BY ROBIN ROBINSON

A PUBLICATION Planning UPDATE

TITLE VIII OF FDAAA, WHICH REQUIRES THE POSTING OF CLINICAL TRIAL DATA WITHIN ONE YEAR FROM LAST PATIENT LAST VISIT, PUTS THE SQUEEZE ON PUBLICATION PLANNERS TO GET STUDY RESULTS PUBLISHED IN A VERY TIGHT TIME FRAME.

The Title VIII section of the Food and Drug Administration Amendments Act (FDAAA) — pronounced fa-dah by industry insiders — does not address publication planning directly, but industry publication planners are still feeling its effect. The Title VIII section covers requirements concerning registration of clinical trials and posting clinical trial results on clinicaltrials.gov. The legislation requires study sponsors or investigators to report summary results within one year after the estimated or actual completion date, whichever is earlier. Completion date is defined in the legislation as the date that the last patient in a trial is evaluated for the primary outcome. (For more information about the legislation, go to prsinfo.clinicaltrials.gov.)

Under these circumstances, investigators and sponsors have no time to lose if they wish, as many do, to publish a peer-reviewed report in a medical journal before results are posted on the clinicaltrials.gov site. Getting a report into peer-reviewed journals is considered priority one for investigators. Posting results on the site first could undermine the report's importance or open the trial results up to misinterpretation.

"Anybody within academia and the industry will say that the gold standard for the communication of scientific information, including clinical trial data, is a peer-reviewed publication," says Laurence Hirsch, M.D., VP, global medical affairs, at BD Medical/Diabetes Care.

This impetus from investigators forces publication planners to dramatically speed up the process to get the publication data out first.

"I think the biggest challenge with FDAAA is going to be meeting the hard deadline resulting from the need to post trial results within one year from last patient last visit," says Mark Fedele, Ph.D., clinical communication leader in the respiratory therapeutic area for Novartis. "The problem is not posting the results in that time frame, but the rush to get the study analysis published in a professional journal beforehand. FDAAA creates a sense of urgency for publication teams to get the communication completed sooner and managing the timing of this is often very difficult."

Not only is it difficult to prepare a document in that amount of time, there are other complications as well. For instance, if the trial is set up to evaluate secondary outcomes at a later date, the primary trial results will need to be posted before the trial is complete.

"FDAAA creates a sense of urgency for publication teams to get the process completed sooner; managing the timing is often very difficult."

DR. MARK FEDELE
Novartis

There is a provision in the bill that may allow reporting 18 months after the last patient is evaluated, but even this may not be enough time to complete the second outcome part of the trial, our experts say.

Under the new rule, another hurdle is that many in the industry are concerned that posting the raw data with no explanation may confuse patients and physicians and open up the possibility for the public and the media to misconstrue the information they find on the site.

"Without an introduction or the background, explanation of methodology, the results put into context, and a robust discussion on why the findings are relevant, the data are just data," Dr. Hirsch says.

With clinical trial results available online and open to "interrogation by everyone," this

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"The broader issue is trying to accommodate the FDAAA timelines while allowing the normal peer-review process to proceed."

DR. LAURENCE HIRSCH
BD Medical Diabetes Care

will present another major challenge, according to Neil Matheson, CEO of Axis Healthcare Communications.

"The reality of what public access means has not quite dawned on people yet," Mr. Matheson says. "I don't think those involved in the process of clinical research are equipped for the new challenges this will bring."

Mr. Matheson says he expects the publication process to evolve very dramatically as technology drives people's ability to view results online, as opposed to reading a comprehensive analysis of the data first in a medical journal.

"A report is a very, very complex document; the data tables alone are almost indecipherable to someone who doesn't know what he or she is looking at," he says. "There are actual methodologies and ways of interpreting data and types of statistical analytics that are needed to make sense of the data."

Mr. Matheson suggests that the industry will have to address the possibility of filtering information to the right audience.

"For example, data could be viewed by the general public if there was a way to simplify the reports," he says. "I expect that soon there will be a series of filters, similar to the digital publication process, in terms of allowing certain users to see data in a way they can comprehend, as opposed to just giving them raw data."

Without these types of filters or adjustments, the results are at risk of being misrepresented by the media and misunderstood by lay people, patients, and even physicians.

