Summer 2013 Faculty Newsletter

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Editorial

Dr Asad Khan MFPM
Editor of the Newsletter
Advocacy Committee

Finally after six long months, we are seeing some decent sunshine in the UK. When I read the proceedings of the 'unusual weather conference' held by the UK Met Office that we in the UK are in the middle of a rare weather cycle and that we should expect to have a decade of wet summers, I must admit that for a moment, I felt depressed! [Apologies to international readers, but weather is a British obsession]

On the brighter side, this edition contains some very interesting articles. Sharon McCullough has written a thought provoking article on the value of us – pharmaceutical physicians! Two international members have also contributed two excellent articles – one from Germany on the future of monitoring in clinical research and one from Belgium on the case for research in pregnancy.

Finally as I always say, this is your newsletter. Please feel free to contribute and yes, all suggestions for improvement are warmly welcome. Please contact myself or Ben Cottam in the Faculty office (b.cottam@fpm.org.uk) with your ideas.

Happy reading and enjoy the sunshine while it lasts.

News

Faculty 'Strategy Away Day' – 3rd July 2013

The Faculty Board, committee chairs and several staff members met at the Royal College of Surgeons on the 3rd July to establish how the Faculty can develop an effective and worthwhile strategy of work for the short, medium and long-term. The overall theme of the away-day was 'where can the Faculty make a difference?'

Topics discussed included: the professionalism of pharmaceutical physicians; how the Faculty can develop a more independent voice and be more influential; how the Faculty can develop strategic partnerships with other organisations; and how the Faculty can enhance its educational offerings.

A fuller report from the Away Day, with more defined actions, will appear in the next edition of the newsletter in October.

Report from Summer Awards Ceremony 12th June 2013

On the 12th June the first ever Faculty Summer Awards Ceremony took place at the Royal College of Physicians London. Over 100 awardees and colleagues, family and friends attended the event. Photos of some of the awardees are displayed below...

New Fellows (FFPM) of the Faculty

New Members (MFPM) of the Faculty

New entrants onto the specialist register

Events

Revalidation Appraiser Training Courses

It is anticipated that the Faculty will arrange an appraiser training session in October 2013. It is planned that further training sessions will be organised on a 6-monthly basis in the future. To register your interest or for more information please contact Susan Paterson on 020 7831 7662 (ext 24) or s.paterson@fpm.org.uk

Faculty conversation – 'Meet the Board' – 22nd October 2013 – RCP London, approx 6-9pm

A unique opportunity to quiz the Faculty Board on all aspects of the organisation and policies of the Faculty - from international issues to revalidation, transparency to education. There will be the chance for all attendees to formally submit questions and topics for discussion nearer the time, but meanwhile why not get the debate started on our LinkedIn page?

Faculty Annual Meeting

The Faculty Annual Meeting 2013 will take place on the 27th November at the RCP London. More information is available here.

Committee updates

Professional Standards Committee

The Professional Standards Committee is currently involved in two activities linked with revalidation. The first activity is a review of the Faculty's CPD guidance for pharmaceutical physicians. Following the introduction of revalidation in December 2012, both the GMC and the Academy of Medical Royal Colleges have produced a series of guidance documents for doctors about the revalidation process, and the supporting information that they will need to collect for discussion at their medical appraisals. CPD is one piece of supporting information that doctors will need to produce, and the Professional Standards Committee agreed that now was a good opportunity to review the Faculty's guidance to ensure that it covered the guidance that other organisations had provided, and that it address topics specific to pharmaceutical medicine. The second activity is publication of a set of presentation slides and illustrative case histories on how to prepare supporting information for revalidation. These will be uploaded to the Faculty's website for pharmaceutical physicians to access.

Following on from our successful annual symposium in November on the subject of adherence, two small working parties, one led by Dr Charles Phillips and one by Dr Robert Miller, will be considering, respectively, dissemination of the science and good practice of adherence for the pharmaceutical physician, and the outward sharing of good practice in adherence with other professional groups and the broader society. These working parties are supported both by the Advocacy and Professional Standards Committees.

