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Considerations for designing and implementing successful PMCF surveys

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Considerations for designing and implementing successful PMCF surveys

Introduction

The introduction of the European Medical Device Regulation (2017/745, MDR)[1] back in May 2021 has considerably raised the level of regulatory requirements across the medical device industry. To continue to CE mark their devices across Europe, there are increased expectations on medical device manufacturers for continuous post-market evaluation, clinical data collection and evidence generation for their devices. This is addressed by post-market surveillance (PMS) and post-market clinical follow-up (PMCF), which both focus on the lifecycle approach to post-market monitoring. Medical Device Coordination Group (MDCG) guidance 2020-7[2] states:

> 'The Medical Device Regulation (EU) 2017/745 (MDR) considers the post-market clinical follow-up (PMCF) as a continuous process that updates the clinical evaluation and that shall be addressed in the manufacturer's post-market surveillance (PMS) plan.'

The aim of PMCF is to:

- confirm the safety and performance, including the clinical benefit if applicable, of the device throughout its expected lifetime;
- identify previously unknown side effects and monitor the identified side effects and contraindications;
- identify and analyse emergent risks on the basis of factual evidence;
- ensure the continued acceptability of the benefit-risk ratio;
- identify possible systematic misuse or off-label use of the device, with a view to verifying that the intended purpose is correct.

Medical device manufacturers are, therefore, being asked to be more proactive in assessing the safety and performance of their products, backing this up with clinical data and post-market monitoring. The data collected will be used to update risk management and the clinical evaluation of each device. It is also worth bearing in mind that irrespective of whether the manufacturer plans to transition their product to the MDR or obsolete the device during the Article 120[3] transitional period, PMCF data collection and the PMCF report generated are obligatory for all devices under the Medical Device Directive (93/42/EEC, MDD).

There are many ways to collect these post-market data, and it is vital to understand which approach(es) will be most appropriate when creating the clinical strategy and corresponding PMCF plans. Some of the most common approaches are randomised clinical trials (RCTs), registries, literature reviews, and surveys.

When weighing up which approach(es) to take, manufacturers should consider the balance between the level of evidence required and the time and effort to collect it. PMCF surveys offer a very appealing route to take, given that they offer a useful, cost-effective, and timely approach to PMCF data collection. RCTs and registries, on the other hand, may provide a higher level of evidence but they can be time consuming and costly.

This article focuses on PMCF surveys as a compliant approach for post-market data collection to complete a successful Notified Body audit and MDR certification.

Deciding upon PMCF surveys

Deciding on which PMCF activity to implement will require careful consideration, with a need to balance the clinical evidence requirements (e.g. clinical gaps and risk classification of the device) and the feasibility of implementation (e.g. cost and timelines). For example, a Class III long term use device (e.g. a pacemaker) with a risk of clinical gap exposure may not be suitable for a PMCF survey, and instead a clinical investigation may be more appropriate. Surveys, however, can offer a simpler, quicker and cost-effective means of clinical data collection, especially for a more well-established technology with a lower risk of clinical gap exposure.

PMCF surveys must be scientifically justified, and the type of survey will depend on the type of medical device, including the risk classification and previous data obtained. Surveys can be used alongside other PMCF methods to strengthen the evidence of data for all risk classes; however, using them as the sole PMCF data source would not be recommended. Should a manufacturer decide upon PMCF surveys as the appropriate method of PMCF data collection, the first step is to outline the methods and activities within the PMCF plan. The PMCF plan[2] should:

- define the need for PMCF data collection;
- describe the activities/methods of PMCF data collection;
- define the aims of the activities/methods;
- provide a rationale for the appropriateness of the chosen activities/methods;
- provide the timelines for such activities.

Survey approach

Not only should manufacturers consider whether PMCF surveys would be an appropriate source of PMCF data collection, but they should carefully select the type of survey. As Notified Bodies provide more feedback and set their expectations as to what is required, there has been a clear push to try to gather more patient specific/real-time data for higher risk classification devices or those with limited previous data.

The level of evidence, and PMCF survey approach required, depends on the device in question. The variables that must be considered are summarised in Table 1.

