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Giving Data a Voice:
Partnering with Medical Writing for Best Reporting Practices

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ABSTRACT

An active partnership among programmers, statisticians, and medical writers throughout the reporting process promotes efficiency and quality, and assures that the product meets both scientific objectives and regulatory standards. Programmers and medical writers have essential, but significantly non-overlapping, areas of expertise, and when their functions are highly compartmentalized, they apply their skills at separate steps in the reporting procedure. Furthermore, some reporting deliverables, such as client-specific summaries of safety or other data, are produced entirely by programmers. Statisticians interact with both functional groups, and frequently can assist with communication; however, the role and timing of statistical input can vary widely among institutions and projects.

Problems may arise when programming and medical writing function too independently. For example, an analysis program design may be at odds with regulatory requirements or scientific objectives. A medical writer may be unaware of analytical issues and/or assumptions that affect data presentation, and may incorrectly interpret and describe results. A programmer responsible for a final deliverable may have insufficient word-processing familiarity to complete the task efficiently. And regardless of how well integrated the study team may be, some data issues do not emerge until summaries are produced; then discussion is required in order to plan additional programming.

We believe that programmers, statisticians, and medical writers should collaborate from the beginning through the end of a reporting project, to ensure that data are analyzed and presented with the least manipulation of output required in order to create an accurate, easy-to-interpret, and technically acceptable product.

INTRODUCTION

AUTHORS' PERSPECTIVE

- We are a principal medical writer and a senior statistical programmer/analyst.
- Our work in the pharmaceutical industry over the past >2 decades has taken place primarily, but not exclusively, within contract research organizations (CROs).
- The services provided and relationships among functional roles generally are similar within pharmaceutical companies and between pharmaceutical companies and CROs.
- Our term "client" in the following descriptions could mean an **internal** stakeholder / recipient of services, as well as a contracted business client or study sponsor.
- Similarly, because the majority of our work has entailed drug products, our examples typically reflect drug studies. The same concepts, however, apply to studies with medical devices.

CLINICAL DATA REPORTING: IS THERE REALLY A PROBLEM?

The integrity of biomedical research relies absolutely upon accurate reporting of clinical study results. However, disparate sources reveal that problems in the analysis, presentation, and interpretation of clinical data occur with unacceptable frequency.

ClinicalTrials.gov Database

In a recent interview (*Science*, July 2011), the director of the ClinicalTrials.gov database at the National Institutes of Health (NIH) discussed the rampant errors made by sponsors and investigators in presenting study designs,

objectives, and results on the ClinicalTrials.gov web site (which she referred to pointedly as the "sausage factory"). Among the issues she identified were errors in documenting the study plan, treatment arms, etc.; incomplete or inconsistent specification of outcome measures and analyses; incoherent depiction of subject disposition; and unexplained analysis populations among the results (the wandering denominator). She noted studies where the investigator could not explain the data and the statistician could not explain the trial design—indicative of significant fragmentation in the research team's grasp of the study.

Biomedical Research Literature

The current biomedical literature presents abundant concerns over the occurrence of errors in peer-reviewed publications, and especially, the retraction of published papers. A recent review of Medline retractions from 2005 to 2008 indicated a 10-fold increase in retractions since 1980; 0.02% (>800) of some 4 million published articles were retracted during the sampling period. Although publication fraud is an ongoing concern, the most frequent reason for retraction in this sample was honest error or non-replicable findings (40% of retractions), while less common were research misconduct (28%) and redundant publication (17%). Other reviews have noted an even higher contribution of error in published biomedical papers. Furthermore, retracted papers are not always clearly identified as such, and may continue to contribute misinformation long after they have been officially discredited.

Although the process of peer review is intended to safeguard against the publication of flawed study results in the first place, recent studies indicate that this process may be shockingly ineffective. An experimental investigation with test manuscripts and over 600 experienced peer reviewers found that on average, the reviewers failed to detect 2/3 of the most significant errors! This failure rate was consistent with previously reported studies, and surprisingly, did not improve significantly with repetition or even with formal training.

Regulatory Submissions

Defective reporting of clinical study results can impact the timeline for acceptance of regulatory submissions, and errors that increase time until approval of pharmaceutical products can be very costly. In financial terms, delay in bringing a product to market can inflate direct program costs and exert depressive effects on the value of a sponsor's stock. In human terms, delay in availability of vital treatments can have significant effects on the health and even survival of the patient population.