OBoE

The OBoE (Officers of the Board of Examiners) group is a sub-group of the broader Board of Examiners. It comprises the Officers (Chair, Vice-Chair and Secretary), the Panel Conveners for each of the component papers and two or three additional co-opted members of the Board of Examiners. OBoE primarily focuses on the DPM examination, but also has some responsibility for other examinations set by the Faculty. OBoE co-ordinates the work of the Board of Examiners and carries out much of the detailed background activity necessary to set, mark and adjudicate the DPM examination. It is also continually reviewing and, where necessary, refining the structure and processes for the DPM. It meets at least monthly, either in person or by teleconference, during the first 8 months of the year, and more frequently during the last 4 months of the year when the examinations are being conducted. OBoE has just conducted the annual training day for the Board of Examiners and is now turning its attention to the detailed process of setting this year's exam papers.

Linked In conversations

Click on the links below to get involved with Faculty discussions:

Meet the Faculty Board and get your questions answered
On 22nd October there will be an evening conversation with the FPM Board. Please post your questions here so we can start the debate going...

BMA endorses Faculty position on clinical trials transparency and publication of results
The Faculty of Pharmaceutical Medicine has long advocated the timely publication of clinical trial results. Dr Keith Bragman, President of the Faculty, recently recommended to the House of Commons science and technology select committee enquiry into clinical trials that trial results should be made available in the public domain within 12 months of study completion...

What's the value of a pharmaceutical physician?

Dr Sharon McCullough FFPM
Consultant Pharmaceutical Physician, Zygian Ltd.
Chair of the Education Committee

Imagine you have been asked to advise a large pharmaceutical company – one that researches, develops and markets its own products. The CEO has asked 'How many pharmaceutical physicians do I need? What should they be doing? How can I measure their value?'

It's not a very realistic scenario - Andrew Witty and Pascal Soriot almost certainly have much more strategic matters to worry about. But throughout AstraZeneca and GSK individual managers will be justifying the composition of their departments, making sure that the knowledge and skills of employees match the needs of the business, thinking about whether they need to recruit another scientist or a pharmacist or a physician. Why should they employ a physician? What do companies actually need pharmaceutical physicians for? What do industry medics bring that others do not? Do we know the answers? And if we don't – should we?

Fundamentally of course, we are doctors. And as doctors, we have been trained to diagnose and treat our industry's ultimate customers – patients. During our training we have been permitted an immensely privileged relationship with them. We've broken bad news, seen the true impact of the diseases that our products treat and have been given special insights into illness. We bring all those perspectives with us.

We also bring the personal attributes that were part of our selection and developed further in our clinical training. We are scholars in biomedical sciences, psychological and social principles, population health and the scientific method. We learn the practice of medicine: how to run a consultation, diagnose and manage illness, communicate, prescribe, use and record information. And we are taught how to behave as professionals: in line with the profession's ethical and legal principles, as learners, teachers, leaders and team members, but always putting the patient's needs and safety at the centre of our work.

So by qualifying as doctors we've demonstrated that we are intelligent, committed, able to accept responsibility, make decisions and work under pressure. We've undergone an intensive, immersive patient focused training programme with most of us going on to spend a number of years in increasingly independent clinical practice during which we have refined our knowledge and skills.

Then we join the industry – and what do we have to offer? For many of us to start with probably not much. Knowing about disease management, patients, the NHS structure and how prescribers think is useful. But without understanding the industry context - the regulatory environment, how companies work, the process of drug development - our hard earned medical knowledge and experience counts for little. Of course, for the last ten years we have had a gold-standard specialty training scheme. No other group of employees in our industry has anything remotely approaching it. The broad curriculum and competence based structure of PMST mean that after four years the pharmaceutical physician is effectively an expert in the medical aspects of drug development and marketing – able to help their organisation to protect patients and to provide them with the medicines they need.