Table 1. Factors to consider when choosing a PMCF survey approach

	Lower level of evidence required	**Higher level of evidence required**
Risk classification	Lower risk classification	Higher risk classification
Time on the market	Longer time on the market (well established technology)	Shorter time on the market (less well established technology)
Previous data	Clinical data (low risk of clinical gaps)	No clinical data (high risk of clinical gaps)
Duration of use	Transient/short term use devices	Long term use/implantable devices
PMCF survey approach	**End user level**	**Patient level/chart review**

For well established, lower risk classification devices that are used transiently (e.g. gloves, scalpels and other operating room based devices), a more generalised **end user level survey** could be justified for the PMCF survey approach. These surveys can be summarised as being a more general, higher level data collection method, collecting information on the safety and performance of multiple device usages across a set time period (*see* Table 2).

On the other hand, less well established, long term use, higher risk classification devices or those with a lack of clinical data may require a more focused **patient level survey**. These surveys can be achieved via patient record/chart reviews, in which data on the safety and performance of the device are collected on a patient-by-patient or procedural basis (*see* Table 2).

Table 2. Comparison of end user level and patient level surveys

End user level survey	Patient level survey
• Screen users depending on their usage across a set time period (e.g. two months) • Each survey represents multiple device usages • Respondent asked to recollect safety and performance information based upon usage over the set time period • Completion of a one-off survey by each respondent	• Screen users depending on recent and upcoming usage • Each survey represents one patient/case that the device was used for • Respondent asked to complete survey based on each usage by reviewing patient charts/records • Completion of multiple surveys by each respondent
Pros: • quicker to implement • cheaper • less burden on respondents	Pros: • higher level of evidence • case specific data • data provided from patient charts
Cons: • lower level of evidence • recall bias due to recollective nature • data grouped across multiple usages	Cons: • longer fieldwork timeframe • higher cost • more burdensome for respondents

As shown and discussed above, there are several factors that must be considered before deciding upon the PMCF survey approach. Not only do the methods need to be justified statistically/scientifically, but costs, effort and feasibility also need to be accounted for.

Patient-level PMCF surveys are being used more regularly as the need for 'high quality' survey data is increasing. Despite some of the concerns over the identification of patients, data protection and the burden placed upon the healthcare professionals completing the survey, this approach is becoming more widely utilised in the collection of clinical, safety and healthcare resource data. A survey conducted by SurveyHealthcareGlobal[4] among 546 global healthcare professionals, saw 60% of respondents state that they have participated in patient chart research and, of those, 95% cited that the experience was positive. In addition, these patient-level surveys can be conducted in accordance with the ethical principles as outlined in ISO 14155 and the Declaration of Helsinki (e.g. not collecting any personal identifiable data on patients).

Endpoints/acceptance criteria

Once the survey method has been determined, the next step is to think specifically about the endpoints and outcome measures that will be used as the focus of the survey questions, and to help justify the sample size statistically.

As per the objectives of PMCF mentioned earlier, the survey will be used to confirm the safety and performance of the device in question, and this must be based upon the defined intended purpose. The safety and performance objectives should be determined by utilising other key documentation such as the Risk Management Framework, the clinical evaluation report and the clinical evaluation plan. Within this documentation, an assessment can be made based upon state of the art, literature reviews and competitor/benchmark analyses.

Within the PMCF plan, both the primary and secondary endpoints must be defined. These must be defined based upon the intended use of the device, with the primary endpoint commonly covering the performance of the device, with metrics such as technical success being used. The secondary endpoints will often be determined based upon any other performance measures or specific safety measures, such as device failure/adverse event rates.

The acceptance criteria set for each endpoint will be the metric(s) which the data collected from the survey will be compared against. The determination of these will be ascertained through clinical evaluation, a review of state of the art and an assessment of previous data collected on both the subject device and competitor/benchmark devices.

Statistical considerations

Statistical design and analysis must be considered when performing clinical investigations as cited in ISO 14155:2020[5]. This is also relevant for PMCF surveys as MDCG 2020-7[2] indicates to 'describe the rationale for the appropriateness of the chosen methods/procedures, including the justification for sample size, timescales and endpoints'. Due to the lack of clear guidance and experience in this area when it comes to PMCF surveys, the statistical considerations can be a challenge for manufacturers.