"So what do these raw data mean for patients and physicians?" Dr. Hirsch asks. "In other words, the people for whom Congress ostensibly passed the law are likely to be the ones who will use the information the least.

"Congress passed this law so patients and doctors will be better informed, but it's already a challenge for physicians to keep up with all of the major medical journals, plus their own specialty publications, and then go online to look for clinical trial results," he continues. "Similarly, how many patients will benefit from a short statement of results, with no interpretation?"

TRANSPARENCY

Another new challenge for the publication publishing function is ensuring that there is complete transparency of not only the data, but of any contribution made in preparing the document for publication, says Robert Norris, president and CEO of Complete Healthcare Communications.

"There are two issues when it comes to transparency," he says. "First, there is the requirement to present all of the data related to the trial results, and second — and this is really important today — there needs to be complete transparency by disclosing who did what related to a publication."

Transparency of contribution requires acknowledging who had what role in developing the publication, Mr. Norris says. This is a predominant focus of the International Society for Medical Publication Professionals (ISMPP), of which Mr. Norris is a founder and Mr. Matheson and Dr. Fedele are members.

"Transparency is the most important priority these days," Dr. Fedele says. "It has become standard practice over the past two or three years to acknowledge who is responsible for the publication, that is, for example, if an external agency or writer was used. It is perfectly acceptable to use professional medical writers. But the key is to be transparent about it."

"In developing, disseminating, and adhering to guidelines, the medical communications industry can help foster a collaborative and ethical publication environment."

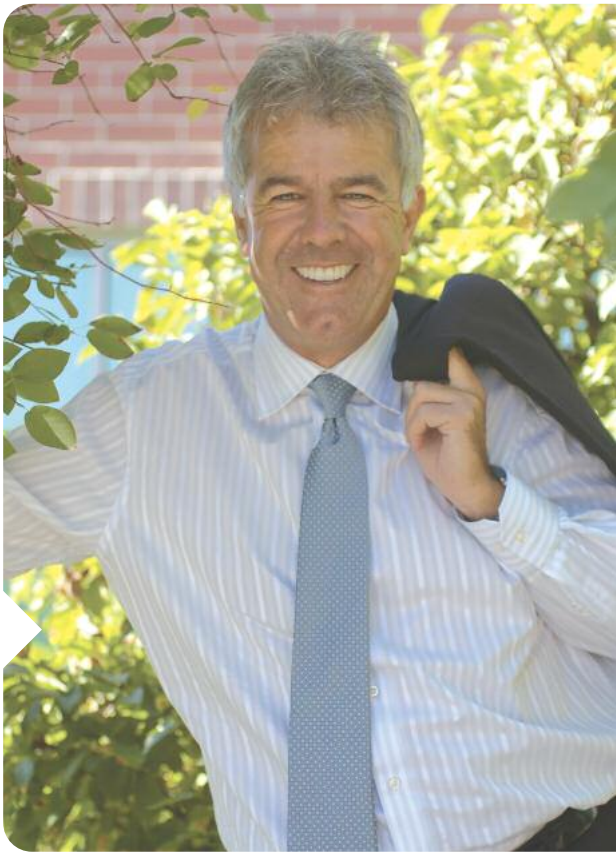
NEIL MATHESON
Axis Healthcare Communications

