Biostatistics and medical writing: Synergy in preparing clinical trials documents

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Abstract
Biostatisticians and medical writers are among the key people who develop important documents for clinical trials. These documents include clinical study protocols, statistical analysis plans, statistical outputs, and clinical study reports. This article demonstrates how biostatisticians and medical writers should work together to streamline the document preparation process and ensure the quality of these documents.

Introduction
Biostatisticians (BSTs) and medical writers (MWs) play key roles in clinical trials (CTs) without visiting a study site or seeing a patient. In spite of their 'back office' positions, their roles are nevertheless crucial to study design, study conduct, and data analysis as they deal with a wide range of interrelated CT documents that include clinical study protocols (CSPs), statistical analysis plans (SAPs), statistical outputs, and clinical study reports (CSRs).

Generally, the MW's core competencies lie in producing words and text, whereas the BST's expertise is in numbers and analysis of data. Though divergent at first glance, the MW and BST skills sets actually have a powerful synergy that can have a major impact on the execution of a CT.

In this article, we describe how the BST and the MW should work together on a CT project. The scenario we describe comes from full-service projects in a global contract research organisation (CRO) environment but the principles are applicable to many CT project configurations.

Communication
At the start of the study, the BST and the MW should get to know each other's names, exchange contact details and time zones/work schedules, and discuss

timelines. In today's digital global office environment, having a strong professional affinity and an open line of communication is especially important.

Collaboration

The CT documents that the BST and the MW produce are all interrelated, as shown in Figure 1. All these documents revolve around common themes: the study design, the study objectives, and the corresponding study endpoints – interconnected by the so-called 'golden thread'.[1] Working together, the BST and the MW need to ensure that the objectives and endpoints are well-defined, congruent, and remain consistent throughout the different documents produced as the study proceeds.

Too often, the transfer of content from one document to the next inadvertently results in errors and loss of information (e.g. during copy and paste). However, this can also happen during the document revision process. To avoid this, any changes to the documents and the rationale behind these changes should be discussed within the team and clearly documented. Both the BST and the MW should be involved in the review of each document.

CSP

The protocol is the main starting point of a CT. In drafting the CSP, the BST and the MW should work together to ensure that the study objectives and endpoints are aligned. The BST should complete the statistical sections of the protocol, including the sample size calculations; the MW should review them. Any ambiguities should be clarified, and any changes that need to be implemented as the study proceeds should be documented.

SAP

Developed early on in the trial, the SAP is the responsibility of the BST. The MW is one of the downstream end users, i.e. during CSR development. Hence, the MW should be able to review and provide feedback on the SAP and the shell ('mock') statistical outputs before their finalisation to ensure consistency between the CSP and the SAP.

Statistical outputs

The BST delivers the statistical outputs in the form of tables, figures, and listings (TFLs), to be used as the primary data source for the CSR. The MW's involvement in TFL review, which started during SAP and mock TFL development, continues with the real statistical outputs. The MW should thoroughly review the draft TFLs and request any necessary revisions or additional TFLs as early as possible so that the BST has sufficient time to deliver them without impacting the CSR delivery date.

The end users of the TFLs will include medical reviewers, investigators, and regulators. It is very important that the MW reviews the outputs from the end user perspective; the individual tables and listings should, as a rule of thumb, be standalone documents. The BST should work with the statistical programmer and the MW to ensure that the TFLs meet the specifications defined in the CSP and in the SAP.

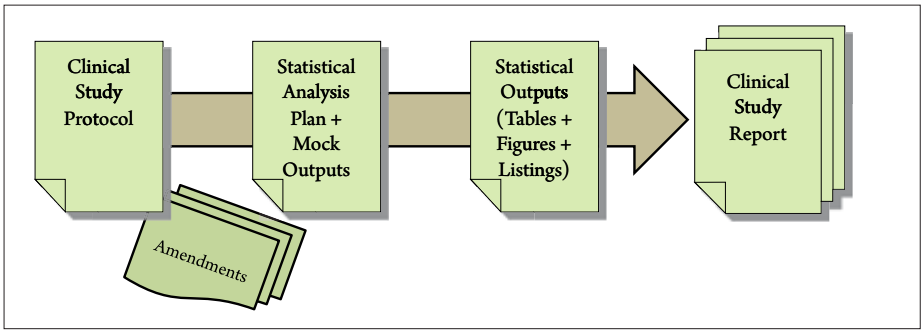


Figure 1. The different documents that the BST and the MW develop during a clinical trial.