DIVISION OF LABOR IN THE REPORTING PROCESS

One apparent source of error in the reporting of clinical data is a breakdown in communication among personnel responsible for different functional components of the work. The production of a clinical study report (CSR) provides an example of a typical reporting process in pharmaceutical research. Programmers, statisticians, and medical writers are all members of the reporting team; their roles, summarized below, encompass the reporting process from data lock to report finalization:

- **Programmer:** Is responsible for data structure, analytical steps, and production methods; interacts with statistician to create programs that adhere to the statistical analysis plan (SAP) or other guidance; produces tables, figures, and listings (TFLs).
- **Statistician:** Is responsible for development of the SAP, review of the programmer's implementation of the planned algorithms, review of p-values, and consistency checking of results.
- **Medical writer:** Is responsible for initial data interpretation and scientific focus, document design, regulatory requirements; interacts with clinician in interpreting and summarizing results; may interact with statistician in reviewing results after data lock and analyses are completed.

Typically, programmers and medical writers perform their functions at different stages in the reporting process. Statisticians collaborate with both programmers and medical writers, but the role and timing of statistical input can vary widely among institutions and projects. **It is often the case that the statistician interacts with the programmer only before the data are analyzed, and with the medical writer only afterwards!**

TYPICAL (LINEAR) PATTERN FOR DATA FLOW

Data, in the form of tabular/figurative summaries and listings, typically flow unidirectionally, from the programmer to the medical writer, with guidance and review by the statistician at various steps in the process:

- The statistician directs the programmer in the design of data summaries and listings.
- The programmer writes and executes analysis programs to produce results output.

- The statistician reviews output and, as appropriate, provides interpretation of analysis results.
- The medical writer receives data summarizations and listings, creates text to summarize and interpret the results, incorporates text provided by other team members (e.g. statistician, clinician), and prepares in-text tables.

Although technically members of the same team, the programmer and writer may have little or no direct interaction in the course of a project!

