JA2- WP7- SG 3 – **SAG and Public** consultation on the guideline "Therapeutic medical devices" - 2nd draft guideline version of October 2015

Number of comment	Page	Line	Comment	Character of comment "major"[1] "minor"[2] "linguistic"[3]	Author/Draft group reply
1	GEN	NA	COCIR appreciates the development of these guidelines. However, we would like to share some general comments: - Availability of RCT data at this stage of technology development is almost extremely limited (only short term). Other evidence will then be required. - We support the need for alternative methodologies (ref The Netherlands methods ref Beschikbaar als pdf) - Database to track long term effects are becoming increasingly valuable and thus should be more used and referred to, but still there is a need to avoid bias of some of those databases	☒ major ☐ minor ☐ linguistic	We agree to both points, (i) that RCT data are limited and (ii) that databases, e.g., registries for long-term effects are important. We believe both issues are adequately addressed in the guideline. The Netherlands report (KNAW 2014) is cited as a review of different MD relevant study designs.
2	3	1	It would be very relevant to add a note on N-of- 1 trials as this might become an important discussion (notably in the regenerative medicine autologous sector).	▪ major ☐ minor ☐ linguistic	N-of-1-trials are not specifically useful in the evaluation of medical devices. For a N-of-1-trial, the condition must be chronic and stable, and the interventions must not induce permanent changes, because the trial includes multiple crossovers between treatment. Therefore, most of N-of-1-

[1] "major" indicates that a comment points to a highly relevant aspect and that the author / the draft group is expected to give a thorough answer
[2] "minor" means that a given comment does not necessarily have to be answered in a detailed manner
[3] "linguistic" labels problems with grammar, wording or comprehensibility

					trials evaluate drug therapy.
3	5 11	3 5	Medical devices are pharmaceuticals in its general meaning. It may be clearer to say: "Health technology assessment (HTA) of medical devices (MD) may present specific challenges as compared to an assessment of **other** pharmaceuticals." Or "compared to an assessment of **medicinal products**".	☐ major ▪ minor ☐ linguistic	We followed the suggestion to write 'medicinal products' in this sentence.
4	5	10	"is also applicable"	☐ major ☐ minor ▪ linguistic	Corrected
5	5	12	"First, the **use** of therapeutic MD"	☐ major ☐ minor ▪ linguistic	Corrected
6	6		Recommendation 4 It should be made clearer that randomised controlled trials are the first source of information when available.	▪ major ☐ minor ☐ linguistic	We think the relevant recommendation regarding this issue is 5 and 6, no need to treat it here
7	6	21	To amend the text as follows: "From the perspective of the HTA assessor both problems can be partially addressed by a more detailed analysis of the available evidence considering these factors" For example, in radiotherapy, detailed RCT will not address the challenges from incremental medical device changes resulting from the fact that many new radiation techniques are clinically introduced to	☒ major ☐ minor ☐ linguistic	We followed the suggestion to add 'partially' in this sentence.

			reduce the risk on side effects. Such changes are introduced without being Documented through RCTs. These are introduced based on a risk reduction principle named ALARA and are reducing the dose given outside the tumour to Organs at Risk (OAR) which automatically will reduce the risk on side effects. Long term effects and side effects of the treatments Are not detected with RCT as long latency times are necessary to detect tumour recurrence, secondary cancers, side effects such as Cardiac complication. Long term trials are one way, but more & more we expect to have those long term effects analyzed through patient registries or clinical databases.		
8	7	1	In table in Fifth recommendation, it mentions that RCT should be preferred and used with some adjustments. As it is known, HTA methods differences between MedTech and Medicines needed to facilitate rapid technology adoption. In large scale randomised controlled trials (RCTs), results often come after technology has been superseded. As it is performed in Radiotherapy in Germany and Netherland, why not keeping the text open for novel approaches based on evidence from retrospective interrogation of linked clinical data sources rather than randomized clinical trials. See: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3981478/ This is more and more common and the HTA guideline	☒ major ☐ minor ☐ linguistic	We think we have shown that there are also RCT designs that can deal with rapid development and registry data were also addressed. Other "real world" data such as administrative data have even more pitfalls than registry data. This doesn't mean that they cannot be used, but usually it is not possible to derive inferences of causal relationship. The cited paper does not describe concrete methods for data analysis to deal with confounding the main issue for causal inference from such data