The first thing to think about statistically is the sample size. The number of subjects you need to survey must be calculated to ensure that a minimum number of data points are collected to allow for statistical analysis and to enhance the reliability of the data. Calculation of sample sizes, however, can be complex, with a variety of methods available, plus feasibility, timelines and costs must also be considered. With this in mind, regulators are requiring rationale to be set out, specifying how the sample size was determined and justified.

To determine sample sizes, clear objectives, endpoints and acceptance criteria must be set. For example, there are differing statistical tests depending on whether superiority, non-inferiority or equivalence is to be tested. In addition to this, the endpoint may be discrete, continuous or time-to-event. These factors will all play a big part in deciding which statistical test to use and this will impact the resulting sample size. Once the above has been decided, the sample size calculations can be

started, and this relies on several variables/inputs such as the statistical hypotheses, the significance level (α) and the level of power (β) to be used.

An example of a sample size calculation from a real world PMCF survey managed by the author is shown below. Please note that values and the names of the devices have been modified to ensure confidentiality.

Sample size example

The primary endpoint for a device is set as technical success (e.g. success rate for facilitating the intended use). The success rate for a state-of-the-art benchmark device is set at 95% and, therefore, established as the minimum performance acceptability criterion. The expected performance of the subject device to be surveyed is 90%.

Using a single proportion (or one sample) non-inferiority test, where p_1 and p_2 represent the technical success rates for the subject device and comparable state-of-the-art benchmark devices, respectively, the null and alternative hypotheses for the non-inferiority analysis are as follows:

H_0: $p_1 - p_2 \leq -\delta$

H_1: $p_1 - p_2 > -\delta$

where p_1 = technical success rate for the subject device and equivalent comparator, p_2 = technical success rate for benchmark devices, and δ is the non-inferiority margin. A non-inferiority margin (δ) of 0.1 (10%) and a significance level (α) of 0.05 have been established for the performance assessment. Non-inferiority is established at the 0.05 significance level if the lower limit of the one-sided 95% confidence interval is greater than -10%.

Acceptable subject device performance is defined as a technical success rate for the subject device (p_1) that results in the lower bound limit (LBL) of the one-sided 95% confidence interval for ($p_1 - p_2$) > -0.10.

Rejection of H_0 will establish with 95% confidence that the technical success rate for the subject device/equivalent comparator is greater than the non-inferiority limit (p_2 – 0.1) and is non-inferior to the technical success rate for the benchmark devices.

Using the following single proportion (or one sample) non-inferiority formula and the values outlined below:

$$n = p(1-p)\left(\frac{z_{1-\alpha} + z_{1-\beta}}{p - p_0 - \delta}\right)^2$$

Variable	Value	Description
n	?	The sample size
p_1	90% (0.90)	The true proportion (the technical success rate of the subject device)
p_0	95% (0.95)	The null hypothesis proportion (the technical success rate of the benchmark device)
α	5% (0.05)	Confidence intervals
β	20% (0.2)	Margin of error
δ	-10% (-0.1)	The non-inferiority margin

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

This example calculation would give you a desired sample size of at least 223 surveys/individual cases to be completed.

Sample considerations

Once the sample size has been determined and statistically justified, the next step will be to consider the make-up of the sample, specifically the demographic of the respondents. It is important to think about how to create a sample that is representative, to consider all the end user types (e.g. specialties) and to collect data across the markets/countries in which the device is sold. That being said, there must be a balance between achieving a fully representative sample, and the feasibility and costs. For example, it would make more sense to target respondents from a select number of countries in which the device is most widely sold rather than every single country that it is marketed in. Working closely with marketing to assess sales volumes is critical to ensure a successful and cost-effective sampling plan.

As only CE marked devices sold in Europe will come under scrutiny of the MDR, the gold standard data would be data that are gathered from European markets, the major European markets being the most recommended (e.g. France, Germany, Italy, Spain and the UK) due to the logistical ease of fieldwork and the relatively low costs associated with translations. Collecting data from other countries outside of Europe, however, can be approved if there is appropriate justification, such as there being a lack of sales across European countries. If that approach is required, then utilising countries where the patient characteristics and the healthcare systems are not too dissimilar from those across Europe (e.g. the USA) would be advised.

