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Post-Market Clinical Follow-up under Regulation (EU) 2017/745 on medical devices: Regulatory and statistical considerations

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Address: 1 Cooks Road, London E15 2PW, UK
Editorial Director: Victoria Clark BSc, MSc
Tel: +44 (0)1305 264797
Email: editor@globalregulatorypress.com
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Post-Market Clinical Follow-up under Regulation (EU) 2017/745 on medical devices: Regulatory and statistical considerations

Introduction

The new Regulation (EU) 2017/745 on medical devices (MDR)[1] introduces a paradigm shift for Post-Market Surveillance (PMS)[2–4]. According to ISO/TIR 20416:2020[5], six major functions of a medical device's lifecycle interact with PMS processes, namely design development, clinical evaluation, activities to meet regulatory requirements, performance optimisation, marketing and sales, and risk management. According to Article 83 of the MDR, PMS is intended to prevent a lack of continual monitoring after approval, lack of diversity of sources of monitoring, and lack of alignment with findings of benefit/risk analysis. In other words, 'manufacturers shall plan, establish, document, implement, maintain and update a post-market surveillance system in a manner that is proportionate to the risk class and appropriate for the type of device'. Post-Market Clinical Follow-up (PMCF) is an integral part of PMS, running continuously and in parallel with the processes of vigilance reporting, Field Safety Corrective Actions, internal complaints management, and real-world feedback[4, 6]. The mandatory nature of PMCF aims to bridge the gap in clinical data, which has been further deepened by the increased clinical requirements of the new Regulation. Nevertheless, identification of the scope, sources and resources of PMCF have been a challenge for the medical technology industry, as PMCF is a dynamic process entailing conformity with requirements applicable to clinical investigations. The aim of this article is to frame PMCF under the MDR[1] and ISO 14155:2020[7] and to outline the regulatory and statistical considerations that a manufacturer should consider in order to implement compliant PMCF activities.

Post-Market Clinical Follow-up

As part of the PMS, which is now an integral part of the manufacturer's Quality Management System (QMS)[8], post-market data can be gathered and continuously fed into risk management either reactively or proactively[9–10] (i.e. by responding after an event (reactive) or by predicting, anticipating, and preventing events through the insight into a device's real-world performance (proactive))[3] (*see* Table 1 *overleaf*).

Table 1. Potential sources of PMS data, adapted from ISO/TR 20416:2020[5]

Proactive sources of data	Reactive sources of data
• Written or electronic surveys or questionnaires • Interviews of users • Literature reviews • Use of medical device registries • PMCF studies (i.e. clinical investigations) • Vigilance-related information published by regulatory authorities including, but not limited to, recalls, field safety notices, alerts, etc. • Manufacturer-sponsored device tracking/implant registries • Expert user groups (focus groups) • Physician or healthcare professional (device user) interviews	• Review of complaints, including incident reports, including those coming from in-house testing (if applicable) • Unsolicited user feedback and/or observations (other than complaints) by healthcare professionals and/or any other stakeholders coming to the attention of sales and/or marketing departments of manufacturers • Review of maintenance/service reports • Review of regulatory compliance notifications

Determination of the continued benefit/risk acceptability is established via statistical analysis of real-world vigilance data and literature findings, and their comparison with internal complaints and/or available clinical data[11]. This allows manufacturers to determine whether risk mitigation has reached a level where the device under evaluation is at least as safe as the state of the art, while continuing to perform as intended[12–14]. Within this framework, the MDR[1] upgraded PMCF to an essential and mandatory aspect of PMS (*see* Table 2), unless a justification can be provided to explain why it is not deemed necessary. According to Annex XIV, part B, point 5 of the MDR[1], 'PMCF shall be understood to be a continuous process that updates the clinical evaluation […] When conducting PMCF, the manufacturer shall proactively collect and evaluate clinical data from the use in or on humans of a device which bears the CE marking and is placed on the market or put into service […] with the aim of confirming the safety and performance throughout the expected lifetime of the device, of ensuring the continued acceptability of identified risks and of detecting emerging risks on the basis of factual evidence'.

