

Planting the Seed

The diversity and challenges of post marketing research projects may be daunting, but the importance of a sound research plan, the preparation of high-quality study documents and the targeted and effective communication of results collected in real world conditions are being increasingly recognised

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Post marketing research (PMR) is becoming increasingly important in maintaining drug approval and to achieve broad patient access to a newly developed medication. Because of this, PMR has been the only growing area of clinical research in recent years (1). Historically, PMR was largely driven by marketing needs and was seen as a less important part of clinical development, often leading to inconsistent and unfocused PMR programmes of low scientific quality and consequently weak impact. PMR studies were wrongly conceived as investigations that were simple in design and easy and cheap to perform (2). On the other hand, the design, analysis and communication of results from PMR projects is often more challenging than for typical Phase 3 randomised clinical trials, with a well-established study design, focused reporting, and pre-defined primary and secondary study objectives becoming necessary.

PMR's Growing Importance

Although in the past PMR was often conceived as a marketing-driven exercise and a 'nice to have', there are several reasons why PMR studies are now almost mandatory for the successful launch of most medical products. The regulatory agencies of the US (FDA) and the EU (EMA) frequently require PMR studies to confirm the safety of a newly approved drug under real-life conditions (FDA: Risk Evaluation and Mitigation Strategies

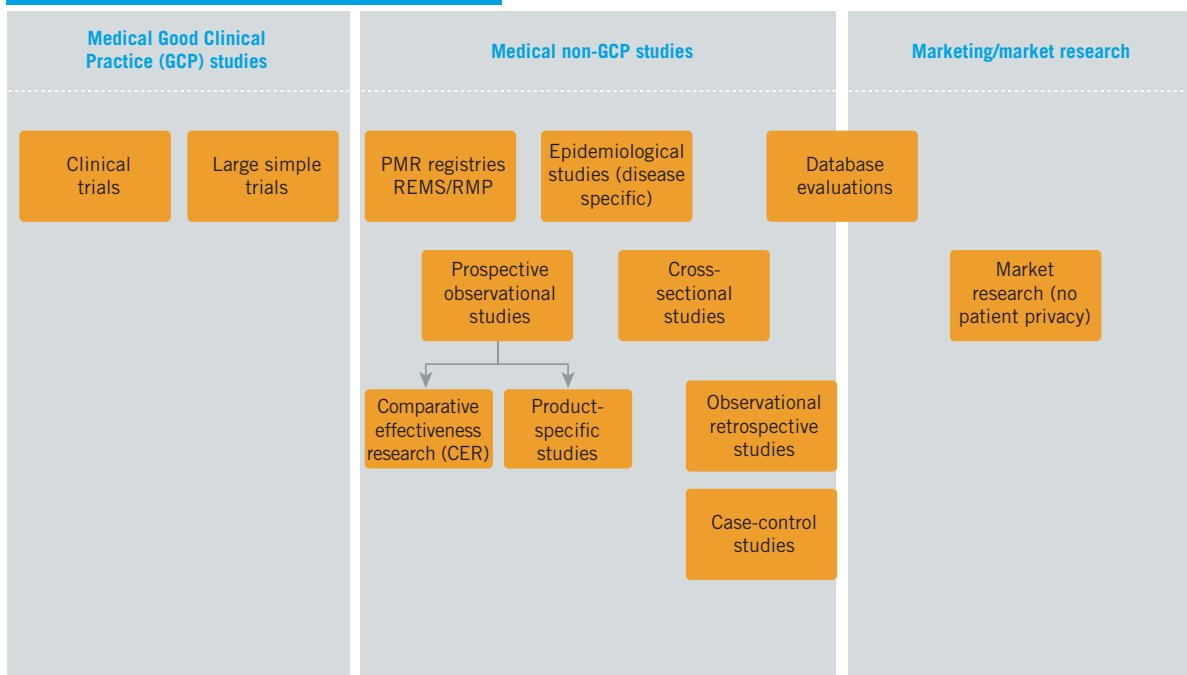
(REMS), EMA: Risk Management Plan (RMP)) (3,4). In a recent guidance for industry, the FDA underscored the importance of REMS for achieving and maintaining drug approval by giving detailed information about types of PMR studies, possible objectives and required methodology (5). The performance, quality and reporting of these studies is closely monitored by the regulatory bodies.

