

# Writing protocols: Collaboration and compromise or conflict and confusion? ICR-EMWA Joint Symposium<sup>1</sup>

by Alex Dedman and Andrew Smith

The challenges of developing clinical trial protocols were the topic of the second annual symposium jointly hosted by the European Medical Writers' Association (EMWA) and The Institute of Clinical Research (ICR) on 24 February 2009. Around 60 delegates discussed the difficulties associated with developing protocols that both meet sponsors' scientific and regulatory requirements, and facilitate the practical conduct of the study.

## Medical writing for protocols: Details and diplomacy

*Debbie Reynolds, Senior Medical Writer, Dianthus Medical Ltd*

Wendy Kingdom, a long-standing member of ICR and the then Treasurer of EMWA, opened the meeting and handed over to Debbie Reynolds, who gave an overview of developing a study protocol.

Debbie noted that the protocol development team includes:

- a medical writer,
- a statistician,
- an investigator (internal and/or external),
- the sponsor, and
- a monitor to advise on practicality.

She highlighted the medical writer's role in integrating inputs, making the complex document easy to understand and implement, and resolving disagreements between contributors. Debbie discussed problems that commonly arise in agreeing a detailed synopsis, coordinating the team, resolving disagreements, coordinating comments, and version control. She gave examples of pitfalls, such as team members missing deadlines, changing their minds, or confusing different versions. To improve the process, she advised using a specialist medical writer, being strict on version control and on deadlines, and then trusting to the writer's skills.

In closing, Debbie mentioned the CDISC protocol standard that facilitates the development of machine-readable protocols. This assists the generation of case report forms (CRFs) and study databases. Each data field is used only once, so any change can flow through every occurrence in the document.

## A pharmaceutical company view of protocols

*Sandra Waechter, Senior Project Manager, Janssen-Cilag*

Sandra Waechter gave the pharma view, outlining the overall development process from global and regional product

strategies, through research concepts and development plans, to individual studies. The development plan, with input from various stakeholders (e.g. medical, regulatory, health economics), is used to decide what studies are necessary. A research concept is sometimes developed, without a specialist medical writer, but always includes, for example, the primary and secondary objectives, and scientific rationale. The review of the concept within the company may be complex because of the range of stakeholders and the need for alignment with global strategy.

Subsequent protocol development always involves medical writers. A physician is responsible for the study, for discussing features with key stakeholders, and for preparing the synopsis for the medical writer using a standard template. Sections are assigned to other specialists. Appropriate pharmacovigilance requirements should be met, and consistent terminology and structure used. The medical writer distributes the draft protocol for review (including to local operations teams), specifying timelines for response. Comments are consolidated and reviewed, with the medical writer arbitrating changes if necessary. Sandra manages the development process, developing a budget, creating a realistic timetable, ensuring appropriate quality processes are followed, and driving execution to time and budget.

She expects medical writers to develop well-written protocols that clearly describe the research question and study objective. The introduction is vital, positioning the research question in the current context with appropriate citations. The protocol must contain enough detail to enable investigators to conduct the study. The medical writer should actively approach stakeholders to collect information, organise study-related materials to be included before submission, and ensure that the document complies with any relevant guidelines. Sandra considered that the whole process should take around 3 months.

## It's never too early to ask a statistician

*Adam Jacobs, Director, Dianthus Medical Ltd*

Adam Jacobs, who has a background in medical writing, but is also a statistician and sits on an ethics committee, emphasised that it's never too early to ask a statistician.

For ease of implementation, a protocol should be as simple as it can be and still achieve its objectives. Once objectives

<sup>1</sup> This report of the joint ICR-EMWA conference will also be published in the ICR members' journal, *Clinical Research Focus*

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are selected, they must be maintained, with anything else being omitted. Key stakeholders must be kept fully informed, so that problems can be identified early.

Adam discussed communication with statisticians (who may seem to speak another language). There is no substitute for face-to-face meetings, and statisticians are used to explaining again if you tell them what you haven't understood.