In its reference to 'PMCF investigations' (Articles 74, 80 and 81)[1], the MDR aims to highlight that there is little difference between a clinical investigation and a PMCF investigation. A PMCF study, however, involves an already CE-marked device that is used within its intended purpose, and includes all patient groups within the stated intended use. A clinical investigation differs slightly, as it may be conducted for devices not yet CE-marked for the intended purpose used in the study, and therefore eligibility criteria are stricter than those in the intended use statement (e.g. label, instructions for

use)[15–16]. Therefore, PMCF investigations must meet the requirements outlined in Article 62(4) of the MDR and relevant ethical standards to protect participating subjects.

Table 2. PMCF overview as per the MDR

Goals to meet via proactive monitoring of real-world experience: • Confirm safety and performance of the device throughout its expected lifetime • Identify previously unknown side-effects • Monitor the rate and severity of known side-effects • Identify and analyse any emergent risks • Ensure continued benefit/risk acceptability • Identify any systemic misuse and/or off-label use
Sources of data: • Relevant literature review including evaluation of the clinical data pertinent to the device in scope as well as equivalent and/or similar devices (whichever is applicable) • PMCF surveys • Registry/hospital database studies • Clinical investigations (in human subjects) • Clinical experience data • Combinations of the above
Aspects to consider when defining the need for PMCF studies: • Novelty: the design of the device, the materials, substances, principles of operation, technology, or medical indications are novel • Equivalence: CE marking is based on equivalence • Inherent risks/intended population: – high risk with respect to the intended population and/or a subgroup (e.g. elderly, paediatrics, patients with a specific comorbidity) – identification of previously unstudied subpopulations that may impact the benefit/risk ratio of the device – difficulty generalising the clinical outcomes of available clinical investigations • Significant design changes: there is a significant change to the device that has resulted or is expected to result in the revision of its original intended purpose • High risk due to anatomical location: the intended use is in a high-risk location such as the central nervous system • High risk due to product specifications: there is a high risk based on design, materials, components, invasiveness or clinical procedures • Unsubstantiated indications: the device's indications for use are not sufficiently supported with existing clinical evidence • Unsubstantiated claims: clinical claims on clinical safety and performance are not sufficiently supported with existing clinical evidence • Long-term safety and performance:

  - emergence of new data (e.g. from vigilance databases) on safety and/or performance of the target device and/or similar devices
  - any unaddressed Corrective and Preventive Actions
- Risk reduction: is there sufficient evidence to support the continued acceptability of the benefit/risk ratio of the device?
- Expected intended lifetime:
  - unanswered questions on the long-term safety and performance of the target device
  - currently available clinical investigations do not cover the whole range of the intended lifetime of the target device
- Insufficient/incomplete previous clinical investigations: unaddressed issues with respect to results of previous clinical investigation(s), including adverse events
- Risk profile of similar medical devices:
  - emergent risks identified in the literature for similar devices in the same intended medical field
  - new information on safety or performance of the target device and/or similar device emerges from the literature
- Health economics/reimbursement/market access: clinical evidence is necessary to support market access and/or continued market acceptance

Sources of clinical data

PMCF sources of clinical data vary. The final choice is usually made by co-addressing the reasons for performing a PMCF (*see* Table 2), the projected cost, the involved timelines, and overall capacity of the manufacturer to balance the level of evidence required and the effort needed to collect this evidence[17–18].

PMCF does not necessarily have to be a randomised trial but when it is, clinical data should result in the highest data appraisal scores (*see* Table 3) and its design should ensure that the activities are appropriate to answer the PMCF plan objectives. For example, if long-term clinical data are needed based on the results of a gap analysis, a PMCF in the form of a customer survey, either for medical doctors/hospitals or end users, might not be the ideal option to capture the required data[17]. However, such surveys are cost-effective PMCF sources with quick turnaround times that can deliver useful information, provided that the evaluated patient data does not require a declaration of consent. A medical device registry can also be a quite advantageous PMCF option, as it provides a single central repository of PMCF data captured from different territories, thus ensuring data are generated in a consistent manner[6, 13, 14, 17, 19].