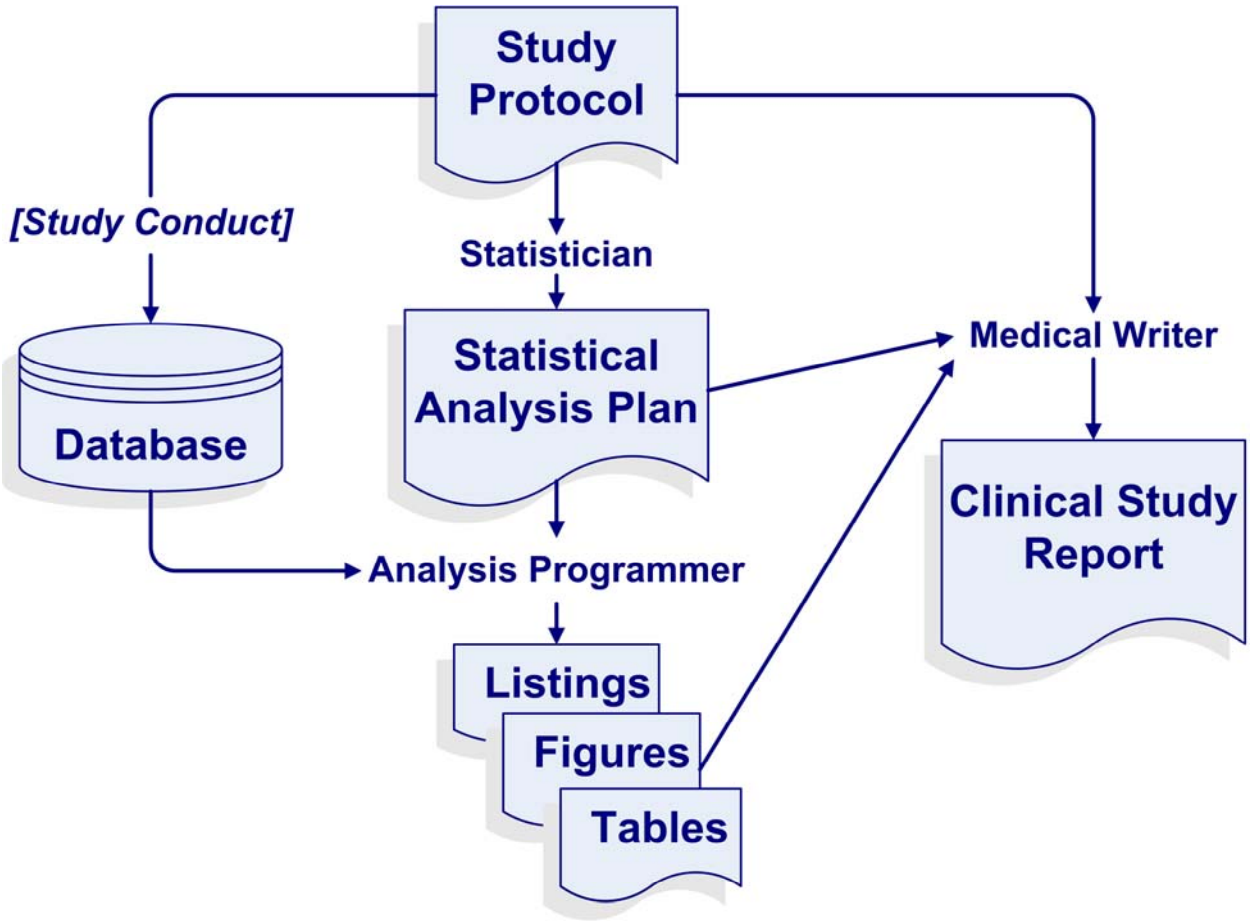

Figure 1. Traditional Data Flow for a Clinical Study Report

RESULTING PROBLEMS

When programming and medical writing function as compartmentalized entities, a number of problems may arise that adversely impact report accuracy, quality, and/or timelines. Among the issues we have encountered are the following examples:

- A well-designed, client-approved analysis program may nonetheless be at odds with regulatory requirements or scientific objectives of the study.
- A medical writer (or other contributor) may be unaware of analytical issues and/or assumptions that affect data presentation, and may incorrectly interpret and describe results.
- A programmer who is responsible for a deliverable may have insufficient word-processing familiarity to complete a contracted reporting task efficiently.
- Some data issues (or interesting patterns) do not emerge until summaries are finalized and reviewed externally; then additional programming must be planned and performed.

STRATEGIC SOLUTIONS AND A FEW CASE STUDIES

PLANNING AND COMMUNICATING ARE ESSENTIAL!

We believe that many reporting issues can be avoided by breaking down the linear flow of data, and by de-compartmentalizing the functions of programming and medical writing.

SOME USEFUL PROCEDURAL TOOLS

Orientation and Planning Sessions for the Entire Team

Orientation sessions—with the programmer, statistician, and medical writer, along with appropriate project management personnel—should be conducted to ensure that all members of the team are familiar with the study design, reporting objectives, analytical plans, and output specifications. Each team member should understand the "big picture" in order to effectively contribute to the reporting process.

Planning sessions—again, including the entire reporting team—should begin before data summarizations are programmed, to ensure that all are familiar with the reporting objectives, analytical plans, output specifications. All of the tasks required to complete the project should be identified, assigned to responsible parties, and organized into an appropriate timeline.

"Check Points"

Specific check points should be incorporated in the design of any reporting process, to identify and fix problems before the next step is undertaken. Appropriate check points will depend on the type of reporting project; some examples include:

- **While developing analysis data sets**, the programmer should work to identify data values or relationships, and definition/use of variables, that could cause problems much later, during the analysis phase.
- The medical writer should have a role in developing output specifications, including table and listing shells and figure mockups, **during development of an analysis plan**. This helps ensure that report output will meet regulatory standards and satisfy scientific objectives.
- The programmer should share plans for any tasks that require a "finishing" word-processing step with the medical writer, who can suggest efficiencies for carrying out these steps and provide appropriate training, if needed. This should be done **before the final analysis are run and output generated**.
- Critical results should be reviewed and discussed by team members and key stakeholders **before data summarizations are released** (e.g., the "bullet point" step). In particular, results should be reviewed for consistency among summarizations, as well as accuracy within them.