But pharmaceutical physicians don't come cheap, and neither does their training. Even though much of it can be done 'on the job' there are the on-going costs of courses and exam fees, and the need for supervision and protected time for meetings and reviews. And of course, after the CCT there is revalidation – a process which demonstrates our professional commitment to maintaining our standards of practice and one that other professional groups in our industry do not have. But again, there are costs attached.

Medics, by their nature – highly trained, independent minded and capable of asking difficult questions – can be tricky to manage. Non-medical – and sometimes even medical – bosses may consider that other professionals

can do most of what medics do, but for less money and with less hassle. Why recruit two medics if you could have a pharmacist, a clinical research associate and a compliance manager for the same price? Would anyone be able to tell the difference? Would the business suffer?

Well, would it? The industry is obliged to hire pharmaceutical physicians in certain areas. The mandatory requirement for physician oversight of clinical studies both as investigators and within sponsor companies is clear. Phase I units with 'patients' in beds must have physician investigators – the clinical pharmacology unit needs doctors to monitor, dose and attend to individual patient safety. In later phase studies the clinical investigator at the study site may have responsibility for managing individual patients, but reviewing and maintaining their safety within the context of the study population as a whole will be the remit of the company's medical monitor. In pharmacovigilance, the safety physician's broad medical knowledge and judgement is critically important with access to it written into legislation for the QPPV role. And in the regulatory environment medical experts are still required to sign-off reports and to review them at regulatory agencies.

So in many parts of the business companies do need pharmaceutical physicians. But are they simply hiring us to meet regulatory requirements? Take UK medical affairs where the regulatory requirement for physician sign-off on marketing materials has reduced in recent years. Pharmacists can do many of the tasks of the physician. There is an increasing emphasis on corporate compliance as the lever for achieving ethical promotion. Some UK company medical departments are being led by a non-medically qualified 'head of medical'. Medical leadership at the commercial cutting edge appears to be no longer the sole domain of the pharmaceutical physician. Does that mean that companies don't see the value in having physicians with responsibility for the medical aspects of pharmaceutical sales and marketing – or that medics don't provide the ethical leadership that puts patients' wellbeing first?

Is what's happening in medical affairs an indicator of what happens when the regulatory requirement for companies to have pharmaceutical physicians is reduced? Do companies see the value of trained pharmaceutical physicians and what we can offer to the business?

I don't know the answers. I'm also not sure how I would answer the CEOs questions that I started this article with. I do know that as physicians we bring special knowledge and skills that help companies to put patients first. I believe that we should be leaders in the medical governance required to build the trust our customers should have in our companies, our research and our products. That trust is badly needed. Global polls show that the pharmaceutical industry falls towards the bottom of 'trust in industry' league tables.[1] We are less trusted than the energy sector or brewing and spirits. We rank just above media, banks and financial services. A trained pharmaceutical physician has a perspective that few other non-medical professionals in our industry can match. I wonder if we shouldn't be doing more to demonstrate the value of that perspective to the businesses we work in.

1. Global Trust Report http://www.edelman.com/insights/intellectual-property/trust-2013/ [accessed 08 July 2013]

Are we still failing our children? The case for research into pregnancy

Dr Lode Dewulf FFPM
Chief Patient Affairs Officer, UCB Pharma

The Guiding Principles for Pharmaceutical Physicians[1] (FPM) serve as key reference for the duties of pharmaceutical physicians, and they explicitly mention the "need for clinical research in special and vulnerable patient groups who fall outside the accepted inclusion criteria approved for marketed products". The document provides the example of the very elderly and the young.

In 2007, European legislation came into force making such research mandatory in paediatric populations[2]. But what about the pregnancy that preceded each of these children? There still seems to be no expectation (legal, ethical or other) or framework for research in this special and vulnerable population, though it affects so many of us.