Table 3. Available PMCF options according to MDCG 2020-6[20]

PMCF option	Cost	Required timeline	Specificity	Level of required clinical details
Clinical literature review	$		+	
Survey	$$		++	
Registry review	$$$		++	
Clinical investigations	$$$$		++	

Although there are multiple sources of clinical data, conducting a PMCF clinical investigation is the gold standard for clinical data generation. Under the MDR[1], such studies must be conducted according to ISO 14155:2020[7], which now applies to PMCF and observational studies. In practice, all exceptions from the standard's requirements will need to be justified. Not all requirements need to be met, but those related to planning, conducting and documenting data are always applicable. Therefore, PMCF activities are linked to a lifetime-long risk management overview of the investigational medical device. Given that the applicability of ISO 14155 extends to all clinical investigations that involve human subjects, Investigator Initiated Studies and registries are impacted. In addition, Annex I to ISO 14155:2000 describes the clinical development stages of medical devices, including the applicability of the standard to every specific stage. For post-market observational studies, possible exemptions are indicated for device accountability, labelling for clinical investigations, the need for an Investigator's Brochure, reporting to regulatory authorities, full informed consent, and the *curriculum vitae* of members of the investigation site team. The revised standard introduces various new requirements to establish a risk-based clinical investigation process and therefore takes a step closer to harmonisation with the MDR[1] and aligns with ISO 14971:2019[21] risk management principles. Within this context, PMCF activities and studies must be designed to focus on the corroboration of the continued acceptability of the device's benefit/risk ratio.

Statistical considerations for PMCF

ISO 14155:2020 has updated the statistical considerations for the description and justification of the Clinical Investigation Plan to reflect the current guidelines of clinical research. The 2020 version provides clarifications for sample size calculation, significance level and power. Bias and confounding management (e.g. adjustment, stratification or stratified randomisation) have been added alongside revised requirements for specification of subgroups, description of procedures for multiplicity control, exploratory analysis and sensitivity analysis. Three completely new requirements have been added, namely:

- identification and description of procedures for reporting any deviation(s) from the original statistical analysis plan;
- development of a strategy for handling the potential imbalance of the numbers of subjects across investigation sites for multicentre clinical investigations;
- development of a strategy for pooling data, if applicable.

However, although statistical considerations are outlined in a more explicit manner, the trial design can still only be determined on a case-by-case basis considering the nature of the clinical investigation.

Manufacturers should use scientifically justified sample sizes[11, 22, 23]. There are several key factors to consider when choosing the appropriate statistical analysis:

- Study objectives and primary endpoints: the biostatistician must use the right method while co-evaluating the expected outcome (e.g. number of device failures over a specific period of time) of the PMCF study.
- The study type must be chosen cautiously. When conducting a new clinical trial, the type of the study (superiority, equivalence, non-inferiority) should be clearly stated, as there are differences in respect to planning, performance, analysis and reporting of the results.
- Expected precision of the estimate: this may be assessed using the manufacturer's past experience or any other published study performed by other manufacturers. The most critical factor, though, is the co-analysis of available PMS data, regardless of origin and nature (either proactive or reactive).
- When conducting a clinical literature review, survey or taking data from registries, quality of the available data is of major importance, as is the examination of variability or heterogeneity in study results.
- Expected PMCF drop-out rate: the manufacturer should be able to determine a rough estimation based on previous experience in the same medical field. There are different ways to complete a statistical analysis when subjects are lost to follow-up, but the final choice will again depend on the nature of the device and the corresponding clinical investigation[24]. For example, when a 'per protocol' approach is used (i.e. when lost subjects are excluded), attrition bias may arise, as removal of subjects after randomisation may raise questions of invalidity by the Notified Body, as the investigation may exclude subjects who intentionally failed to achieve the event of interest. Use of intention-to-treat analysis is another approach to accommodate for lost outcome data, which counts subjects to their original group even though data are not available. It seems that this

approach mimics real-world data more efficiently and excludes bias but introduces higher levels of inaccuracy that may not be beneficial for a PMCF study seeking to compare safety data[24–28].

Sample size estimation

An appropriate sample size estimation for a PMCF study depends on several study parameters. The basic statistical aspects are presented in Table 4. Estimation of the appropriate sample size is critical for a PMCF study[3, 6, 22]. Samples smaller than required may prevent data extrapolation, whereas unnecessarily large samples could amplify detection of differences due to statistical differences that will not be clinically relevant[25]. Sample size estimation is also essential to establish the feasibility of a study in terms of the required cost and time. Upon calculation of the sample size, factors such as subject availability, study duration and required resources must be defined. This is because, for example, larger sample sizes need more sites and therefore a higher budget is required.