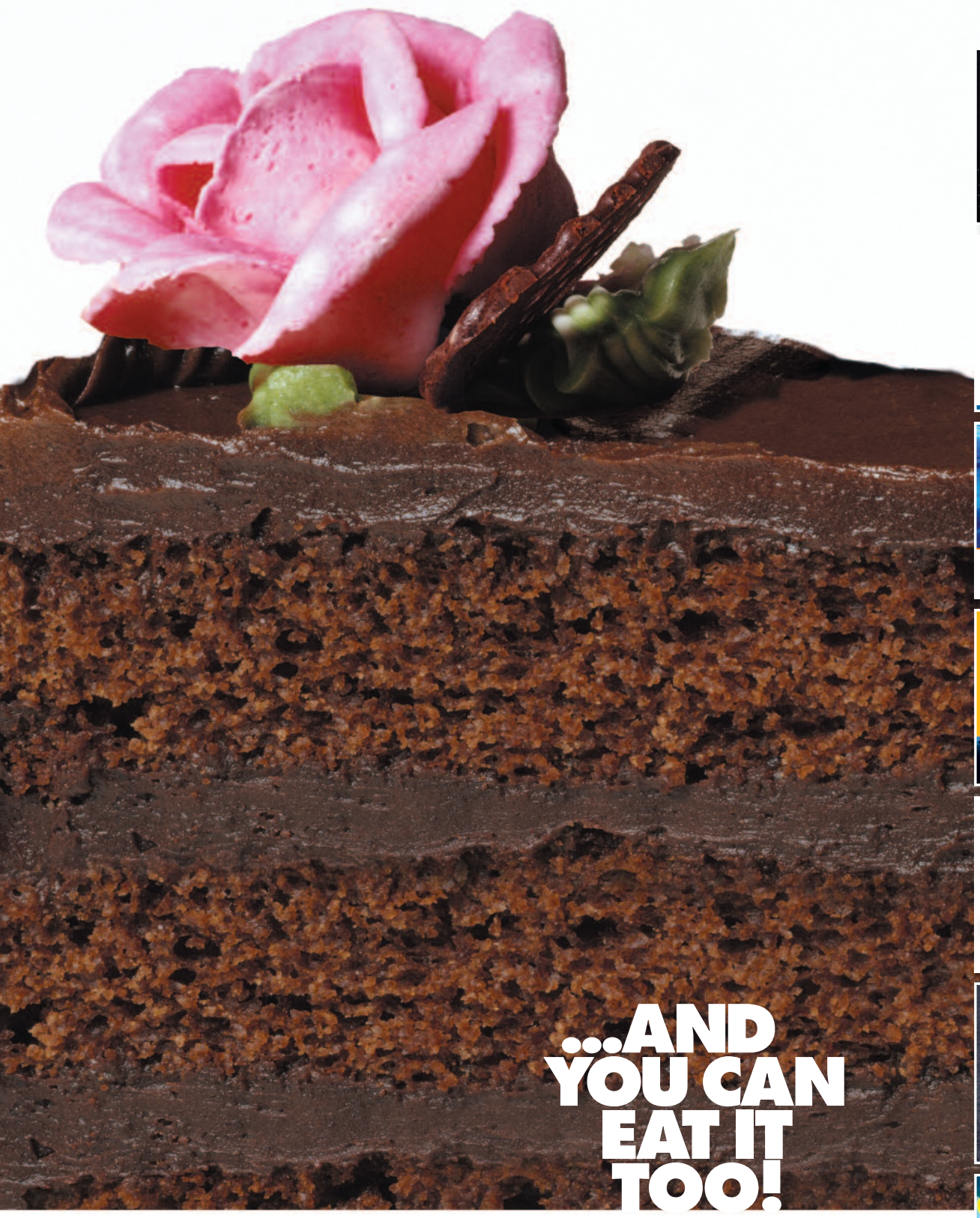
Dr. Fedele says both pharma companies and medical journals have policies that require this type of disclosure and that the information is specifically documented in the acknowledgement section of many medical journals.

"Meeting the transparency requirement is easy as long as the company and all external authors disclose their involvement in the study and the subsequent publication," Mr. Norris says. "Sponsors need to be 100% transparent in the role that everyone plays."

The publication team, the writers, the statisticians, the study coordinators, and the investigators need to establish a real trust and understanding as well as be accountable for their role in creating the report, he says.

Transparency of contribution is a byproduct of the increased scrutiny that was set in motion by several unethical ghostwriting practices conducted by large pharma companies that took place several years ago. The cases, namely against GlaxoSmithKline and Wyeth, continue to appear in today's headlines as more details of the practices are discussed in court. According to New York Times reports, GlaxoSmithKline used a ghostwriting program to publish articles about Paxil; doctors were credited with the





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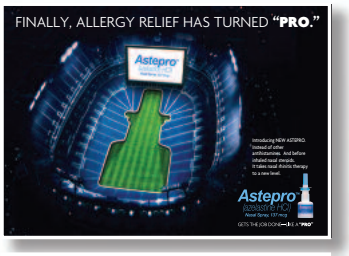

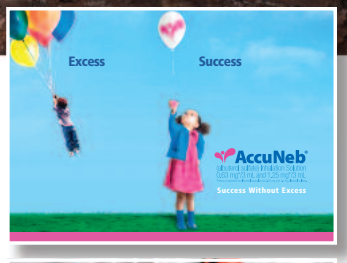

articles when they were written by consultants. Wyeth paid a medical writing company to produce articles about Premarin from 1998 to 2005. The articles were sent to top academics in the ob/gyn field, who reviewed them, made edits, and submitted them to journals under their names. At issue in both cases was the lack of transparency in who actually was responsible for writing the documents.