Up to 25% of women enter pregnancy with a chronic condition that requires medication[3]. Up to 90% of pregnant women use a medicine at least once during their pregnancy[4]. A pregnant woman is estimated to take between 3 and 8 different drugs during her pregnancy[5], which is a similar amount to that which non-pregnant women do. Yet, very little is known about the effects of many medications on pregnancy; even less is known about the effects on fertility and fecundity (in both men and women). As a result, most medicines are not recommended for use in (and around) pregnancy.

Prospective parents and pregnant women want and deserve better advice when it comes to medicine use, especially how this may affect their pregnancy as well as the time before (e.g. fertility) and after (e.g. breastfeeding). In the absence of data, most drug information leaflets, physicians and websites currently provide either no information or information that is often inconsistent and generally not considered helpful. The general lack of proper and systematically coordinated care systems (e.g. communication between the obstetrician and disease specialist) adds to this complexity. As a result, many future parents and pregnant women undertake the journey to parenthood with a lot of anxiety and feeling abandoned by the medical community at this most precious and vulnerable time in their lives.

A key reason for the absence of data in this field is the difficulty to engage in classical clinical research. For many years, our knowledge of drugs was based almost exclusively on prospective randomized clinical trials (PRCT). Based on the principle of avoiding potential harm to both the expectant mother and foetus remains a standard exclusion criterion – this remains probably the most frequent and least challenged – in clinical studies. Pregnancy is also a standard drop-out criterion, forcing women out of a study after they met all the other entry criteria, and listing the pregnancy as an adverse event. The result of this avoidance approach is that decades of PRCT have not addressed the pregnancy-related knowledge gap, and may be unlikely to do so in the foreseeable future.

But, while PRCT remain the golden standard for evidence of efficacy, we have in recent years learned about the complementary value of proactive real-life observational research when it comes to clinical utility, safety and value. Proactivity is the key, however, because passive reporting of pregnancies over decades has so far not fundamentally enhanced our knowledge either. One reason for this is that spontaneously reported pregnancies in the post-launch setting are seen and handled like adverse events, which are subject to great underreporting. Adverse event forms are also not specific to pregnancy, which means that crucial data (e.g. date of last menstruation, timing and duration of suspected exposure) limit the value of an individual case report. Of course, such spontaneous reports, like isolated case reports in the literature, do have a signal-detection value, but without any good reference data in non-exposed women they give rise to very little meaningful conclusions. Abnormality requires a defined normality first.

Observational research into medicine use in pregnancy has many challenges. The number one challenge is to collect enough cases (both exposed and not-exposed) so as to overcome important inherent methodological issues such as the unclear, unconfirmed or missing data, the lack of standardization, comorbidity and co-medication. With the increasing availability and performance of digital health tools (apps, body sensors, even

blog analysis) we are entering an era where for the first time we should be able to capture enough of the data we need. This will, however, require good collaboration between all the stakeholders involved, first and foremost the expectant parents. Many pregnant women are already today self-tracking their pregnancy via one of the thousands of existing Health Apps.

But capturing more data will not be enough. Indeed, many registries are already running, and some have been for decades. Yet, few of these registries have led to significant contributions to the real public health objective: providing more helpful advice to the individual citizen who is pregnant or planning a pregnancy. A key reason is that most registries use different standards and methods, and that in consequence they do not "talk" to each other. Data pooling is further hampered by the academic need to publish. Another reason is that highly technical publications in specialized medical journals do not result in better public understanding or in a change in behavior in clinical practice.

A fundamental change in behavior, in culture is what we will need to break the pregnancy taboo. We need to move from avoiding pregnancy to embracing it. Culture change starts with behavior change. This is where each of us has a role to play. How long can pharmaceutical physicians, be it in industry, regulatory agencies or academia, continue to systematically avoid pregnancy? And with up to 50% of (US) pregnancies being unintended, how can we not consider research into the use of medicines in pregnancy an absolute requirement when launching any drug potentially used by women of childbearing age?