Table 4. Input for sample size calculation – Basic definitions

Statistical hypothesis (null and alternative hypothesis)	A statistical hypothesis is a statement about the nature of a population. A null hypothesis is the hypothesis a researcher is usually trying to disprove. It often proposes that there is no difference between certain characteristics of a population. In contrast, the alternative hypothesis suggests there is a relationship between two (or more) variables in a study. A hypothesis test uses sample data to determine whether to reject the null hypothesis. If there is not enough data then it may not be possible to reject the null hypothesis, even if it is false.
Significance level	The significance level, also known as type I error, is the probability of rejecting the null hypothesis when it is true. It is denoted as 'a' (alpha level) and conventionally a 5% level of significance is acceptable in clinical investigations. Depending on the characteristics of the investigational medical device, different levels of significance can be used. The lower the level of statistical significance used, the larger the required sample size.
Power	A type II error is the risk of a false negative (disregarding a significant difference when it exists), usually denoted as β. Statistical power represents the probability of finding a statistically significant result when one exists. It is denoted as 1-β. Power ≥80% is generally considered adequate. Contrary to significance level, the lower the level of power, the smaller the sample size required.
Minimally clinically meaningful difference	In a clinical trial, the minimal detectable difference refers to the smallest difference between treatments that is considered as clinically significant. The larger the clinical difference, the smaller the sample size needed to detect a difference.
Variability	Variability refers to how spread out a set of data is in a specific population. Smaller variability denotes a more homogeneous population and therefore a smaller sample size. Variability can be assessed from previous studies or pilot studies. In case of binary outcomes, there is no need to estimate variability to calculate the appropriate sample size.

Margin of error	The margin of error is a statistic expressing the random sampling error, which is the likelihood that the sample results vary from the population. Margin of error is proportional to the sample size.
Drop-out rates	Sample size should be adjusted to account for the expected number of dropouts. A common method is to divide the sample size by 1-d, where d is the dropout rate.
Treatment allocation	The ratio of intended participants in each comparison group is referred to as the treatment allocation ratio. The maximum statistical power for a fixed sample size is achieved when the groups are of equal size/allocation. The power is reduced as the imbalance increases. There are various, user-friendly, free software/online calculators for power and sample size calculation, but researchers must choose based on the needs of their PMCF study.
Critical values	Critical values are the values that indicate the edge of the critical region. Critical regions (also known as rejection regions) describe the entire area of values that indicate one can reject the null hypothesis. In other words, the critical region is the area encompassed by the values not supportive of the default assumption – the area of the 'tails' of the distribution.

Preparation of sample size calculation is a multi-step process that must always start with the explicit determination of the PMCF study's purpose. Different study designs need different methods of sample size calculation and therefore different sample sizes. For example, testing superiority usually requires larger sample sizes than testing non-inferiority and equivalence[19]. All sample size calculations are made assuming a normal distribution. When the distribution of the underlying data is unknown or not normal, adjustment to sample size must be made. The sample size must be increased by a factor depending on the statistical test that will be used to analyse the data. Adjustments should be made for any confounding factor(s) that should be considered. Definition of study objectives and endpoints (e.g. discrete versus continuous endpoints and time-to-event endpoints), must be set before the study design, which precedes selection of statistical tests. The choice of statistical tests relies upon data structure and distribution, as well as variables to be used in the PMCF study (*see* Table 5). Some of the most used are IBM® SPSS® Statistics, SAS/STAT®, STATA® and Minitab®. Microsoft Excel could also be used on a theoretical level but it cannot undertake more sophisticated statistical analyses without prior validation, which will inevitably increase the total cost of the PMCF programme. Non-commercial statistical packages are also available; the most popular among them seems to be the R Project for Statistical Computing[29].

