Critical examination of MED/DEV 2.12/2 rev 2 on *Post*-market clinical follow-up studies

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Introduction

The European Commission published an update of MEDDEV 2.12/2 entitled Post Market Clinical Follow-Up Studies - A Guide for Manufacturers and Notified Bodies, dated January 2012.
MEDDEV 2.12/2 rev 2 (Post market clinical follow-up studies) (published January 2012), written by undisclosed authors, is the latest in the set of legally non-binding guidelines promulgated instead of actual legislation or official guidance by the European Commission. The appearance of the document suggests hasty publication. § Preface of the guidelines (incorrectly) states that they constitute a guide on how to perform Post market clinical follow-up (PMCF) to fulfil various, specified Post-market surveillance (PMS), however, recognises that such PMCF studies are simply one of several (but un-stated) options available in PMS. Few critical analyses of the guide have been published, this article examines it critically.

The guidance provided in the updated MEDDEV follows the recommendations of the Global Harmonization Task Force and refers to EN ISO 14155:2011. It also purportedly reflects the changes introduced by Amending Directive 2007/47/EC. MEDDEV 2.12/2 rev 2 provides specific advice on:

- The circumstances where a PMCF study is indicated
- The principles of PMCF studies involving medical devices
- The use of study data and
- The role of a Notified Body in assessment of PMCF plans and results obtained from the plans as part of conformity assessment

The guidance does not apply to *in vitro* diagnostic devices.

One of the goals stated by the second revision of MEDDEV 2.12/2 is emphasis on the importance of appropriate use and conduct of PMCF studies to attend to issues linked to residual risk.

Although PMCF studies are conducted using devices carrying the CE Marking of Conformity within their intended use, the provisions of section 2.3.5 of Annex X to Council Directive 93/42/EEC do not apply; however, the requirements in Council Directive 93/42/EEC concerning notification of adverse events after placing a device on the market apply fully, Manufacturers of medical devices must be aware that compliance with these notification provisions is necessary in order to fulfil legal obligations under

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European legislation. Further, manufacturers should recall the conditions of the General Product Safety Regulations; therefore, PMCF constitutes only part of the obligations on *post*-production obligations.

§2 Scope asserts the intention to not impose new regulatory requirements – hardly surprising, since guidelines by nature cannot substitute for regulation.

PMCF is defined as:

> a study (performed) following CE Marking of a device … Intended to answer specific questions relating to safety or performance (*ie*, residual risks) … when used in accordance with its approved labelling

The following appear inconsistent with the Directive:

- Risk remaining after application control measures ≠ residual risk (contrary to what EN ISO 14971 espouses)
- Approved labelling

The term PMCF plan is defined as:

> The documented, proactive, organised methods and procedures set up by the manufacturer to collect clinical data based on the use of a CE-marked device corresponding to a particular design dossier or on the use of a group of medical devices belonging to the same subcategory or generic device group as defined in Directive 93/42/EEC. The objective is to confirm clinical performance and safety throughout the expected lifetime of the medical device, the acceptability of identified risks and to detect emerging risks on the basis of factual evidence

and that of residual risk given as § 2.15 EN ISO 14971:

> Risk remaining after risk control measures have been taken

Analysis of the body of the guidance suggests inherent logic could be represented graphically and expanded for logic and plausibility as illustrated by Figure 1.

The guidance takes no account of obligations for a medical device to fulfil the State-of-the-art, particularly as the notion of innovation (*ergo*, not State-of-the-art test obliged by the Directive) and concepts absent from the regulations (*viz*, elevated product-related risk, hazardous anatomy, pathological demographics, *etc*), inferring recognition of ALARP and corresponding thresholds that are not accepted universally throughout the EU are proponed. Introduction of certain factors question validity of CE Marking on a given device poses concern about legality if the guidance is used in defence: particularly worrying is use of PMCF to ***verify*** safety and performance by *post*-market study (read: clinical investigation in human subjects) on *larger, more varied* (*ie*, non-homologous) populations. The implications are profound: if safety and performance of a medical device can only be demonstrated or requires verification in a larger or more varied population, how could the device have fulfilled the State-of-the-Art test

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required for CE Marking originally? Further, how could warranties expressed by the Manufacturer have been demonstrated according to Council Directive 2001/95/EC?

Among the PMCF methodologies espoused, the notion of premarket investigation is absent from the European Directives on medical devices so was evidently imported from (non-European) GHTF guidance; once again, this contradicts European legislation, however sensible such notions may seem to observers. It would seem essential for the MEDDEV guidance to be subjected to appropriate judicial scrutiny in order for Manufacturers to avoid or protect against liability.