Pharmaceutical physicians and their professional associations have an important societal responsibility to help improve the care for prospective parents and pregnant women. It is time to step up to the plate.

1. Faculty of Pharmaceutical Medicine. Guiding principles for Pharmaceutical Physicians, 2010
2. Regulation (EC) No. 1901/2006 of the European Parliament and of the Council
3. Karen Rosene-Montella, Sandra Lowe and Catherine Nelson-Piercy: The growing importance of medical problems in pregnancy: Obstet Med 2010 3: 1
4. Mitchell AA, Gilboa SM, Werler MM, Kelley KE, Louik C, Hernandez-Diaz S. Medication use during pregnancy, with particular focus on prescription drugs: 1976–2008. Am J Obstet Gynecol. 2011;204
5. Drugs, during pregnancy and lactation/ edited by Christof Schaefer, Paul W.J. Peters, Richard K. Miller. (2007)

The future of monitoring in clinical research

Dr Eva Ansmann
GCP-QA Consultancy and Early Intervention Management for Sponsor/CRO-Cooperation

This article is a summary of the following publication: The Future of Monitoring in clinical research – a holistic approach linking risk-based monitoring with quality management principles. Published in German Medical Science 2013, Vol.11, ISSN 1612-3174

Many of those involved in clinical research, from industry and academia to the regulatory authorities, are keen to demonstrate better monitoring efficiency by reducing monitoring visits, monitoring time on site, monitoring costs and so on. Many argue with the use of risk-based monitoring principles. The fact that the use of risk-based monitoring is only adequate if all mandatory prerequisites at site and for the monitor and the sponsor are fulfilled is often forgotten. Based on the relevant chapter in ICH-GCP, this article takes a holistic approach by identifying and describing the requirements for future monitoring and the use of risk-based monitoring. As the authors are operational managers as well as QA-experts, both aspects are represented to come up with efficient and qualitative ways of future monitoring according to ICH-GCP.

Because clinical development costs for drugs are increasing steadily over the years [1], attempts have been made on all sides to lower these costs through more efficient study-management. Since monitoring accounts for a substantial proportion of the total study costs, many efforts are targeted to show how savings in

monitoring costs can be achieved through the technically assisted pre-analysis of electronic Case Record Forms (eCRF) and a risk-based Source Data Verification (SDV).

Many implemented methods of targeted or triggered monitoring are useful, since they provide the monitor with valuable information about the quality standard of the trial site in preparation for the monitoring visit. However, the problem with these proposals is that they almost always focus just on SDV and a reduction in the number of visits: "*...it may be possible to limit on-site monitoring to those sites where central monitoring suggests that there might be a problem*" [2], whereas many other tasks that have to be undertaken by the monitor, according to the ICH-GCP Guidelines, are neglected. In addition, SDV often focuses exclusively on correcting mistakes that have already been made, whereas the primary goal of monitoring should be preventing mistakes.

The Draft Guidance published by the FDA in August 2011 also focused very strongly on a risk-based monitoring approach [3]. At the same time, FDA points out that the correspondingly qualified monitor must ensure that the preconditions are satisfied. This conflicts with the experience accumulated from audits and inspections, during which weak points are seen in almost all areas of monitoring.

The original publication has listed the complete ***tasks of the monitor according to ICH GCP 5.18.4*** to demonstrate the holistic approach.

Out of the whole range of monitor's tasks, two examples are illustrated here:

Training/coaching

The monitor should prepare and train the centre staff right at the beginning of the study. The study protocol should be discussed and special attention should be directed to critical activities and processes that the monitor knows from his or her experience. The monitor should also review, together with the study team, "internal" site processes (e.g. cooperation with different departments, availability of staff) to ensure proper conduct of the trial at the site and its integration into daily routine. In addition, the monitor should support the site in analysing the impact of the information and implementing appropriate measures, and should share best practices as well as bad experiences from other study sites to help the team to improve their performance/skills and to avoid mistakes.