Table 5. Commonly used statistical tests

Parametric test (based on normality)	Corresponding non-parametric test	Purpose of test
Continuous variables		
One sample t test	One sample median	Compares a sample with a known population
Independent sample t test	Mann-Whitney U test, Wilcoxon rank-sum test	Compares two independent samples
Paired sample t test	Wilcoxon matched pairs signed-rank test	Examines differences between the same set
Pearson correlation coefficient	Spearman correlation coefficient	Assesses the linear association between two variables
One way analysis of variance	Friedman two-way analysis of variance	Compares groups classified by two different factors
Categorical variables		
Binomial test	–	Compares a sample proportion from a known (or hypothesised) population proportion
Chi square test (or Fisher's exact)	–	Compares categorical variables
Meta-analysis	–	Systematically assesses previous research studies to derive conclusions about that body of research

Sample size calculation examples

The following examples come from real-world projects managed by the authors. Numerical aspects and types of medical devices have been modified to prevent disclosure of the actual parameters of each project. Equations and calculations were performed as per Chow *et al* (2017)[22].

1. Testing superiority compared to the standard treatment option

One of the critical complications after surgical treatment of a trochanteric fracture is fixation failure. A study has estimated that the incidence of fixation failure, when using a standard treatment available on the market for more than 20 years, may be as high as 20% within one year from the placement, especially in unstable fractures. A new hip screw system with the same intended purpose as the standard treatment has been designed to ensure that only 10% of patients will suffer fixation failure. This is a clinically significant benefit, as failed management of trochanteric fractures, especially among the elderly, is associated with pain that prevents the subject from performing daily activities, disability

resulting in recurrent surgical interventions, and increased mortality. The manufacturer of the hip screw system needs to conduct a study to conclude that there is a significantly lower difference in fixation failures when their device is compared to the standard treatment, and therefore that the new device is superior in the standard treatment for this particular outcome measure. What sample size does this manufacturer need?

In this example, it is of interest to establish superiority of the screw system compared to the standard treatment. A difference of more than 5% is considered to be of clinical importance. Thus, the superiority margin is chosen to be 5% (i.e. δ = 0.05). It is assumed that the true incidence rates of the screw system and the standard treatment are 10% and 20%, respectively. Sample size calculation will be performed for achieving an 80% power at the 5% level of significance. Equal allocation and zero dropout rate are assumed. The values n1 and n2 represent the two groups that will be compared to test the superiority hypothesis (n1= screw system, n2=standard treatment). The sample size can be determined by the following equation[22]:

$$\text{n1 = n2 = } \frac{(z_a+z_\beta)^2}{(\varepsilon-\delta)^2}\left[\frac{p_1(1-p_1)}{\kappa}+p_2(1-p_2)\right]$$

In this equation, p1 and p2 are the proportion (incidence) of the two groups, here 0.10 and 0.20 respectively. ε is the difference between the two groups, in this case –0.10, and δ is the superiority margin of –0.05. Z is the critical value for a given a or β. As the sample size calculation will be performed for achieving 80% power, then β = 0.20 and the corresponding critical value is 0.84. The level of significance is set at 5% and the corresponding critical value for –0.05 and one-sided test (as this is a case of superiority) is equal to 1.64. K is the allocation ratio and in this case is 1 as the two groups will be of equal size and a is the probability of type I error and β the probability of type II error. Adding those numbers, the above equation results in:

$$\frac{(1.64+0.84)^2}{(-0.10+0.05)^2}\left[\frac{0.10(1-0.10)}{1}+0.20(1-0.20\right] = 615 \text{ (n total = 1230)}$$

2. Testing difference between a treatment and control

Using the same example as above, it may be necessary for the manufacturer to make a direct comparison of the new hip screw with the standard treatment to identify whether there is an actual difference in the percentage of fixation failures when the two devices are used under the same

intended purpose (i.e. whether there is a statistically significant difference between the two treatment groups).