According to Dr. Fedele, these types of blinded ghost writing practices are not as common today due to the bad publicity and public scrutiny around pharma-sponsored publications.

Instead, authors are engaged along the entire process, from data analysis to writing, editing, and approving all content that ultimately appears in print.

"Quite frankly, being an author is much more work now, so much so that some investigators and prominent physicians aren't as excited about authoring as much as they were in the past," he says. "They recognize the current environment and view being an author as a much larger and more time-consuming commitment and responsibility."

Dr. Fedele says to his knowledge, most companies are developing or already have their own publication policies regarding transparency.

"In the last few years, it has certainly become more common for companies to have and follow a formal publication policy," he says. "I think most companies start by following existing publication guidelines offered by industry organizations and associations and then adapt them to their own needs."

"We recommend that every company should have a formalized set of publication practice guidelines," Mr. Matheson says. "These guidelines should clearly articulate the roles and responsibilities of the various people involved in the process and clearly outline the process flow for how data are disseminated. Care should be taken that the integrity of data is maintained and that any potential bias is excluded."

To keep trial documents compliant and transparent, companies can use the publication planning guidelines from organizations such as ISMPP, American Medical Writers Association (AMWA), and PhRMA.

Another major challenge facing the publication function is the misperception of the role of the planner, Mr. Norris says.

"There is a perception that assisting investigators editorially or with the publication process, which is the publication planner's job, can taint a publication," he says. "But it can, in fact, ensure the clarity of the science using the publication professionals can speed getting the science published. The industry needs to overcome the public's misconception and constructively show the benefit we bring to pharma, investigators, journal editors, and ultimately to patients."

"Companies that have a well-defined policy that is enforced usually do very well when it comes to being in regulatory compliance."

ROBERT NORRIS

Complete Healthcare Communications

TIMING IS EVERYTHING

The time it takes to get a paper published in a medical journal depends on many variables. Publication of trial results can take as little as a few months if the study warrants a fast-track status, but more often, the process takes 18 months or more.

"The timeline for publication entirely depends on the novelty, importance, and prominence of the study," Dr. Hirsch says. "In a couple of cases, major studies have published in a prominent journal within a few months of completion, sometimes simultaneous with presentation at a medical conference. Of course, these are outliers."

Our experts say studies can be published within one year from completion date, but it takes extra measures, a significant trial, willingness from journal editors, and a planning process that started far down the timeline. Large companies with hundreds of clinical trials going on at once, or smaller companies that don't have the resources to focus on several trials at once, could have difficulty getting this task done. Publication planners need to start formulating a schedule early on to be able to facilitate a quick turnaround, our experts say.

A successful plan will also require the planner to be able to work well with investigators to make realistic decisions on where to publish.

"Investigators may have an overly ambitious view of the study's importance and believe it can be published in the New England Journal of Medicine or The Lancet; meanwhile a specialty publication might be a better first choice," Dr. Hirsch says. "But investigators generally control decisions to submit, and if they decide on a top-tier journal, that's what happens. If the report is rejected, the clock keeps ticking and the paper will be revised for another journal or even a third journal, which means three to six months have been lost. This is an issue independent of FDAAA and is driven more by differences in opinions on where to submit manuscripts. But it is now exacerbated by FDAAA timelines."

To meet this challenge head on, publication planners should prepare as much of the primary report as possible before the final trial results are in. Companies need to look forward far enough to estimate when studies will be completed and allocate resources and a timeline based on those best estimates, Dr. Hirsch says.

"Don't wait for the statistical report to come in before starting to write the paper," he says. "Do as much as possible in advance."

Many parts of the report can be written ahead of time, with the results and discussion sections saved for last and completed as soon as the trial results are available. Proactive approaches to data management — such as cleaning data in a blinded manner as the study is ongoing and writing up the background/introduction, and the methods sections of the study — can speed the turnaround time when the trial is complete. Dr. Hirsch suggests blocking out the results section as well, with primary outcome measures, adverse events, tables, and figures. Knowing the requirements or limitations of the journal to which submission is planned is important.

