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Observational studies in cardiosurgical devices in light of Regulation 2017/745 on medical devices, and the provisions of Polish law

Badania obserwacyjne *in-label* sprzętu w kardiochirurgii w świetle rozporządzenia 745/2017 o wyrobach medycznych

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Abstract

Act will replace national regulations that are based on the current system of medical devices directives ("MDD"). The Act on Medical Devices currently in force will be repealed and replaced by a new Act (the draft is currently being consulted). The new regulations will change the conditions for observational, non-interventional studies in which medical devices are used as intended by the manufacturer (in-label). Today's law provides for a liberal approach to this type of studies, but from May 2020 they will be treated like full clinical trials, except for the obligation to obtain administrative permission. The article describes this problem and also provides arguments supporting the thesis that such research will not require the prior opinion of the bioethics committee.

Key words: medical devices, clinical evaluation, clinical trial

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On 26 May 2020, Regulation 2017/745 of the European Parliament and of the Council of 5 April 2017 on Medical Devices [1] ("MDR") becomes fully applicable in all Member States of the European Union, including Poland. This Act will replace all national laws that were enacted as measures of harmonisation introduced by the system of medical devices directives (MDDs) — i.e. Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices [2] and Council Directive 93/42/EEC of 14 June 1993 concerning medical devices [3]. This means that Poland's current Act on Medical Devices 2010 [4] will be repealed and replaced by the new law. The draft new bill (hereinafter referred to as 'The Draft Law') has been recently published by the Ministry for Health and made available for public consultation.

Regulation 2017/745 (MDR) provides for a complex set of rules relating to clinical trials and the standards of clinical evaluation of medical devices. This new law is particularly important in two contexts. Firstly, the Regulation directly addresses the standard of clinical evidence necessary in order to deem the medical device compliant with minimal legal requirements. These standards are significantly raised when compared to the previous legal framework (binding under the system of MDD directives).

Secondly, MDR introduces a legal obligation to create and uphold a post-marketing clinical follow-up system

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(PMCF). The Regulation lays down detailed rules for PCMF, in particular in the field of high class devices (IIa, IIb and III). PCMF includes clinical review and post-marketing studies performed by the producers with respect to their products.

The requirements for clinical investigation in MDR are based on existing ethical and legal regulations. The new provisions adhere to general good clinical practice, the Helsinki Declaration and other important foundations of modern clinical trials (*see* point 64 of the preamble to MDR). Specific and customised rules have been enacted to protect the interests of groups of patients such as pregnant and breastfeeding women, minors, and incapacitated subjects. Moreover, the MDR provides for regulation of inclusion of patients in a state of emergency. The regulation of the "clinical experiment as *ultima ratio*" issue is especially welcome — especially when there is no equivalent rule under Polish law and many patients are denied access to last resort methods or technologies only due to the lack of a legal option in this respect.

The clinical investigation measures set out in MDR are not controversial — both in light of the existing EU and Polish law. This paper calls for attention with respect to the issue regulated in a less transparent way — *i.e.* the legal status of purely observational studies with no experimental component.

To clear the grounds for discussion, several legal terms need to be explained in detail. The term *'clinical investigation'* was a widely used, although non-defined, term under MDD system. Under art. 2 of MDR it means *"any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device"*. *'Clinical evaluation'* is to be defined as *"a systematic and planned process to continuously generate, collect, analyse and assess the clinical data pertaining to a device in order to verify the safety and performance, including clinical benefits, of the device when used as intended by the manufacturer"*. The new wordings clearly indicate that the lawmakers wished to disengage from their semantic range experimental activities in cases aiming primarily at saving an individual patient's life or health as well as to keep 'under one roof' different scientific methods, *i.e.* not to limit 'clinical investigation' to large, randomised, double-blinded clinical trials *sensu stricto*.