In this example, it is of interest to design a non-inferiority study of the screw system compared to the standard treatment. The same difference as before is considered to be of clinical importance. Thus, the non-inferiority margin is chosen to be 5% (i.e. δ = 0.05). It is assumed that the true incidence rates of the screw system and the standard treatment are 10% and 20%, respectively. The sample size calculation will be performed for achieving an 80% power at the 5% level of significance. Equal allocation and zero dropout rate are assumed. The sample size can be determined by the same equation[22]:

$$n1 = n2 = \frac{(z_\alpha + z_\beta)^2}{(\varepsilon - \delta)^2}\left[\frac{p_1(1-p_1)}{\kappa} + p_2(1-p_2)\right]$$

The only difference in this case is that it is a non-inferiority trial. The difference between the two proportions would be 0.20 (standard treatment) – 0.10 (new treatment) = 0.10. Thus, the above equation changes to:

$$\frac{(1.64+0.84)^2}{(0.10+0.05)^2}\left[\frac{0.10(1-0.10)}{1} + 0.20(1-0.20)\right] = 68 \text{ (n total = 136)}$$

As expected, testing superiority usually requires larger sample sizes than testing non-inferiority. In case of dropouts, the adjusted sample size would be calculated by dividing the total expected sample size by one minus the proportion expected to dropout. For example, for a dropout rate of 10%, divide the total sample size by 1 – 0.10 = 0.90.

3. Testing superiority compared to the standard treatment option using only one sample

Using the same example as in number one, but this time with only one sample testing the incidence of fixation failure of the new hip screw system, which will be compared to the incidence of the standard treatment, taken from previous studies or clinical literature reviews (meta-analysis).

In this case, the sample size can be determined by the following equation:

$$n = \frac{(z_\alpha + z_\beta)^2}{(\varepsilon - \delta)^2}[p(1-p)]$$

Where p is the proportion (incidence) of the new hip screw system and is 0.10. ε is the difference between the proportion of the new hip screw system and the standard treatment (–0.10) (taken from previous study) and δ is the superiority margin (–0.05). Z is the critical value for a given a or β. As previously, a is the probability of type I error and β the probability of type II error. Adding in the numbers, the equation results in:

$$\frac{(1.64+0.84)^2}{(-0.10+0.05)^2}[0.10(1-0.10)] = 221$$

All critical values (z) can be found using the corresponding critical value tables or can be calculated using any statistical software.

Conclusions

In practical terms, the MDR expects PMCF to bridge the gap in clinical data that may be preventing manufacturers and Competent Authorities from monitoring the performance and safety of medical devices in a proactive manner throughout their lifecycle based on methodologically sound data. To demonstrate clinical compliance, manufacturers must consider PMCF requirements as early as the design input phase of a medical device by addressing its novelty, invasiveness and expected lifetime with respect to usability and use-associated risks. This translates into the need to plan PMCF as early as possible based on factual evidence and to incorporate efficient practices for real-world clinical data collection into the QMS.

However, it must be noted that although the MDR has significantly upgraded the role of PMCF, there is still no consensus on the statistical aspects of its design. Therefore, manufacturers need to implement a stepwise process starting by the identification of their portfolio's PMCF needs and proceeding to choose the appropriate PMCF activity taking into account sample size calculations as well as the level of required clinical evidence.

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Kyriaki Antonopoulou holds a master's degree in Biostatistics and has worked in the field for more than eight years in academic research programmes, University hospitals and State hospitals.

Dr Vasiliki Valla holds a PhD in Applied Medicinal Chemistry and has been working in global regulatory affairs, mainly in the USA and Europe, for more than 22 years. She has extensive experience in medical writing, research and development, and regulatory approval of pharmaceuticals and medical devices.

Dr Amy Lewis holds a PhD in Psychology and has spent four years as a Postdoctoral Researcher in Aarhus University, where she designed and implemented psychological memory experiments for human and non-human populations. She has been working as a medical writer for the last two years.

Dr Bassil Akra is Chief Executive Officer of AKRA Team GmbH. He was the Vice President of Global Strategic Business Development for TÜV SÜD for 10 years. He has extensive experience in research and development, quality management, and regulatory approval of medical devices, combination products and Advanced Therapy Medicinal Products. He was involved in the drafting of several European guidance documents (e.g. MEDDEV, Medical Device Coordination Group).

Dr Efstathios Vassiliadis is Chief Executive Officer of Evnia Group and OARK. He has a dual research and development and business background and more than 17 years of experience in biotechnology and pharmaceuticals in the USA and Europe, with multi-disciplinary projects involving compliance, research and development, and cross-functional senior management. He holds 11 international patents.