General principles expected to be present in a clinical investigation plan/study plan are un-controversial, although it is observed that analysis is expected to be used to ensure continuous risk management, a term that is difficult to understand how it could be fulfilled.

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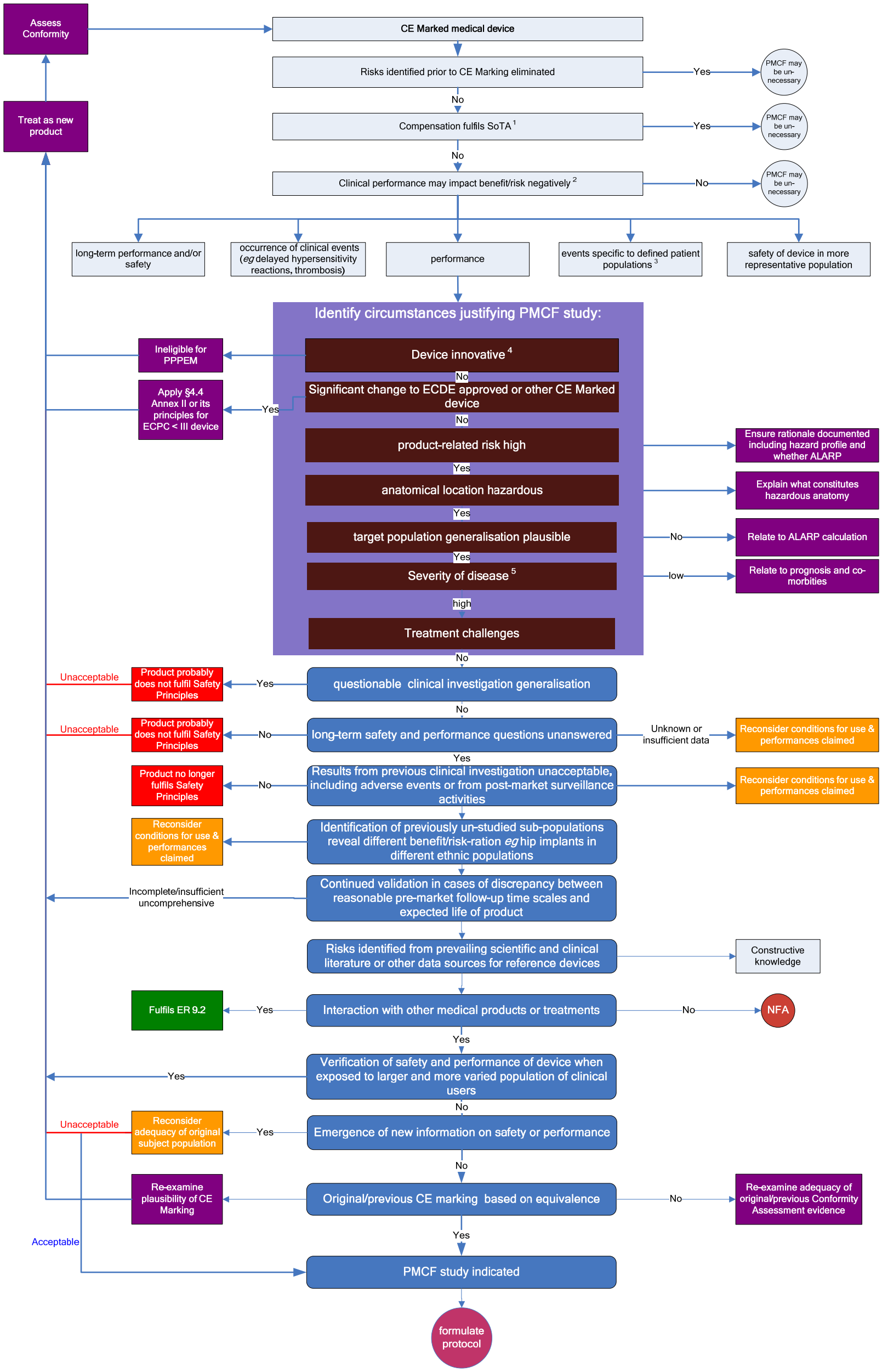

[1] = State-of-the-Art
[2] = semi-qualitative/quantitative index/actuarial figures
[3] = re-examination of warranties (product claims)
NFA = no further action

Figure 1 Graphical representation of MEDDEV 2.12/2 rev 2 expanded for logic and plausibility

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Table 1 Critical analysis for PMCF study according to MEDDEV 2.12/2