During the ongoing trial the monitor must ensure that new or updated information is given to the trial site in a timely manner, as well as proper training before implementation of new documents. The main objectives of the monitoring strategy around training and coaching should be risk reduction and the prevention of protocol violations or other major deficiencies.

Source Data Verification

It is not sufficient to check a certain percentage of data for one patient during SDV, but to have an overall picture of the respective patient. The monitor therefore needs to scan the whole medical file, even if the SDV plan specifies just 20%. While much has been described and said about the extent of SDV, the crucial factor is the active identification of inconsistencies and not mere comparison of the CRF against the source data. The monitor must consider the data for a patient as a whole in order to ensure that the presentation of the patient in the CRF is correct. This overall picture can, among others, prevent adverse events from being overlooked.

The purpose of monitoring as specified in ICH-GCP clearly highlights the need to ensure the three following aspects: the safety and well-being of the patient, the quality of the data and compliance with regulatory requirements. However, the discussion in recent years about the further development of monitoring [4, 5, 6] and the changes noticed by ourselves, reveal a disproportionate degree of concentration on the retrospective checking of data that has already been entered (Source Data Verification). This strong focus on SDV, which can take up to 75% of the time available for monitoring, means that too little attention is paid to the processes at the centre, despite the growing volume of documentation and administration. There is a risk that the options offered by risk-based monitoring are used exclusively for reducing SDV - and thus the time spent by the monitor on site. But it is frequently forgotten that **all** of the preconditions for risk-based monitoring must be fulfilled both by the centre and the sponsor. Examples include risk assessments at study level in respect of patient safety and data validity, which also determine the extent of monitoring, but also the careful centre selection taking into account study experience and the technical and personnel-specific preconditions.

As requested in the ICH GCP Guidelines, the monitor has a key function in the study. In order to fulfil this function, he or she must acquire the necessary skills to act as a centre coach that communicates all the study aspects to the centre and helps with their implementation, rather than performing pure checking activities.

One of the simplest, but often forgotten, and most effective methods for saving costs is to not open up centres that can be expected to show serious quality deficiencies or fail to recruit patients. However, what can be achieved at any rate through the application of the procedures outlined are the early detection of such shortcomings and the immediate closure of these centres in order to avoid further expenses.

This publication illustrates embracing ways for major improvements of quality in clinical trials. The key is prevention of non-compliance and this requires well-trained and experienced CRAs. The importance of their work needs to be acknowledged as well as their expertise valued. Fulfilling the ICH-GCP criteria for a proper monitoring requires the CRA to be provided with decision-making competence for their tasks.

The authors, some of them QA-personnel for many years, acknowledge the progress made in managing clinical trials and monitoring clinical trial sites over the past 15 to 20 years. However the very same difficulties, problems, and non-compliances are repeated. Clinical teams and QA are too often too isolated to allow the QA experience to be fully integrated into planning and setting up new trials. Bridging these barriers would avoid problems in the first place. Some recent changes to a more proactive quality management approach by close and early cooperation of clinical teams with QA staff can be seen within the pharmaceutical industries. Unfortunately this seems not yet to be the case to the same extent for CROs.

As a perfect “one sentence summary” the authors agree with William Edwards Deming: "*Eliminate the need for massive inspection by building quality into the product in the first place”* [7].

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5. Tantsyura V; Grimes I; Mitchel J; Fendt K; Sirichenka S; Waters J; Crowe J; Tardiff B; Risk-based Source Data Verification Approaches: Pros and Cons; Drug Information Journal Vol 44; pp. 745-756, 2010
6. Korieth K; The High Cost and Questionable Impact of 100 % SDV; The CenterWatch Monthly Vol 18 (2); 2011
7. Deming, W.E. Quality, Productivity and Competitive Position, Massachusetts Institute of Technology, Center for Advanced Engineering Study, Cambridge, MA, 021139,1982