			should allow for the analysis of massive amounts of multi-modal and multi-sourced data as hidden patterns can be retrospectively detected and knowledge created, complementing traditional ways of doing clinical research (prospective clinical trials). This predictive analytics (predict the future by looking back) and prescriptive analytics (decision support) shows the promise of considerable support of the anamnesis and the diagnostic process.		
9	7	1	In table in Fifth recommendation, it mentions that RCT should be preferred but evidence is frequently lacking for medical device interventions. Same comment as comment#2 and: As it is known, HTA methods differences between Medical Technologies and Medicines needed to facilitate rapid technology adoption. In large scale randomised controlled trials (RCTs), results often come after technology has been superseded. As it is performed in Radiotherapy in Germany and the Netherlands, why not keeping the text open for novel approaches based on evidence from retrospective interrogation of linked clinical data sources rather than randomized clinical trials. See: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3981478/ This is more and more common and the HTA guideline should allow for the analysis of massive amounts of multi-modal and multi-sourced data as hidden patterns can be retrospectively detected and knowledge created, complementing traditional ways of doing clinical research (prospective clinical trials). This	☒ major ☐ minor ☐ linguistic	See #8 We recognize current developments and novel approaches; however, we see no MD-specific methodologic issues for this guideline. The possibility of 'sequential prospective cohort studies' is encompassed in the concept of adaptive trial designs in the guideline.

			predictive analytics (predict the future by looking back) and prescriptive analytics (decision support) shows the promise of considerable support of the anamnesis and the diagnostic process. ☐ Sequential prospective cohort studies with standard follow up programs (usually named "Model based SELECTION and VALIDATION method") are more common in comparing new treatment modalities to already applied ones (=relative effectiveness assessment (REA)) in radiotherapy		
10	11	26-27	It is sometimes difficult to have RCT for specific MD, especially regarding the choice of time for the clinical evaluation, the eligible population that may be too small in comparison with the majority of drugs, the acceptability of the clinical studies by patients, randomised and blinded trials, choice of the comparator, effect of the MD while it is used with other treatments, experience of the user. Thus, in some cases, other studies than RCT are used to justify the clinical efficacy of the MD. In that context, see notably: - Vinck I, Neyt M, Thiry N, Louagie M, Ramaekers D, Introduction of emerging medical devices on the market: a new procedure in Belgium, Int J Technol Assess Health Care. 2007 Fall;23(4):449-54. - HAS, Methodological Choices for the Clinical Development of Medical Devices. Haute Autorité de Santé, 2013. http://www.has-sante.fr/portail/upload/docs/application/pdf/2014-	▪ major ☐ minor ☐ linguistic	The guideline addresses the use of alternative data sources to RCT, for safety issues and also for efficacy. However, it also states that other study designs have shortcomings which limit their ability to draw definite conclusions on treatment effects. The guideline considers and references HAS 2013.

			03/methodological_choices_for_the_clinical_development_of_medical_devices.pdf		
11	12	3	"Health technology assessment (HTA) is aiming to inform decisions on adoption to benefit catalogues, reimbursement, best practice, and on disinvestment of health technologies" If payers & providers were to say they will not pay for any device until it's undergone an HTA, then due to the current randomised Clinical trial (*) methodology requirements of HTA any non-drug technologies, would already be obsolete by the time it is fully approved for full release and distribution. The current benefits afforded patients by the use of technologies early in their lifecycle by the current CE marking process, EC/93/42 Directive, would be markedly affected, and the resultant anticipated affect in slowing of innovation and development of technologies within the European setting might also be expected to be impacted. (*): to avoid such delays, Medical Devices should need to apply new predictive analytics (predict the future by looking back) and prescriptive analytics (decision support) to support HTA studies in collaboration with "EUnetHTA JA3 WP7 - Methodology development and evidence generation". In Medical Devices, Relative Effectiveness Assessment (REA) implementing sequential prospective cohort studies with standard follow up programs (usually named "Model based SELECTION and VALIDATION method") are common for comparing new treatment modalities to already applied ones	☒ major ☐ minor ☐ linguistic	See #8 and 9 With respect to the first point, our view is that HTA ends with an assessment, but the decision is a separate task. Therefore, HTA does ‚only' inform decisions, and HTA methods could be adapted to the importance of a decision. For example, if a reimbursement decision is temporary, weaker evidence might be sufficient. In essence, however, the question of reimbursement is out of the scope of the present guidelines. Regarding the issue of slowing innovation, we want to stress that, firstly, the term ‚innovation' should be used only for new interventions with (probable or) proven effectiveness. Immediately after CE marking, the effectiveness of many device interventions is largely unknown, so these devices are only ‚new' but not necessarily ‚innovative'. Secondly, slowing the clinical application of new devices with uncertain effectiveness often turns out to be extremely beneficial for patients. If effectiveness is later found to be non-existing, many patients have been spared an ineffective, invasive procedure.