"Companies need to block out what they expect to put in the results section and when the final results are available, the manuscript can be turned around and submitted for review in a couple of weeks," he advises.

A key to making this work, Dr. Hirsch says, is to have an up-front agreement as to who the principal author is, who the other key authors will be, and what everybody's role is going to be.

"It's important to avoid having four people writing the first draft of the paper," Dr. Hirsch says. "Some authors will take more of

a writing role; others will do more reviewing and revising."

Contacting the editors of the desired publication(s) and giving them a heads up and the expected outcomes of the trial can move the process forward as well. Speaking to an editor ahead of time and describing the study and inquiring if the publication would be interested can help expedite the process. If the trial results will represent a significant finding, sometimes the journal will agree to fast track the publication of the document through a rapid response or priority publication process, Dr. Hirsch says. ✦

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Experts on this topic

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BY ROBIN ROBINSON

Publication Planning: A JOURNAL RESPONSE

Medical journals also have had to change their processes because of Title VIII of FDAAA, which requires the posting of clinical trial data within one year from last patient last visit.

"Most major medical journals adhere to the so-called Inglefinger rule, named after a former editor of the NEJM, which means that the journals will not accept an article for publication if the study results have already been published somewhere else," says Laurence Hirsch, M.D., VP, global medical affairs, at BD Medical/Diabetes Care. "The International Committee of Medical Journal Editors decided to exempt results posted in the format required by clinicaltrials.gov from being considered a prior publication."

It is important to note that the ICMJE clinical trial registration policy requires prospective registration of all interventional clinical studies, but does not require results reporting for registered trials. While the ICMJE recognizes the potential problems associated with posting preliminary research results that have not yet undergone an independent peer-review process, it acknowledges that the Food and Drug Administration Amendments Act of 2007 (FDAAA; U.S. Public Law 110-85, Title VIII) mandates the posting of summary results data for certain trials on clinicaltrials.gov. Thus, the ICMJE will not consider results data posted in the tabular format required by ClinicalTrials.gov to be prior publication.

Editors of journals who follow the ICMJE recommendations may consider the posting of more detailed descriptions of trial results beyond those included in clinicaltrials.gov to be prior publication. The ICMJE anticipates that the climate for reporting results for registered trials will change dramatically in the coming years and the ICMJE may need to amend these recommendations as additional agencies institute other mandates related to results reporting. ✦

GPP Guidelines

The following is a sampling of the guidelines developed to address the role of agencies in the development and publication of biomedical information and the issues faced by such agencies. The guidelines were created collaboratively by a working group of employees within the Axis group of medical communications agencies and the full report can be found in the medical journal Current Medical Research And Opinion, Vol. 25, No. 2, 2009, Pg. 453–461.

ROLE OF THIRD-PARTY MEDICAL WRITING/CONTRIBUTIONS OF MEDICAL WRITERS

Third-party medical writers and editors make an honorable and important contribution to the dissemination of scientific/clinical data to the medical community and society at large by providing expertise in publication preparation. Medical writers and editors collaborate closely with the authors, the originators of the research data, as well as the sponsor of the research, to develop scientifically rigorous, clear, and concise publications in a timely manner in adherence to journal or congress guidelines and existing good publication guidelines.

AUTHORSHIP CRITERIA

MedComm GPP guidelines uphold the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, which state: "Authorship credit should be based on (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3."

According to the Uniform Requirements, a third-party medical writer generally does not merit authorship; however, the writer should be included in the acknowledgments (see Transparency and acknowledgments).

TRANSPARENCY AND ACKNOWLEDGMENTS

MedComm GPP guidelines support the fundamental principle of full transparency in the publication process. Accordingly, the contributions of the individual third-party medical writers/editors, the agency involved, and the funding source should be fully disclosed in the manner required by the journal/congress (e.g., in the online submission process), as well as in the acknowledgment section of the publication. MedComm GPP guidelines include two recommended wordings for acknowledgments (similar to those developed by EMWA10), depending on the contributions of the medical writer(s)/editor(s) to the development of the publication: "The authors thank Jane Doe, Ph.D. [M.D., Pharm.D., etc.], in association with MedComm group for providing medical writing assistance supported by ABC Pharmaceuticals."