Device groupings/gap analysis

Devices within the same product group, with a very similar intended use, location of use, patient demographic and end user can be covered under one PMCF plan and within a single PMCF survey. A common pitfall with PMCF surveys is when the final data do not adequately address all models and/or variants. It should be ensured that all variants, including models and sizes, are covered under the survey plan, and it is recommended that minimum quotas on the number of survey responses for each of those variants are considered when setting up the survey design.

Survey/questionnaire design

Once the survey approach, endpoints, acceptance criteria and sample size have been determined, the next stage is to design a questionnaire that ensures the appropriate data can be collected whilst keeping it concise and not overly burdensome for the respondents.

Depending on how the respondents completing the survey are recruited (*see* the 'Survey implementation' section), it may be required to begin with some screening questions that allow only those who fit specific screening criteria (e.g. specialty types, usage thresholds) to qualify. Once qualified, the main survey should be focused on the specific safety and performance objectives, keeping the aims of PMCF in mind.

Table 3 illustrates an example of how to break the survey questions up in a focused manner, regardless of which survey method is taken (e.g. physician level versus patient level).

Table 3. Suggested categories for PMCF survey questions

Category	Suggested content
Screening	• speciality • years of experience • device usage • usage volumes
Device usage	• indications • off-label usage • sizes/configurations • age ranges
Safety	• adverse events • device malfunctions • relationship with the device • clinical/patient impact • further surgical intervention

Category	Suggested content
	• adverse event reporting
Performance	• benefit/performance claims • Likert scales • performance in line with the instructions for use • other benefits
Other	• potential improvements • duration of use
Contact information	• name • telephone number • email address

Depending on the question, and the data that need to be collected, a range of question formats including single code, multi code, numerical and free text may be used.

When it comes to the differing survey approaches – end user versus patient level surveys – although the set up and format of the surveys differ, the focus of the questioning should be consistent with that outlined above. The difference will be that the end user surveys will ask questions at a higher level, based upon multiple devices or usages, while the patient level surveys will be more focused and specific to an individual device or case in which a device is used.

Some best practices to consider when designing a PMCF survey are as follows:

- Targeted and appropriate screening questions:
  - ensure screening questions tie back to inclusion criteria;
  - avoid exploratory questions and only include necessary screening questions;
  - add in open-ended questions to provide a quality control check;
  - do not asking leading questions.
- Ensure that the survey is short and concise:
  - should be able to gather all the required information/data without making it timely and burdensome for the respondent;
  - recommend to limit to 15–20 minutes per survey.
- Focus survey questions on the objectives/endpoints:
  - avoid too many exploratory questions (these should be left for marketing surveys);
  - ensure questions will provide answers that can be tied back to objectives and endpoints.

Compliance considerations

It is important to consider any compliance requirements when designing both the PMCF survey protocol and the survey itself, and specific standards, guidelines and best practices must be followed. These include, but are not limited to:

- Annex XIV to the MDR on clinical evaluation and post-market clinical follow-up[1]
- MEDDEV 2.12/2 rev 2, *Guidelines on medical devices – Post market clinical follow-up studies – A guide for manufacturers and Notified Bodies*[6]
- ISO 14155:2020, *Clinical Investigations of medical devices for human subject – Good clinical practice*[5]
- Regulation (EU) 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation, GDPR)[7]

With potential adverse event information being collected, manufacturers often prefer to receive the contact information of those who take part should they require a follow-up on specific issues reported within the survey. If that is the case, specific wording should be included prior to the main survey outlining what data will be collected, how it will be stored and transferred, and what it will be used for to comply with GDPR requirements. Data controllers, data processors and the data transfer methods must be agreed upon prior to survey implementation and the relevant agreements executed between the appropriate parties.

When it comes to the requirements for informed consent (Declaration of Helsinki and ISO 14155), Institutional Review Board approval or Ethics Committee reviews, these must be considered within the PMCF survey protocol and, if not required, a rationale for why not must be provided.

