



Effective scheduling of Clinical Study Reports

by Sam Hamilton

The Clinical Study Report (CSR) is a highly complex, multi-component document which slots into a wider clinical-regulatory documentary process jigsaw. It is this overall process that drives a drug's clinical development.

For those of us working in a clinical-regulatory environment, there is a tacit understanding that even days shaved off a deliverable timeline can make 'all the difference'; but at whose expense? As a CSR author burning the candle at both ends, you probably realise you are not alone. Does the empathy of medical writers the world over alleviate your feelings of stress? Not even marginally? Then let us consider the wider picture.

For every 10,000 chemical entities screened, of the 1,000 or so with biological activity, only 10 will ever be administered to humans, and only one will reach the marketplace. Then consider that the patent life on that single drug that you are writing about started on the day the molecule was registered. By the time 'your' drug is launched, only 5 or 10 years of its patent life may remain [1]—a relatively short period during which the marketing authorisation applicant must claw back some return on their huge investment. So all things considered, the applicant's drive to minimise each individual timeline, including that of your CSR, along the way to drug launch, should now be a little easier to comprehend, if not fully accept.

Meanwhile, back in your world, that still leaves the problem of how to meet that exacting timeline whilst remaining calm, professional, and in control at all times. The answer has to lie in effective and proactive scheduling. This is a subject that I feel strongly enough about to have delivered my first advanced EMWA Professional Development Programme (EPDP) workshop in Barcelona (May 2008) entitled 'Scheduling and proposal writing: The clinical study protocol and report'. I shared my scheduling experiences in the workshop and enjoyed hearing first-hand from participants that it seems that we all have common issues and similar gripes.

The results of the pre-workshop assignment are worth sharing. Participants were asked to collect information based on their personal experience, to ascertain the timelines to

which other functional groups (data management and statistics) and medical writers are currently expected to work to when cleaning, analysing and reporting study data. I asked those working for a Clinical Research Organisation (CRO) or for a pharmaceutical company to determine typical average durations (working days, not ranges) in their company for the tasks listed below for a moderate complexity Phase 3 study in 200–400 subjects. Freelancers were asked to draw on their experience of past projects to make an estimate of average durations. For the purposes of the exercise, the moderate complexity CSR was defined as having no more than 8 secondary efficacy variables; statistical analysis rather than simple summarisations of the efficacy data, and approximately 24 summary tables (including disposition, demography, efficacy and safety) in the statistical output. The tasks for which average durations were required were:

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- Last subject data in-house to database lock (DBL)
- DBL to draft tables, figures and listings (TFLs)
- Draft TFLs to final TFLs
- Draft report writing from final TFLs to first draft CSR (only medical writing hours)
- First draft CSR to final CSR, including client review steps, with the usual number of review cycles
- Quality assurance (QA) on the final integrated CSR

Nine of the participants, with representation across the CRO, pharmaceutical and freelance sectors, completed and returned the assignment. The results are presented in Table 1:

Table 1 Results of the Barcelona 2008 pre-workshop assignment on CSR scheduling

Task	N	Mean duration (working days)	
		Mean	Range
Last subject data in-house to DBL	8	19.3	10–30
DBL to draft TFLs	9	16.0	5–38
Draft TFLs to final TFLs	9	9.5	5–14
Draft report writing from final TFLs to first draft CSR	9	13.9	10–25
First draft CSR to final CSR, including client review	9	23.5	6–100
Usual number of client review cycles	9	2.2	2–3
QA on final integrated CSR	9	3.6	1–10

DBL, database lock; TFLs, tables, figures and listings; CSR, clinical study report; QA, quality assurance.

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Most participants gave the proviso that these ‘ideal’ timelines were not always adhered to. The take-home message is that wide variability of durations for analysis and reporting tasks is inherent within the industry. It will be interesting to see figures collected from future workshops, not to mention cumulative figures across successive workshops. I am sure that wide variability will remain apparent.

This real state of affairs underpins the fact that as ‘mini’ project managers for CSRs, we can control the timelines we are expected to work to, with careful planning and scheduling, simply because there is no industry standard. The starting point of this ‘control’ is the proposal you prepare for the client for the preparation of their protocol, or report.

Like many of my colleagues, over the years I have encountered enough challenging scheduling scenarios, inadequate writing resources, poor or even no planning, and creeping scope on projects to help crystallise my thoughts, and indeed actions on this subject.

I apply three self-determined and simple guidelines when preparing a client proposal for a CSR. These are largely based on my time served as a salaried employee in CROs, where medical writers can be expected to write to timelines originally set some time ahead of reporting, often by business development associates or by generic proposal writers with responsibility across all functional areas. Medical writers are aware that individual project scope can significantly affect standard algorithms for calculating CSR timelines, but business-orientated functions may not fully appreciate this. One solution may lie in educating those who agree on reporting timelines. If the end result is involvement of medical writers earlier on in overall project scheduling, then the educative process must be worthwhile. For writers working directly in pharmaceutical companies, where there is room for improvement in internal processes, volunteering for process development committees may be the first step. Following my more recent foray into freelancing, I maintain that the freelance contingent has a degree of individual control perhaps not enjoyed by others: a well-researched proposal, I have found, often wins the day.

This brings me to my first guideline:

1. The scoping information apparent to me is not always apparent to others, so I must share it.

With this in mind, I determine the scope of the project and share it, along with the rationale behind my conclusion, with my prospective client. Prerequisites for scoping include the clinical study protocol (CSP) synopsis and any CSP amendments. The likely complexity of the CSR can be gauged from these documents. Although a strict set of criteria cannot be defined, a rough guide, modifiable as appropriate to an individual project, is as follows:

- Low complexity CSR—few subjects; possibly an early phase (Phase 1/2) study; simpler indication; up to six secondary efficacy variables; few unique TFLs; no complex statistical analysis.

- Medium complexity CSR—more subjects; possibly a Phase 2b/3 study; more complex indication; six to twelve secondary efficacy variables; some complex statistical analysis.
- High complexity CSR—larger numbers of subjects; Phase 3/4 study; complex indication (hence more ‘interesting’ laboratory test results, adverse events and narratives likely); twelve or more secondary efficacy variables; multiple unique TFLs; much complex statistical analysis.

Once project complexity is determined, a timeline and the necessary hours, based on project scope, can be proposed.

The second guideline is:

2. The staging approach for CSR components is not always apparent to others, so I must share it.

I explain that the CSR will be broken into components that will be authored in a staged manner. Components include the mock/shell/prototype CSR; the draft CSR; the clinical narratives; the appendices and the final CSR. I create a timeline for each component and list the prerequisites which drive individual component development.

The third guideline is:

3. Make all assumptions clear at the outset.

I clarify my expectations of the client and what my client can expect of me in a list of assumptions. I divide these into general and project-specific assumptions. If an assumption is not met during the course of the project, then the ensuing task may be outside the scope of the agreement. With clear assumptions at the outset, both parties are more likely to recognise changes in scope before they occur. Changes in scope, however, may often be accommodated with reasonable regard for existing timelines and budget.

With growing freelance experience, I have found that application of these three general guidelines facilitates the construction of robust proposal text, which ultimately keeps the CSR on track and within budget...and saves on candle wax!

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Reference:

- 1 Di Giovanna I, Hayes G (Eds). *Principals of Clinical Research*. Petersfield, UK and Philadelphia, USA: Wrightson Biomedical Publishing Ltd, 2001.