CASE STUDIES

These illustrations were gathered from our own and our colleagues' combined decades of experience in pharmaceutical reporting. In an effort to keep the focus on the process rather than the technical details, the selection of examples was based on their (extreme) simplicity, rather than their overall significance. The same considerations apply to situations of far greater complexity.

The Client Likes It, but FDA Doesn't

Problem: The client specified a data table structure for a clinical study report, and the programmer created the tables accordingly. Because the study in question entailed a large number of treatment groups, the tables were difficult to fit on even a landscape page. The final table mock-ups were produced in 7-point font with 1/4-inch page margins…

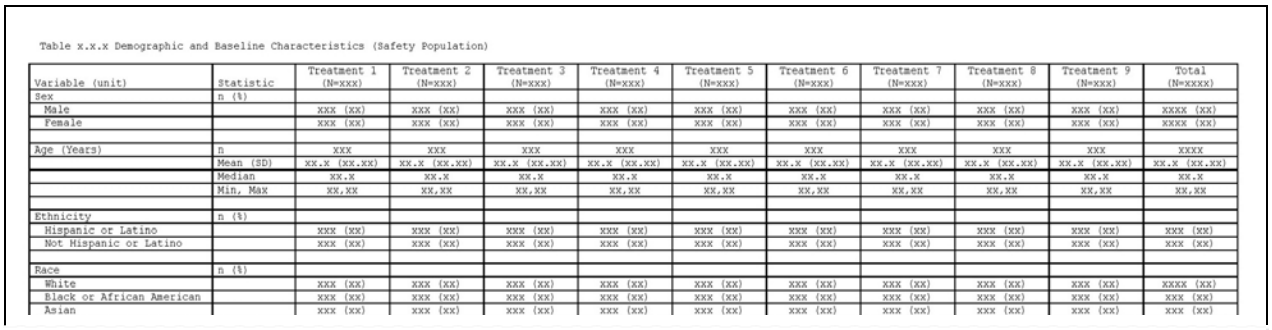

Table x.x.x Demographic and Baseline Characteristics (Safety Population)

Variable (unit)	Statistic	Treatment 1 (N=xxx)	Treatment 2 (N=xxx)	Treatment 3 (N=xxx)	Treatment 4 (N=xxx)	Treatment 5 (N=xxx)	Treatment 6 (N=xxx)	Treatment 7 (N=xxx)	Treatment 8 (N=xxx)	Treatment 9 (N=xxx)	Total (N=xxxx)
Sex	n (%)										
Male		xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxxx (xx)
Female		xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxxx (xx)
Age (Years)	n	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxxx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx,xx	xx,xx	xx,xx	xx,xx	xx,xx	xx,xx	xx,xx	xx,xx	xx,xx	xx,xx
Ethnicity	n (%)										
Hispanic or Latino		xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
Not Hispanic or Latino		xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
Race	n (%)										
White		xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxxx (xx)
Black or African American		xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
Asian		xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)

Figure 2. An Unfortunate Table Design

Both the U.S. Food and Drug Administration (FDA) and the International Council on Harmonisation (ICH) mandate a minimum font size of 9 points for data tables, and page margins of at least 3/8". The medical writer reviewed the mockups and recommended that the tables be re-configured to meet regulatory standards. This necessitated the modification of analysis programs.

Solution: When medical writers participate in the design of tables, figures, and listings, potential conflicts with regulatory requirements (or other issues) can be identified in advance, and costly corrections avoided. Furthermore, medical writers are skilled communicators, and can help interact with clients in order to explain issues and negotiate solutions.

To Be, or Not to Be? Zero Versus Missing Values

Problem: While building and checking analysis data sets, the programmer noticed that values entered for a particular variable, prescribed dietary protein, were usually either a positive number or missing, but a number of them were zero. The programmer raised the question to the team about whether these values of zero were plausible, i.e., 0 g protein was prescribed, or should they be set to missing, as it seemed likely that most sites simply would have left the field blank if nothing was prescribed. The medical writer agreed that prescribed dietary protein would be very unlikely to have a value of zero. The client was consulted, and agreed that zero values should be set to missing for this data field. The programmer then worked with the statistician to redefine the affected analysis variables.