Adam described the statistician's role in specifying the objectives, trial design, analysis method, timing and choice of outcome methods, and sample size. Objectives should be agreed early, particularly in later phase studies, and must be in a form that can be tested statistically. Study design may be dictated by these objectives, but other elements need to be considered. Methods must avoid bias, though practical or ethical constraints may necessitate compromises.

Even in sample size, the many non-statistical inputs include consideration of a 'clinically relevant difference', which significantly affects the sample size and should be more widely discussed. Sample sizes may need to be significantly greater than anticipated by non-statisticians, which may raise budgetary issues.

Considering protocols from his perspective as an ethics committee statistician, Adam highlighted the importance of completing the application form correctly, and giving the committee the information it needs. In this case, the application form is the primary document, rather than the protocol, which may not be read.

On the subject of sample size, too large is unethical (but rare, because of cost), and too small is unethical because the study won't answer the question. The committee needs to decide whether the balance between the risks and benefits of the study is acceptable. This depends on the scientific validity of the study and thus an appropriate sample size.

### Putting the square peg into the round hole

*Sue Mackay, Research Nursing Team Manager, CDSS Ltd*

Sue Mackay leads a team of field-based study nurses, who use protocols on a practical level. The problem for her is trying to fit the square peg of a protocol into the round hole of practicality, and she regrets that practical issues are not properly considered earlier.

A well-written and consistent protocol facilitates implementation. She advocated feedback into protocol development on how patient selection and study procedures are done in the field. For example, timelines for study procedures and frequency of patient visits might not be feasible or acceptable for patients. Sue suggested that protocol developers should consider these aspects from the patient's viewpoint bearing in mind whether timings will fit easily with family and work commitments. Also, hospital departments might not be flexible enough to meet protocol timelines, given their primary role in general patient care.

Sue suggested that more communication is vital, although the route between nurses and medical writers is less clear. Similarly, involvement of other site staff (e.g. laboratory, radiography, physiotherapy) in protocol development would be beneficial.

A project manager in the audience, who sends draft protocols to investigators, was surprised to find that the drafts are not circulated to the site study team at that stage. Perhaps research nurses could help educate their investigators on consulting more widely at the draft stage.

### Panel discussion

Discussing the inclusion of summary lists and flowcharts in protocols, Sue Mackay agreed that they would be useful, though some sponsors prefer to avoid duplication. A delegate asked how site staff schedule visits and activities. This depends on the type of study but Sue tries to create a schedule whenever possible.

Adam Jacobs stressed the importance of allowing time to do the job properly: although writing the protocol may take as little as 3 days, 3 months would be more appropriate for discussion, reviewing and negotiation.

### Protocols: A monitor's wish list

*Laura Parkes, Clinical Trial Monitor, Merck-Serono*

Laura Parkes defined a good protocol from the viewpoint of a clinical trial monitor. She emphasised that the protocol is a 'monitor's bible', used extensively as a first point of reference. As Laura put it, "If it is written in the protocol, then it has to be done—this is a great help for a Monitor!". Laura explained how best to present the sections of the protocol of special interest to her. Clearly defined inclusion and exclusion criteria, for example, are paramount, because of the large numbers of related site queries that arise.

Laura emphasised that detailed information is the key to making her task easier, especially for feasibility studies, site training, blinding requirements, concomitant medication lists, and acceptable patient compliance levels. Detail is especially important in the study drug and safety monitoring sections, which are often used as stand-alone sections by pharmacists, investigators, and other protocol users. Laura commented on the need for user-friendly timetables and flowcharts, noting that monitors often have to generate task sheets and tick lists based on the protocol.

Despite the need for a huge volume of information, Laura favoured a concise protocol, with supplementary information (i.e. declaration of Helsinki, study questionnaires, and specific assessment schedules) in appendices. She mentioned the importance of protocol formatting and of strict version control, a common theme of the session. Finally, Laura presented the monitor's protocol wish list. In summary, from the monitor's viewpoint, protocol developers should consider all those who will use the protocol and

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write suitably specific requirements in a clear, succinct, and precise format.