Survey implementation

Once the questionnaire has been approved, initiating and implementing the survey is the next stage in the process. An important decision to be made will be whether to take control of this part of the process internally or to look for third party suppliers to help.

With a typical PMCF survey taking anywhere from three to six months to complete, comprising several stages across the timeline, from questionnaire design, programming, link checking, recruitment, fieldwork management, data processing through to reporting, time and resources will

need to be focused across the entire process. The key stages of survey implementation are outlined, along with questions to consider:

1. **Programming**
    - What software/system will be used?
    - Does the questionnaire incorporate the appropriate routing and logic?
    - Has time been allocated for link testing and updates to programming?
2. **Recruitment**
    - How will respondents be targeted? Existing relationships with customers or utilisation of healthcare panels?
    - Will respondents be compensated and, if so, how will that be managed?
3. **Fieldwork management**
    - How will fieldwork be monitored and how often?
    - Will quality controls and regular data checks be in place?

Whichever method of survey implementation and data collection is used, it is important to assign roles and responsibilities and set out a clear timeline. In case the minimum number of surveys, as determined by the statistical calculations, is not achieved, backup options must be set out. These could include lengthening timelines, expanding the targeted reach (e.g. additional sites or countries) or completing the survey and back calculating the statistics based on the number of responses received.

Data analysis

As per the MDCG 2020-7 template[2], the data analysis for all PMCF activities, including surveys, should be statistical in nature and described in detail. The analysis plan should be outlined prior to survey execution within the PMCF survey protocol. Once the collection of survey data is complete, the findings will then be documented by the manufacturer in the form of a PMCF evaluation report. This will eventually be used to update the clinical evaluation report, the risk management documentation, the PMS plan, and the summary of safety and clinical performance, if applicable.

When it comes to the analysis itself, it will depend on the types of questions, individual data points and how they relate to the specific endpoints. The data can be analysed simply via raw data in Microsoft Excel or can be statistically analysed via software or tabulation systems.

In the final PMCF report, the number and percentage of participants completing the questionnaire should be summarised. Descriptive statistics can be used to summarise the data, at a

participant level, based on observed responses. Rates for outcome measures should be reported along with the defined confidence intervals.

There should be a review of the reported adverse events and complaints, and these should be collated and categorised accordingly. All reported incidents, including any reports of misuse and off-label use, will need to be reviewed and assessed. The review of adverse events will allow the identification of any emerging unexpected risks or any unexpected increase in known risks, focusing back to the PMCF objectives outlined in MDCG 2020-7[2]. The overall purpose of these assessments is to monitor the continued acceptability of the device's benefit-risk.

Data on the primary endpoint and secondary endpoints, based on performance and safety data, should be collected and analysed, and the success/adverse event rates should be calculated (including confidence intervals) as documented in the PMCF survey protocol and analysis plan, including comparison with the defined acceptance criteria. If the acceptance criteria are not met, results from a user survey should be used to review risk management documentation.

Data on aspects for which no acceptance criteria are defined should also be analysed and, when needed, be used to review risk management documentation and any other potentially relevant documentation.

Conclusions

The MDR has placed greater responsibility on proactive data collection by medical device manufacturers to help assess the safety and performance of CE marked devices on a continuous basis. This is addressed by PMCF activities, of which PMCF surveys offer a low effort, cost effective and timely approach.

Although a PMCF survey approach is simpler than RCTs and registries, surveys still require thorough planning, from the survey protocol, design and analysis, to reporting. When deciding whether PMCF surveys are appropriate, considerations and decisions must be made based upon the device type, risk classification and level of previous data. These factors must also be considered for the survey approach, be it generalised end user surveys or the high quality, patient level surveys that are being recommended more regularly by Notified Bodies. Statistical justifications must be made in relation to the sample size and must be based on specific safety and performance objectives, which in turn will determine how the data will be analysed.

Finally, when it comes to the survey implementation (including programming, recruitment, and data collection), proper planning must be undertaken and resourcing considered.

With this in mind, and the ever-changing landscape surrounding PMCF surveys, thinking about PMCF activities as early as possible, providing appropriate resourcing and setting realistic timelines is critical.

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