If this issue had not been recognized and addressed, the summary statistics for this variable would have been depressed by inclusion of the zeroes, and the reported results would have been incorrect. In addition, this observation highlighted a data field in the case report form (CRF) that could benefit from more explicit instructions—a potential improvement for subsequent studies, or during a long-term study with periodic data review and updates.

Solution: Programmers can become very familiar with the data while developing analysis data sets, often at a much earlier stage than statisticians or medical writers. With early orientation to the study content and interaction within the team, the more likely it is that the programmer can recognize data values or relationships that could cause problems during the analysis phase. It makes sense for **all team members** to understand the "big picture"!

A Variable Variable, or: When Was Day 1?

Problem: Identifying and counting treatment-emergent adverse events:

- Tabular summarizations of adverse events (AEs) in Phase 1-3 clinical study reports typically display and enumerate only those events that were "treatment emergent", that is, AEs with a start time after study treatment has begun. (In contrast, all AEs reported by study subjects are presented in the listings).
- However, the definition of "treatment emergent" is not universal; depending on the study phase and other characteristics, the start point may range from the date of informed consent to the date of first exposure to study drug / device.
- Medical writers and clinicians often have to make close examinations of certain AEs and use this information in evaluating individual cases and cross-checking between listings and summarizations. Confusion can arise, with resulting waste of time and possible reporting errors, when appropriate documentation is lacking.

In the example below, changing the definition of Day 1 from the date of first drug dose to the date of informed consent results in a 2-fold difference in the number of treatment-emergent AEs! Clearly, significant problems may arise if the analysis documentation does not specify the definition of Day 1, or if the definition used in the analyses differs from that specified by the protocol.

Table 1. Identification of Treatment-Emergent Adverse Events: The Effect of Day 1

	Day 1 Definition	
	First Dose Date	**Informed Consent Date**
Subject 253, AE “dizziness”	not treatment emergent	treatment emergent
Subject 271, AE “sedation”	treatment emergent	treatment emergent
Subject 117, AE “headache”	not treatment emergent	treatment emergent
Subject 201, AE “nausea”	treatment emergent	treatment emergent
Subject 187, AE “orthostatic hypotension”	treatment emergent	treatment emergent
Subject 148, AE “headache”	not treatment emergent	treatment emergent
Subject 239, AE “back pain”	not treatment emergent	not treatment emergent
Subject 089, AE “dizziness”	treatment emergent	treatment emergent
Subject 166, AE “fatigue”	treatment emergent	treatment emergent
Total # treatment-emergent AEs:	**4**	**8**

Solution: Including medical writers in development / review of the analysis plan can help ensure that critical assumptions are documented and implemented consistently throughout an analysis. Greater understanding and clear documentation of the analytical methods, before results are produced, can result in fewer data questions subsequently.

The Not-so-easy Table Generator

Problem: A client-specified report was designed to present summary study data, in multiple tables of varying configuration, at quarterly intervals. Commercial table-generating software was used in an effort to expedite presentation of SAS® analysis results in a Microsoft Word document, to be produced and delivered entirely by the project programmer. However, it developed that extensive post-hoc formatting was required to meet client specifications for the resulting multi-page, multi-section document. The programmer was unfamiliar with the use of styles in Word, and also struggled to configure page layout, apply breaks, create an automated table of contents, and perform other word-processing functions. This effort required a substantial increase in hours above the original programming estimate, and threatened the delivery timeline.

Solution: Although not contracted as part of this project task, the medical writer was consulted in order to meet a deadline. The writer fixed the problem document, but also identified correct default settings and key word-processing tasks needed to prepare future versions more efficiently, and instructed the programmer accordingly.

CONCLUSION

AN ACTIVE PARTNERSHIP INCREASES QUALITY AND EFFICIENCY

Functional teamwork at all stages in the production of data reports increases efficiency of the procedure as well as quality of the product. Whether the goal is a final submission, a clinical study report (CSR), a periodic safety report, or an ad hoc client request, we recommend ongoing collaboration within the analysis team throughout the reporting process. In particular, programmers and medical writers should interact in planning as well as reviewing data analyses; and as team members who work with both, statisticians can expedite communication between these functional areas.