MEDICAL WRITER/EDITOR COLLABORATION WITH AUTHORS

The role of third-party medical writers and editors is to assist the authors with content development. Accordingly, the authors should control and approve all aspects of the publication from concept to completion.

Depending on the individual project and authors involved, the medical writer or editor may provide services ranging from limited editorial support (e.g., copy editing and styling) to full medical writing assistance (e.g., performing literature searches, developing tables and figures, writing outlines and drafts).

Source: Axis Healthcare Communications. For more information, visit axis-healthcare.com.

GPP Resources

The following resources all have published guidelines and recommendations on the role of medical writers in developing manuscripts submitted to peer-reviewed journals and congresses.

- **AMERICAN MEDICAL ASSOCIATION (AMA):** The AMA impacts the daily work of all physicians, residents, fellows, and medical students in the United States and publishes the Journal of American Medical Association, JAMA. For more information, visit ama-assn.org.

- **AMERICAN MEDICAL WRITERS ASSOCIATION (AMWA):** AMWA's mission is to promote excellence in medical communication through an extensive educational program and various publications. For more information, visit amwa.org.

- **ASSOCIATION OF AMERICAN MEDICAL COLLEGES (AAMC):** AAMC strengthens the world's most advanced medical care by supporting the entire spectrum of education, research, and patient care activities conducted by its member institutions. For more information, visit aamc.org.

- **BLACKWELL PUBLISHING:** Blackwell Publishing's Best Practice Guidelines on Publication Ethics describes the company's position on the major ethical principles of academic publishing and considers factors that may foster ethical behavior or create problems. For more information, visit blackwellpublishing.com/publicationethics.

- **COMMITTEE ON PUBLICATION ETHICS (COPE):** COPE is a forum for publishers and editors of peer-reviewed journals to discuss issues related to the integrity of work submitted to or published in their journals. For more information, visit publicationethics.org.

- **COUNCIL OF SCIENCE EDITORS (CSE):** CSE serves members in the scientific, scientific publishing, and information science communities by fostering networking, education, discussion, and exchange and by being an authoritative resource on current and emerging issues in the communication of scientific information. For more information, visit councilscienceeditors.org.

- **EUROPEAN MEDICAL WRITERS ASSOCIATION (EMWA):** EMWA supports medical writers and medical editors through training and networking opportunities. For more information, visit emwa.org.

- **INTERNATIONAL COMMITTEE OF MEDICAL JOURNAL EDITORS (ICMJE):** ICMJE is a group of general medical journal editors whose participants meet annually and fund their work on the Uniform Requirements for Manuscripts. For more information, visit icmje.org.

- **INTERNATIONAL SOCIETY FOR MEDICAL PUBLICATION PROFESSIONALS (ISMPP):** ISMPP is the only not-for-profit organization founded by medical publication professionals for medial publication professionals. For more information, visit ismpp.org.

- **PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA (PHRMA):** PhRMA represents the country's leading pharmaceutical research and biotechnology companies. For more information, visit phrma.org/about_phrma.org.

- **WORLD ASSOCIATION OF MEDICAL EDITORS (WAME):** WAME is a voluntary association of editors from countries throughout the world who seek to foster international cooperation among editors of peer-reviewed medical journals. For more information, visit wame.org.

- **AUTHOR'S NOTE: CLINICAL TRIALS DATA ON SOCIAL MEDIA:** As noted on the Icarus Consulting blog Pharma Strategy, the Journal of Clinical of Clinical Oncology not only published an early release of the study "Cancer-Related Direct-to-Consumer Advertising: Awareness, Perceptions, and Reported Impact Among Patients Undergoing Active Cancer Treatment" days before the print version arrived in mailboxes, but it also bookmarked several social media sites at the bottom of the abstract to allow readers to share the information. The sites included CiteULike, Connotea, Del.icio.us, Digg, Facebook, Reddit, Technorati, and Twitter. It will be interesting to see if this publication tactic is a trend that will grow and if the blend of science and social media will be a good mix to create awareness of successful trial results.

  The study, from the Center for Outcomes and Policy Research and the Division of Women's Cancers, Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, was written by Gregory A. Abel, Harold J. Burstein, Nathanael D. Hevelone, and Jane C. Weeks.

Source: PharmaVOICE.