12	12	14-15	Same comment as comment#3 (No.)	☒ major ☐ minor ☐ linguistic	See #3
13	12	23-24	It would be necessary to complete this guideline, when possible, to take into account cost-effectiveness and other ethics, legal and social aspects such as other non clinical benefits and harms that are fundamental parts of HTA.	▪ Major ☐ minor ☐ linguistic	We agree these topics are important, but the scope of the GL is limited to clinical effectiveness (see section 1.3).
14	15	36-38	To review the sentence.	☐ major ☐ minor ▪ Linguistic	We rephrased the sentence.
15	22	12	If this is referring to big data analytics, and in this case the reference material from internal publication should be mentioned such as: "HOW SHOULD HEALTH DATA BE USED? Privacy, Secondary Use, and Big Data Sales", Bonnie Kaplan, PhD, FACMI - Yale Interdisciplinary Bioethics Center, Yale Information Society Project, Yale University, ISPS14-025 ; 7 OCTOBER 2014	☐ major ☒ minor ☐ linguistic	p22, l12 is about literature search in bibliographic databases. Maybe the comment refers to **p21**, l12? There, administrative databases are only mentioned as one example data source. We do not want to go into details of administrative database analyses.
16	25	12-19	This paragraph is very important as such situation may be more frequent than expected, especially regarding innovative and high risk MD. It may be highlighted in this methodological guideline.	▪ Major ☐ minor ☐ linguistic	The challenges for MD RCT and lack of regulatory prescription are repeatedly addressed in the guideline.
17	26	18	Radiotherapy makes also comparative studies available and examples can be found in:	☐ major	Probably, the comment refers to **p25**, l18. The reference emphasizes the role of RCT.

			In [..] rapid-learning [..] data routinely generated through patient care and clinical research feed into an ever-growing [..] set of coordinated databases. *Abernethy, J Clin Oncol 2010;28:4268*	☒ minor ☐ linguistic	
18	28		This table is very interesting. However, horizontal lines should be added to facilitate its understanding especially regarding disadvantages related to different designs.	☐ major ▪ minor ☐ linguistic	We followed the suggestion.
19	30	30	Reference to the ISPOR method is coming from Pharmacoeconomics. For medical devices such as in radiotherapy, other modelling studies validation is used such as the model for prospective cohort studies on multivariable normal tissue complication probability (NTCP). This could be mentioned as to vary from the Pharmaceutical industry used methods	☒ major ☐ minor ☐ linguistic	We assume the comment refers to **p.29** l.30. The correct reference is: Caro, J., et al. (2014). "Questionnaire to assess relevance and credibility of modeling studies for informing health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report." Value Health 17(2): 174-182. As stated in section 2.1 (p.15, l.16-17) the literature review found no MD-specific tools for decision-analytic modelling studies. Therefore we believe the ISPOR checklist is applicable. The NTCP is not a method for decision-analytic modelling, as far as we can tell.

COCIR

REGenableMED [Dr Aurélie Mahalatchimy, Prof Alex Faulkner and Prof Andrew Webster]

COCIR – Radiation Focus Group [Michel Baelen]