is most likely intended to be "Incidence of VT/VF"	2	Accepted.

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Carla Zema, ZOLL	19	Table 6. Ethical 1.1	(1) There is no evidence to suggest "marginal benefit and cost-effective reasons" are the reasons that the WCD "cannot be all covered in practice." Lack of universal reimbursement creates ethical issues with providing access to the WCD in a manner that is social just. Furthermore, limited and finite health care funding availability create the necessity of potentially reducing access to health care goods and services. Therefore, it is imperative that health care resources be allocated to goods and services that are clinically effective, safe, and cost-effective. (2) "…prefers those who are better-off to begin with." Cognitive impairment and physical disability affects people of all socioeconomic status. Therefore, there is no bias based on socioeconomic status for those that are unable to interact with the device. (3) The ethical issue that is not addressed is the "value" of saving a life. Given limited health care funding, it can be more "cost-effective" for patients to die rather than providing life-saving therapy. Hence, assumptions around the value of a life must be made in order to determine the overall cost-effectiveness of the intervention. Since how life is valued can drive the overall cost-effectiveness of a life-saving intervention, valuing life can create ethical issues for health care organizations and agencies that must make reimbursement and other choices that affect patient access.		(1) As Table 6. is a "Checklist for **potential** ethical, organizational, patient and social and legal aspects", no evidence is needed to confirm the WCD cost-ineffectiveness. It is a potential problem that is also highlighted in the literature (see pg. 8 of WEARIT/BIROAD trial by Feldman et al.). It is surely an "imperative that health care resources are allocated to goods and services that are clinically effective, safe, and cost-effective", which is precisely why it is a potential ethical issue that a WCD (without any comparative data and hence no established effectiveness) with its marginal benefits may be a cost-ineffective option that may not be able to be covered in practice. (2) Accepted. The sentence will be corrected as follows: "…prefers those who are **cognitively** better-off to begin with." (3) Because WCD in an intervention used in life-saving situations, this aspect of the technology is surely of importance. However, concerning cost-effectiveness thresholds, the focus of the current EUnetHTA assessment is for the most part concerned with efficacy and safety issues and not reimbursement.

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Carla Zema, ZOLL	19	Table 6. Organisational 2.1	Unlike other devices, the device function does not depend on health care provider knowledge and skill of operating the device. ZOLL is completely responsible for the training and support of patients in how the WCD works. Moreover, data monitoring is not a mandatory function of the WCD. In other words, the WCD will still protect patients from SCD even if health care providers choose not to access WCD data available to them. The responsibility of the health care provider is to educate patients on their condition and their risk of SCD. This must occur regardless of whether the WCD is a therapy option or not.		Once the possibility of increasing the number of information that can be gathered by a WCD (compared to an ICD) is considered a benefit, it follows that this increased patient-doctor contact-time is to be considered a cost (that is to include the time required for monitoring and evaluation). If one of the points of a WCD is to, for instance, see if an ICD or medical therapy are needed, monitoring is required. Hence, even though the monitoring function can be disabled, it is to be considered a cost.
Carla Zema, ZOLL	20	Table 6. Legal 4.1	It is unclear why there might be "legal issues with respect to responsibility and insurance…in situations of false shocks when delivered in inappropriate moments such as when driving a car." False or inappropriate shocks generally occur when a conscious patient fails to press the response buttons when VT/VF triggers an alarm sequence. Patients are instructed to stop their current activity and press the response buttons if they are conscious. Given the timing of the alarm sequence, patients are given the opportunity to respond prior to being treated, even when driving. If a patient is driving and experiences a VT/VF event and loses consciousness then a shock treatment is appropriate regardless of the type of activity the patient was engaged in at the time, such as driving.		Even though you "instruct patients to stop their current activity and press the response buttons if they are conscious", it does not mean that all activities can be stopped with such ease. Driving a car was used as an example that illustrates a cognitively demanding activity that, in certain situations, cannot be stopped in order for the patient to press the response buttons if conscious. As you put it, because shocks "generally occur when a conscious patient fails to press the response buttons", it remains to be a potential legal issue with respect to patient's responsibility and insurance if there is a harm/damage caused (especially in cases of false shock delivery).

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