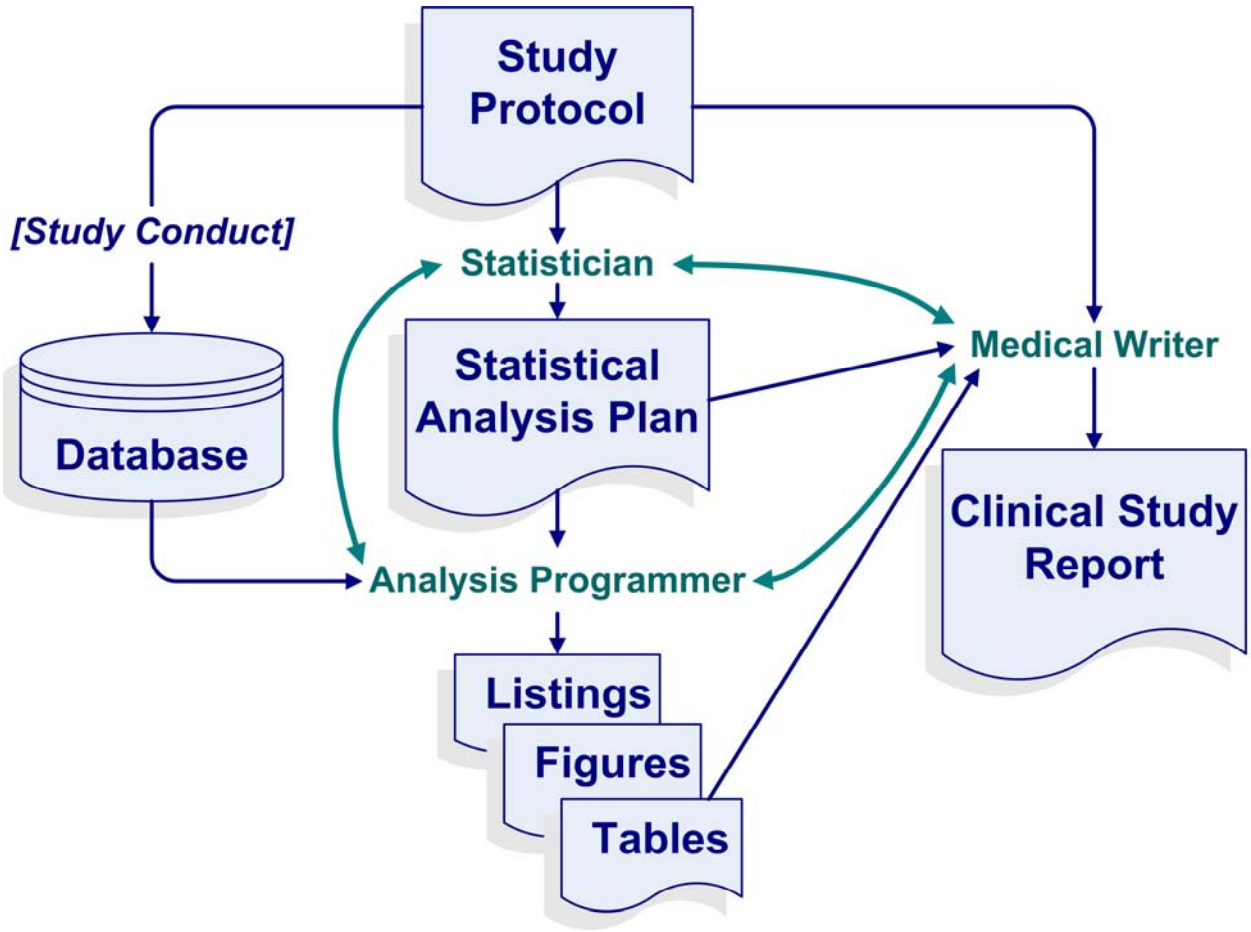

Figure 3. Team-Based Data Flow for a Clinical Study Report

GIVING DATA A VOICE

- The collection of good data represents a tremendous investment of time, labor, and expertise; furthermore, our clients are staking their reputations, as well as their resources, upon the quality of the results.
- It is the responsibility of a reporting team to sustain this investment by designing analyses and presenting results with accuracy, clarity, and efficiency; and by ensuring that the final product meets both scientific objectives and regulatory standards.
- This is the ultimate goal of our multidisciplinary approach: to do our best to **help the data tell their story!**

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