The new law does not recognise the observational and non-interventional study as a sub-type of clinical investigation. This approach differs greatly from the one taken in pharmaceutical law. Article 107m and other provisions of the Directive 83/2001 on medicinal products for human use [5] specifically address and regulate non-interventional post-authorisation safety studies which are initiated, managed or financed by the marketing authorisation holder voluntarily or pursuant to legal obligations. In spite of a certain degree of ambiguity as concerns legal terminology [6], the Polish Pharmaceutical Act [7] provides for an even more farfetched rule. The said Act renders the entire body of regulation dedicated to pharmaceutical clinical trials inapplicable with respect to non-interventional, observational, in-label studies (subject to certain restrictions such as off-label studies — *see* article 37al of the Pharmaceutical Act) [8]. This means for example that under the Polish Pharmaceutical Act, an observational study of patients treated with acetylsalicylic acid in cardiovascular disease prevention, according to the medical standards, in-label and with no additional monitoring procedures, will not trigger any legal obligations that would normally be applied in the case of full-scope clinical trials.

Under the new medical devices regulations, things look quite different now. Article 74 of MDR sets out the legal rules that apply to a situation where a clinical investigation regards a device bearing the CE marking. It makes a distinction between two classes of situation: the first one where CE marking bearing device is to be investigated outside the scope of its intended purpose (off-label), and the second one where CE marking bearing device is to be investigated within the scope of its intended purpose, *i.e.* purpose set out by the producer (in-label). This latter is defined as 'PMCF investigation' (PMCF stands for 'post-marketing clinical follow-up'). With respect to the first situation (example: use of cardiovascular stents in deep artery of penis angioplasty), the new law says simply that such investigations must be treated as clinical investigations and all legal requirements must be met. This makes sense, as off-label assessment of a medical device creates risk for patients *ex definitione*.

The provision relating to PMCF investigation, however, is somewhat trickier in its wording. The body of legal text stipulates that *"if the investigation would involve submitting subjects to procedures additional to those performed under the normal conditions of use of the device and those additional procedures are invasive or burdensome, the sponsor shall notify the Member States concerned at least 30 days prior to its commencement by means of the electronic system […]"* and *"the content of such notification must include documentation set out in Chapter II of Annex XV as part of the notification, dealing with specific requirement of clinical investigation"*. The last sentence of the first section of article 74 says moreover that rules provided in points (b) to (k) and (m) of article 62(4), article 75, article 76, article 77, article 80(5) and (6) and the relevant provisions of Annex XV shall apply to all PMCF investigations. This must be understood to be covering both PMCF investigations that are accompanied by invasive or burdensome procedures

as well as those investigations that are free of such additional measures.

To make the matter clearer, it might be useful to consider an example of a study of a transcatheter aortic valve replacement procedure where the only endpoint is time of procedure vs. clinical appraisal of the patient before surgery (using some available scale) and the hypothesis is that a given technology is more time-efficient than eligible comparators. Such a study would aim at an appraisal of efficiency of a medical device already available on the market, bearing CE markings (PMFC). However, it would not yield any additional risk for the patient, as no additional interventional procedures are applied and the equipment is used inside the scope of intended purpose (in-label).

Therefore, what strikes MDR's reader in this respect is the fact that the discussed provisions leave completely unattended all those situations where the CE marked device is investigated within the scope of intended purpose (in-label) and the study protocol is free of any invasive or burdensome procedures — where there is no shift in risk for the study subject whatsoever compared to the normal use of the device. This type of clinical investigation is very important in all fields of medicine, including cardiology and cardio-surgery. These studies do not create any additional risk for patients and may yield useful information — from epidemiological [9], clinical [10] and pharmaco-economic perspectives [11].