A further hurdle to overcome is achieving patient access via private or statutory health insurance systems. In the majority of developed countries, reimbursement of newly-approved, often more expensive medications, is dependent on additional data showing improved effectiveness or tolerability of a new medication, or cost savings, and ideally both (6). The data needed for this include patient-focused treatment outcomes, quality of life, direct and indirect treatment costs, and information on real life use of the medication. These data are usually not available, or even achievable, from typical registration studies and require a tailored PMR programme.

PMR's Challenges

In contrast to registration studies where well established and largely standardised study designs are used, a broad diversity of methodological approaches can be employed in PMR (7).

Figure 1: Post-marketing research (PMR) study types





In the recent guidance for industry on post-marketing studies, the FDA gives a detailed evaluation of study types and possible study objectives for safety assessments in PMR (5). There have also been a number of recent publications emphasising the importance of PMR methods for assessing post-marketing safety and tolerability with REMS and the urgent need for high quality comparative effectiveness research (CER) for newly approved medications (8-11). Figure 1 gives an overview of the diverse PMR studies and other research tools that can be used effectively in a PMR programme.

Related to the methodological diversity of PMR, the diversity of goals that can be addressed by the studies adds to the complexity of a PMR programme. Medical knowledge is needed, for example for safety and effectiveness objectives, along with knowledge of other areas such as quality of life, treatment costs, local and regional healthcare systems, and reimbursement requirements. Figure 2 shows research objectives that are often addressed by PMR studies and the organisational areas typically responsible for these projects in a pharmaceutical company.

Standard clinical trial designs, including blinding and randomisation, cannot be used in most PMR projects, as this leads to an unacceptably high selection bias. In turn, a straightforward analysis of descriptive data with simple statistical tests comparable to Phase 3 studies is usually not possible in PMR. The analyses generally require increased efforts to achieve appropriate study designs, tailored data management, and appropriate statistical methods to overcome biases and noise. Also, selecting measurements that are easy to use in clinical practice but still achieve meaningful, validated and generally accepted outcomes is a challenge

(12-14). To top this off, the legacy of largely marketing-driven implementation of low-quality PMR in previous years has led to a high level of scrutiny and strict quality criteria (15). Those have recently been established by the FDA for REMS and by research groups that established (or are currently establishing) criteria for reporting (STROBE) and design and conduct of observational PMR trials (GRACE) (5,16,17).