	Elements of PMCF study according to MEDDEV 2.12/2		Explanation stated by MEDDEV 2.12/2	Comment
a.	Conditions of Use	Post-market clinical follow-up studies performed on device within intended use/purpose according to instructions for use	Conduct study according to: - applicable laws - regulations - appropriate methodology follow appropriate guidance standards recommended	No information of what applicable laws, regulations *etc* apply
b.		PMCF clinical investigation or study plan	- Clearly stated research question and objective and related endpoint - Scientifically sound design with appropriate rationale and statistical analysis plan - conduct clinical investigation according to appropriate standard - analysis of data and drawing appropriate conclusion	Application of Standards is voluntary
c.	Objectives of PMCF study	formal hypothesis clearly expressed	Clearly stated study objective should accommodate residual risks identified formulate to accommodate one or more specific questions relating to clinical safety or clinical performance of device	It is unclear how residual risk would be accommodated: does the guidance seek to impose clinical investigation of residual risk?
d.	Design of PMCF studies	scientific soundness to allow valid conclusions to be drawn	PMCF study design to fulfil formal objective design may vary based on objective, study hypothesis research question and endpoints	
e.		PMCF methodologies	- extended follow-up of patients enrolled in premarket investigations - new clinical investigation - review data derived from device registry or - review of relevant retrospective data from patients	Extending follow-up of pre-market investigations means that the device could not have fulfilled

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	Elements of PMCF study according to MEDDEV 2.12/2		Explanation stated by MEDDEV 2.12/2	Comment
			previously exposed to device	Conformity Assessment legally, therefore cannot be endorsed
f.		PMCF plan describing design and methodologies appropriate for addressing stated objectives	Clinical investigation plan/study plan identifying and where needed justifying: - study population (corresponding to CE-mark scope) - inclusion/exclusion criteria - rationale and justification of chosen study design including use of controls/control groups (where relevant; randomised or not) - selection of sites and investigators - study objectives and related study endpoints and statistical considerations - number of subjects involved - duration of patient follow-up - data to be collected - analysis plan including any interim reporting where appropriate to ensure continuous risk management based on clinical data - procedures/criteria for early study termination - ethical considerations - methods of quality control of data where appropriate	
g.		retrospective data review		Since examination of data is always retrospective, it is unclear what the guide means
h.		Implementation of PMCF study, analysis of data and conclusions		
i.		Study execution	- adequate control measures to assure compliance with clinical investigation or study plan - data analysis with conclusions drawn according to	

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	Elements of PMCF study according to MEDDEV 2.12/2		Explanation stated by MEDDEV 2.12/2	Comment
			analysis plan appropriate expertise - final report stating conclusions relating to original objective and hypothesis	

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The notion of equivalent device for initial Conformity Assessment introduced by § 8 ¶4.2 MEDDEV 2.12/2 is not found in the European regulations on medical devices but could be equated to the State-of-the-Art reference device.

The guide implies obligation to update clinical evaluation and risk management.

Conclusion

MED/DEV 2.12/2 rev 2 introduces numerous elements absent from the European regulations on medical devices, therefore, may pose questions about legitimacy particularly in the context of liability. Certain notions and concepts, especially, apparent truncation of (so-called) pre-clinical investigation— presumably equating to clinical investigation according to Article 15/Annex X, for instance — and commute to *post*-market (*ie*, after CE Marking is affixed) study, appears not only dangerous but inconsistent with the regulations.

It is uncertain whether the guidance fulfils its stated objective, given the source document and inconsistencies against European regulations, plus errors discovered.

Bibliography

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About the Author

Haroon ATCHIA – CEO & Technical Director

Haroon Atchia is the founder of Quality First International Limited (now part of Adveniunt Medical International Limited). A microbiologist and plastics technologist with considerable experience in design and development of medical devices, regulatory assurance and Quality Management Systems implementation and compliance, Haroon was formerly Senior Professional Technical and Scientific Officer at the Medical Devices Agency, UK Department of Health, specialising in cardiovascular and other implantable devices, with previous roles in agricultural nematology, diagnostic microbiology and industrial development of in vitro diagnostic devices. A recognised expert in safety and reliability engineering, and hazard evaluation (including risk management), Haroon has hands-on experience of preparing regulatory submissions, ranging from Product Design Dossiers, Technical documentation, 510(k) notifications, Investigational Device Exemption (IDE) submissions to clinical evaluation

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protocols. Haroon is also a specialist EC-design examiner and technical assessor for a number of Notified Bodies, enforcement defence specialist, CMDCAS assessor and medical devices Expert Witness. Haroon is a member of the Editorial Advisory Board of the *Journal of Medical Device Regulation* and formerly served in the same capacity for *The Regulatory Affairs Journal (Devices)* for several years and a visiting lecturer in medical device regulations at University of Cambridge and Cranfield University, *inter alia*.

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