CSR

The CSR is the responsibility of the MW. However, the BST should take an active role in providing input, not only on the statistical sections, but also on the results sections with respect to the endpoints and their interpretation. There was a time when a separate statistical analysis report was issued by the BST. The industry trend nowadays is to integrate the clinical and statistical text and analyses into a single document – the CSR as we know it today.[2,3] The BST accompanies the MW throughout the CSR review cycles, always ready to answer questions and clarify queries.

At the end of the study, the MW and the BST should produce an 'integrated' CSR that is actually a whole dossier containing all the CT documents they worked on during the study. And all throughout, the golden thread connecting the initial CSP to the final CSR and the other documents in between should remain unbroken.

Sharing information

The BST and the MW should keep each other in the loop. In full-service CRO CT projects, the BST is generally involved with the trial on an ongoing basis while the MW is often brought back in near database lock. As a result, it is possible that the BST will become aware of issues in trial conduct (e.g. delayed enrolment, early trial termination, protocol amendments, randomisation issues, and protocol deviations) which could impact the timeline or content of the CSR. It is vital that the BST passes this information to the MW as it becomes available to ensure that the MW becomes aware of these critical issues.

During review of the CSP and the CSR, the MW is responsible for addressing reviewers' comments. The MW needs to keep an eye on any changes that have an impact on the statistical methods and data analysis and should immediately flag these changes to the BST for re-validation.

Knowing each other's procedures and processes

The BST and the MW standard operating procedures (SOPs) should be aligned and not contradict one another. It is best for the

BST and MW teams to consult each other when developing and revising SOPs and processes. If this isn't done, the two teams should at least share with each other their relevant SOPs and process guidelines.

The BST and the MW should inform each other of their expectations in terms of templates and style guides, number of review cycles, expected review time, and level of review (e.g. text/content only or formatting/grammar, full document or only certain sections).