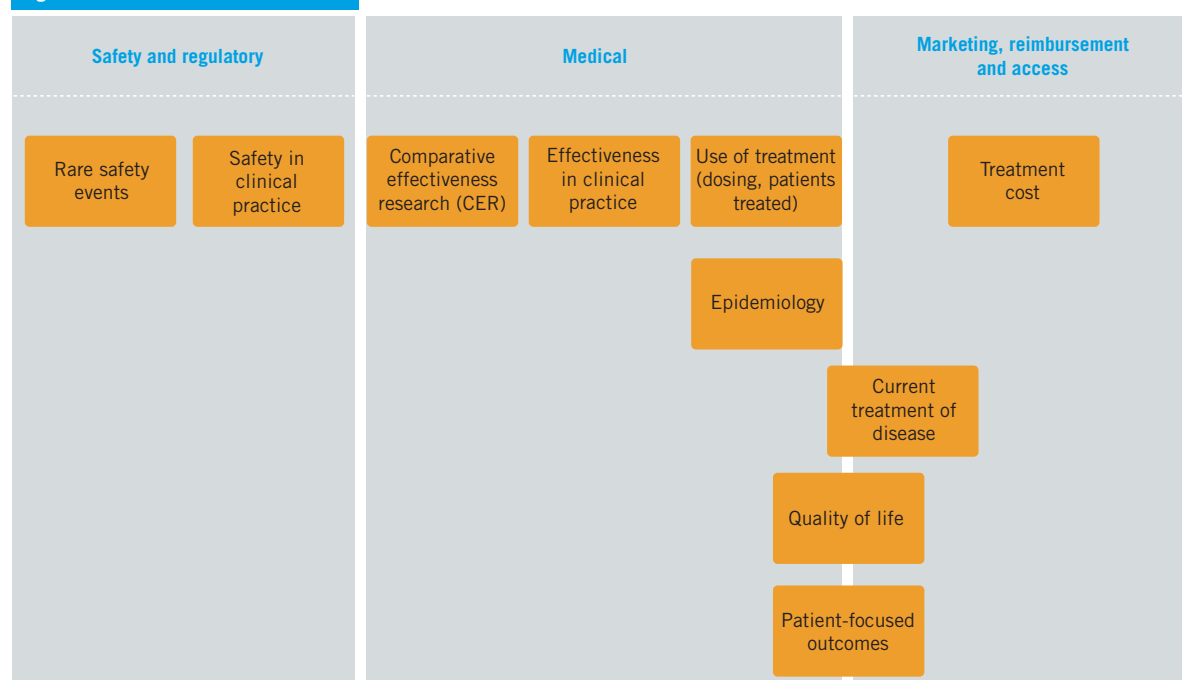
Designing a Successful PMR Plan

Heterogenous research tools and an often less stringent and decentralised planning and approval process for PMR in pharmaceutical companies often lead to poorly planned, inconsistently performed and insufficiently published/communicated PMR plans or results. This sometimes results in spending large amounts of money without a measurable benefit.

A thorough and consolidated PMR plan needs to be established already during Phase 3 of drug development. The focus of this plan should be to consolidate the various needs expected for PMR (approval, reimbursement, CER, costs, local needs) and to transfer this into a single plan. However, due to the historically lower importance of PMR, experienced personnel is often lacking. At this point of drug development, the main focus of clinical research is still on the registration studies, leading to a low level of support by in-house resources. Therefore, it is advisable to set up a dedicated PMR team and to partner with experienced consultants and/or specialised CROs to prepare a successful PMR plan.

The result should be a consolidated plan of studies and other PMR projects that address the key needs of a programme. Ideally, consistency with ongoing or planned registration

Figure 2: Goals of PMR



trials and the proposed labelling should be assured, and duplications or potentially conflicting projects avoided. The study designs and objectives should be tailored to the specific needs of maintaining registration and achieving broad access to the product. Each project has to be focused on its primary goal, such as achieving reimbursement or observing titration practices of a new drug in a real-world setting to be successful and cost-effective. The 'one study for all' approach should be avoided. In addition, despite the preparation of a global consolidated plan, specific local or regional needs should be addressed and tackled by specific projects.

To achieve this ambitious goal, a centralised and strategically focused lead team for the overall post-marketing plan is needed, alongside an experienced medical writing team that is available to prepare high quality key documents such as the PMR plan, study protocols, statistical plans, consistent CRFs, and so on. Ideally, consulting on the overall plan and the writing of the crucial documents should be in the hands of one dedicated PMR team. Of course, the study conduct, data management, and in particular statistical planning and analysis should be performed by specialised teams and/or should be outsourced by the PMR team.

Successfully Communicating PMR Results

Before completion of the PMR studies, a thorough communication plan should be set up. It is important to think about the different messages that are to be achieved and how they can be best conveyed to the appropriate target audience. The language of reporting results from PMR studies needs to differ from the typical reporting language for randomised clinical trials, due to the different scope and methodology of PMR projects. A variety of different communication channels can and should be used. These range from clinical study reports and peer-reviewed publications to trial registries, scientific posters and slide sets, as well as reimbursement dossiers (such as for NICE in the UK and IQWiG in Germany), all of which require specific formats and different content. Furthermore, knowledge of the most current versions of the requirements of regulatory and scientific bodies is needed to achieve a timely, targeted and effective communication of the outcomes of PMR projects (5,16,17). A consolidated team of experienced medical writers working together with dedicated medical, statistical, regulatory, and health economic experts can ensure this and the expertise of external service providers should be leveraged if necessary.

Conclusion

PMR programmes will continue to gain importance and will become more challenging in the future. They are needed to achieve and maintain widespread access to new medications with benefits for patients, physicians, health care providers and the pharmaceutical industry alike. To handle these programmes as intelligently as possible, a dedicated team that is experienced in PMR projects should be established early and include experienced consulting and writers teams that are able to set up consistent documents capable of achieving a fast and focused communication of PMR programme results.

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About the author



After receiving his PhD in Neurobiology and working for several years as an Assistant Professor, **Thomas Wagner** started his career as a medical writer in 1999. He was with Lilly Deutschland for a considerable time, before joining Trilogy Writing & Consulting in 2009, taking the position of Medical Writing Manager. He has more than 10 years of experience in post-marketing research (PMR) and regularly runs workshops on effective science communication for PMR for the European Medical Writers Association (EMWA) and pharmaceutical companies.

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