Under the existing Polish Medical Devices Act, the issue is regulated in the following manner. Article 40 section 3 states that *"a designed and planned systematic study of the device bearing CE marking in humans shall not be deemed a clinical trial if it is entered into with the aim of verifying safety or efficacy of the device and the studied device is used in accordance with its intended purpose"*[1]. This means that the Polish law (still in force up to 25 May 2020) provides for an absolutely different approach to observational, non-interventional, in-label studies. The current law does not consider such studies to be a part of the box labelled 'clinical investigations' [12]. The result is that no clinical investigation requirements are applicable to such investigational activities [13].

Notwithstanding the current approach, under MDR it must be assumed that in-label, observational, non-interventional studies will still be caught by the general definition of 'clinical investigation'. This means that all obligations set out in MDR with respect to PMCF investigation must be observed, notwithstanding the fact that such studies are limited in their scope, and yield no additional risk to patients. The said provisions of the Regulation cover the requirement to acquire informed consent from the patient. Moreover, they provide for the obligation that the sponsor must be established in the European Union, that anticipated benefits to the subjects or to public health justify the foreseeable risks and inconveniences and compliance with this condition is constantly monitored, that the rights of the subject to physical and mental integrity, to privacy and to the protection of their data are safeguarded, that medical care provided to the subjects is the responsibility of an appropriately qualified healthcare professional, and that no undue influence, including that of a financial nature, is exerted on the subject to participate in the clinical investigation.

As concerns the ethics committee's opinion, article 62 section 4 letter (b) of the Regulation (that applies to all PMCF investigations) requires that, with respect to a given investigation, it is verified that *"an ethics committee, set up in accordance with national law, has not issued a negative opinion in relation to the clinical investigation, which is valid for that entire Member State under its national law"*. The discussed provision of MDR refers to national laws on ethics committees — in the case of Poland, the Medical Profession Act [14]. However, under the said Act, hardly can there be found any legal obligation to acquire a prior opinion of the ethics committee in the case of in-label, observational, non-interventional studies in medical devices. Such a study is not covered by the definition of medical experiment.

This observation is very important because the borders for legal medical experiments are defined very narrowly under the Polish legal regime [15]. No other provision of Polish law would require the investigator or sponsor to seek the ethics committee's approval before commencement of the discussed type of study.

To conclude, the MDR's premise of a "lack of negative opinion" will be met with respect to observational, non-interventional, in-label investigations, even in a case where no ethics committee's opinion is obtained whatsoever. However, all other premises, including patient consent, must be met, and this will necessitate a change in the Polish practice of the said investigations with respect to medical devices, including those used in cardiosurgical procedures.

[1]"A planned systemic investigation of the CE-marked medical device in humans, aiming at assessment of efficacy or safety of the device, is not to be considered a 'clinical investigation' if the medical device under scrutiny is used in accordance with its intended purpose"

Streszczenie

Od 26 maja 2020 roku Rozporządzenie Parlamentu Europejskiego i Rady 2017/745 w sprawie wyrobów medycznych (dalej zwane „MDR") będzie podlegać stosowaniu w Polsce. Regulacja zastąpi przepisy krajowe uchwalone na podstawie dotychczasowego systemu dyrektyw o wyrobach medycznych („MDD"). Obowiązująca obecnie ustawa o wyrobach medycznych zostanie uchylona i zastąpiona nową ustawą (projekt jest obecnie konsultowany). Nowe przepisy zmienią warunki prowadzenia badań obserwacyjnych, nieinterwencyjnych, w których wyroby medyczne są stosowane zgodnie z przeznaczeniem producenta (*in-label*). Dzisiejsze prawo przewiduje liberalne podejście do tego rodzaju badań, jednak od maja 2020 roku zaczną one przypominać pełne badania kliniczne, z wyjątkiem obowiązku uzyskania pozwolenia administracyjnego. W artykule opisano ten problem, a także podano argumenty na rzecz tezy, że mimo wątpliwości takie badania nie będą wymagały uprzedniej opinii komisji bioetycznej.

Słowa kluczowe: wyroby medyczne, ocena kliniczna, badanie kliniczne

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