Laura's presentation prompted discussions on the need to balance the level of detail in a protocol against the increased likelihood of amendments, and on the need for frequent communication to ensure that the protocol is helpful to all users.

**Recruiting patients: Trials and tribulations**

*Abhijit Chaudhuri, Consultant Neurologist,  
Queens Hospital, London*

Abhijit Chaudhuri discussed clinical trial design and patient recruitment. He explained that the most important issues for investigators and patients considering participating in a trial are whether the trial is asking a relevant and scientifically sound question, and the risk to benefit ratio of taking part.

Abhijit pointed out that 90% of clinical trials fail to enrol on time, and more than half are delayed by at least 6 months, suggesting that potential delay should be factored into timelines. The protocol, one of the 'seven Ps' (product, protocol, place, people, participants, price, and promotion) essential for a successful trial, must be flexible and have well-designed inclusion and exclusion criteria. Abhijit illustrated this point with 'Lasagna's Law', which demonstrates that a pool of eligible patients can shrink by 70% after applying stringent inclusion and exclusion criteria, and taking account of patient drop-out rates and lack of trial promotion. Abhijit, like other speakers, considered communication to be the key to a successful trial, especially communication with the patient.

Abhijit predicted that the ever-changing economic landscape would influence future clinical research priorities, especially in the UK and the USA. He wondered whether the exciting prospects of pharmacogenomics and personalised medicine might shape a new era in which 'patient minorities' are recruited into smaller clinical trials.

Abhijit's talk led to a discussion of patient information leaflets, which many delegates agreed have become cumbersome. The consensus view was that patient information should be presented in a clear and simple format.

**Top team tactics**

*Dr Martin Robinson, Principal Training Consultant,  
Institute of Clinical Research*

The final talk of the day was a light-hearted and informative presentation about team dynamics from Martin Robinson, who illustrated his points with references to sporting teams, contrasting, for example, the successful Manchester United football club with the not-so-successful Newcastle United. Martin showed that flexibility, mutual dependence and reliability, and a common drive to succeed are essential when working together. Drawing on his examples, he showed that the common traits of successful teams

include good training, strong lines of communication, stable and continuous leadership, a clear sense of collective purpose, and good resources.

Martin discussed the four different team development stages. The first stage represents team creation, when individuals with specific skills are first brought together. Next comes a developmental phase, when the team becomes 'experimental'. During this, the most difficult stage, roles and responsibilities are uncertain and power struggles may develop. In a third 'consolidation' phase the team finally starts to work well as a single unit. Eventually, in the fourth and final stage, the team develops into a mature and productive working unit. Martin emphasised the need for definite and flexible leadership throughout.

To conclude Martin listed twelve 'top team tips', the first of which was great leadership. Discussion of the role of medical writers in a multidisciplinary clinical research team followed. Delegates pointed out that many medical writers do not feel they have a leadership role, although their coordination skills are often called upon to drive the project forward, sometimes within the difficult paradigm of working for a client who is technically 'in charge'. Martin clarified that leadership is behavioural; a 'team leader' can be someone who acts to coordinate members and facilitate team success irrespective of whether they have been assigned a formal leadership role.

**Concluding thoughts**

This panel of speakers, with diverse perspectives on the development and use of clinical study protocols, gave an interesting and informed overview of the challenges of protocol development.

Potential sources of conflict during protocol development were highlighted. For example, having an accurate and finalised protocol synopsis at the start of the project seemed to be a higher priority for medical writers than for project managers. It was agreed that more feedback was needed from protocol end-users and that perhaps clinical research nurses and clinical trial monitors should be more actively involved in protocol development. Concern was, however, expressed that having too many reviewers can lead to confusing differences and difficult management issues.

Alongside the small differences, were many areas of consensus, including the need for clear version control, for inclusion of simple checklists and user-friendly schematics in the protocol, and for clear and more concise patient information leaflets. Above all, the value of broad and consistent communication throughout the protocol development process was repeatedly emphasised.

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