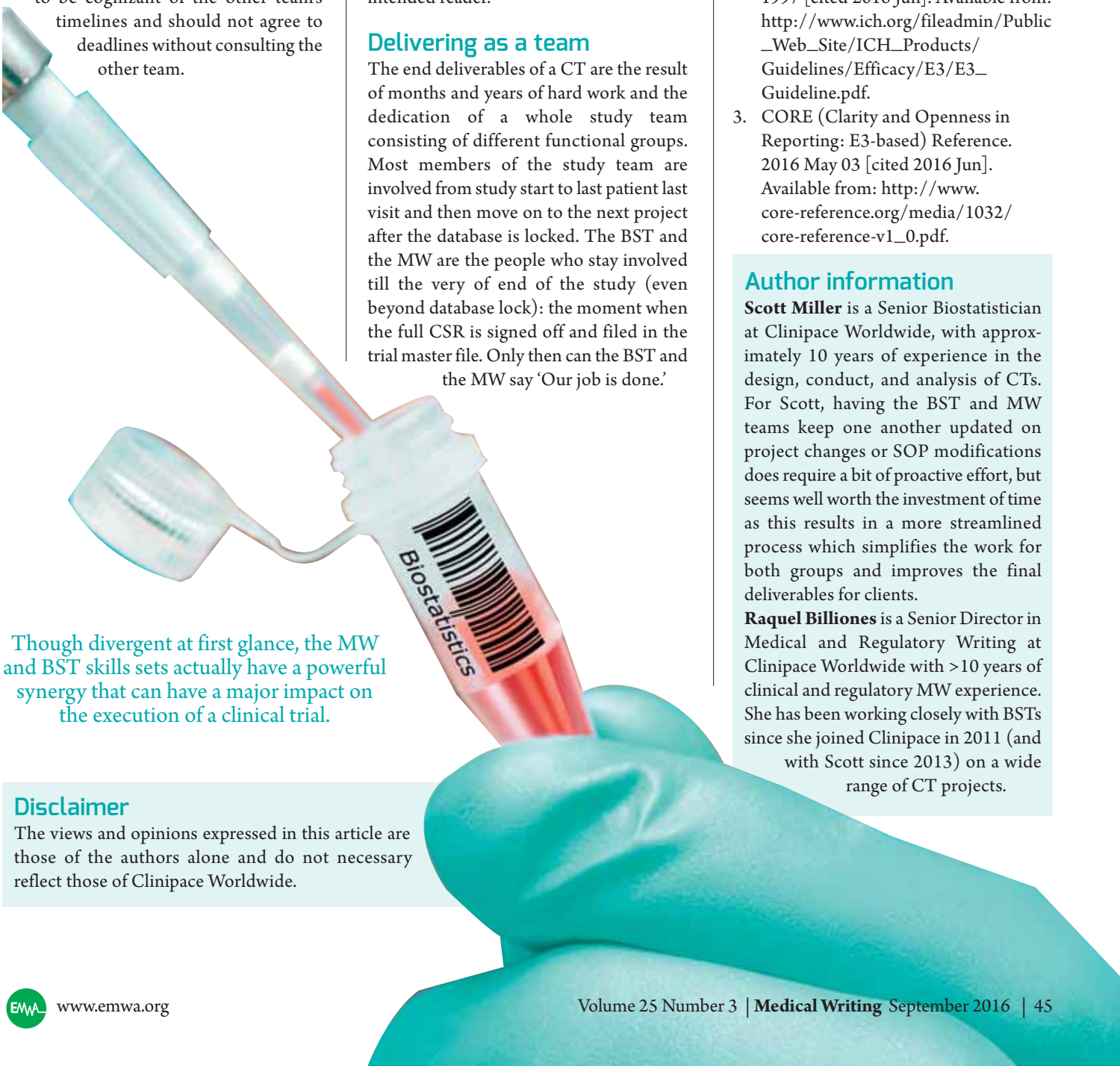
The deliverables of the BST and the MW are interdependent. Each team has to be cognizant of the other team's timelines and should not agree to deadlines without consulting the other team.

Leveraging each other's expertise

The MW should not hesitate to ask statistical questions, even if they seem basic or have been discussed before. For their part, the BST should consult the MW on textual, content, and formatting issues, as well as for guidance on regulatory requirements, if necessary. The MW should be cognizant of the needs of a document's target audience; the BST should take advantage of this expertise and collaborate with the MW to customise technical documents to the level of the intended reader.

Delivering as a team

The end deliverables of a CT are the result of months and years of hard work and the dedication of a whole study team consisting of different functional groups. Most members of the study team are involved from study start to last patient last visit and then move on to the next project after the database is locked. The BST and the MW are the people who stay involved till the very of end of the study (even beyond database lock): the moment when the full CSR is signed off and filed in the trial master file. Only then can the BST and the MW say 'Our job is done.'



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Disclaimer

The views and opinions expressed in this article are those of the authors alone and do not necessary reflect those of Clinipace Worldwide.

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Author information

Scott Miller is a Senior Biostatistician at Clinipace Worldwide, with approximately 10 years of experience in the design, conduct, and analysis of CTs. For Scott, having the BST and MW teams keep one another updated on project changes or SOP modifications does require a bit of proactive effort, but seems well worth the investment of time as this results in a more streamlined process which simplifies the work for both groups and improves the final deliverables for clients.

Raquel Billiones is a Senior Director in Medical and Regulatory Writing at Clinipace Worldwide with >10 years of clinical and regulatory MW experience. She has been working closely with BSTs since she joined Clinipace in 2011 (and with Scott since 2013) on a wide range of CT projects.