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AMWA JOURNAL MISSION STATEMENT
The AMWA Journal expresses the interests, concerns, and expertise of members. Its purpose is to inspire, motivate, inform, and educate them. The Journal furthers dialog among all members and communicates the purposes, goals, advantages, and benefits of the American Medical Writers Association as a professional organization.
Preface
Theme Issue: Clinical Trials

If you have ever taken a pill, received a childhood vaccine, taken a spoonful of cough syrup, or received any of the thousands of other benefits of modern medicine, then you have been on the receiving end of a clinical trial. Clinical trials are research studies that explore whether a medical strategy, treatment, or device is safe and effective for humans. Nearly every man, woman, and child alive today has received a medical intervention that at some point was the subject of a clinical trial. More than 4000 experimental drug therapies are active today, and that number will continue to increase. Millions of Americans depend on medications, which is why researchers are devoted to exploring the best treatments available.

It is also why I chose to devote this issue of the AMWA Journal to clinical trials. Clinical trials are just one type of research that’s done before a new treatment becomes available to people. New medicines must first be discovered, purified, and tested in preclinical trials before researchers even consider clinical trials. According to the American Cancer Society, about 1000 potential medicines are tested before one makes it to clinical trials. On average, a new medicine to treat cancer has been studied in the laboratory for at least 6 years (and sometimes many more) before the first clinical trial is started.

One of the final stages of a long and careful research process, clinical trials are a key research tool for advancing medical knowledge and patient care. An important step in discovering new treatments for diseases as well as new ways to detect, diagnose, and reduce the risk of disease, clinical trials show researchers what does and does not work in people. Clinical trials also help researchers and doctors decide if the side effects of a new treatment are acceptable when weighed against the benefits. These studies also may show which medical approaches work best for certain illnesses or groups of people, providing the best data available for healthcare decision-making. Many of today’s advances are direct results of clinical studies, and because of the diligent work of researchers, people live longer and healthier lives. Diseases that affect millions, like diabetes or cancer, are at the forefront of medical development. These clinical studies are of particular importance to the general public because they serve to help a large proportion of the population.

Because of the vital importance of clinical trials in the advancement of medical science, in this issue we have gathered together several articles that touch on varied aspects of clinical trial design, implementation, and analysis.

Laurie Endicott Thomas leads off this issue with some basic science—where all clinical research begins—by presenting the third in our science series on how cells communicate, discussing how cells respond to signals.

Lisa Ambrosini Vadola and Robin Whitsell help us move from basic science to study design by introducing the new National Institutes of Health—Food and Drug Administration Clinical Trial Protocol Template.

Helen Bridge and Thomas Schindler help us close the gap between trial objectives and statistical analysis by introducing us to the “estimand,” and William Sinkins helps us manage our statistical currency by showing us how to wisely “spend the alpha.”

Sandra Shpilberg gives us some guidance on how we can leverage social media for clinical trial patient recruitment.

Kristina Wasson-Blader shares some industry insight into the new clinical trial data sharing statements soon to be required by the International Committee of Medical Journal Editors.

Providing background for beginning medical writers, Lori Alexander reviews the book How to Write and Publish a Scientific Paper, 8th ed., and Laurie Endicott Thomas reminds us to describe our methods in our methods section.

Our Forum contributors Brian Bass, Mark Bowlby, Gail Flores, and Cathryn Evans provide clinical trials-related insights for our freelance colleagues.

Taking us Around the Career Block, Susan Towers provides a continuation of last issue’s introduction to gene therapy by discussing what it is, how it is different from CRISPR/Cas9, and why it is getting so much media hype.

Tami Ball gives us something to think about when considering the ethics of genetics.

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How Cells Communicate, Part 3: How Cells Respond to Signals

By Laurie Endicott Thomas, MA, ELS / Author and freelance medical writer, Madison, NJ

Each cell is a living organism that interacts with its environment. Cells alter their behavior and even their size and shape in response to information they receive from their environment. For the cells in the human body, some of this information comes from chemical signals produced by other cells. Part 1 of this 3-part presentation explained that many bodily processes are regulated by messages that are passed between cells. Part 2 described the kinds of chemicals that are used to pass messages from one cell to another and described the proteins that serve as receptors for these signaling chemicals. This final installment describes what happens within a cell in response to a chemical signal or to some other external stimulus.

Many of the chemicals that carry messages between cells never enter their target cell. Instead, they activate a receptor that passes through the cell membrane. The activated receptor then triggers a sequence of chemical signals within the cell. These intracellular signaling pathways play an important role in health and disease. For example, some oncogenes (genes that can cause cancer) are genes that code for a receptor protein (e.g., the estrogen receptor) that is in a constitutively activated state (i.e., it is in the “on” state all the time). A constitutively activated receptor activates its signaling pathway even if its ligand is absent. For this reason, signal transduction pathways are becoming increasingly important as therapeutic targets, particularly in oncology but also in immunology. In oncology, the goal is to find some way to suppress the proliferation of cancer cells without causing undue harm to the body as a whole. In immunology, the goal is typically to find some way to suppress an inappropriate inflammatory response without causing dangerous immune suppression or other undesirable side effects. Scientists have discovered that some “old” drugs, such as theophylline and caffeine, work by inhibiting an enzyme involved in an intracellular signaling pathway. Scientists are now developing other agents that are specifically designed to act selectively on a particular target within a particular intracellular signaling pathway within a particular set of cells. To understand how those drugs work, you need to understand intracellular signal transduction pathways.

Proteins play crucial roles in intracellular signaling pathways, both as signaling chemicals and as receptors (sensors). As Part 2 explained, each protein tends to take on a predictable shape that depends on its genetically determined chemical structure. This precise shape allows each receptor to bind selectively to some ligands but not to others. Because this binding is selective and generally reversible, it is often described as a lock-and-key relationship. The bond between the ligand and its receptor can cause a temporary change in the conformation (shape) of the receptor protein. This temporary conformational change can then trigger other events. For example, a ligand that is outside the cell can bind to a receptor that crosses a cell membrane. The resulting change in the shape of the intracellular domains of the receptor protein can thus transmit a signal into the cell, even though the ligand remains outside of the cell. Some receptor proteins do not have a chemical ligand. Instead, they undergo a conformational change in response to other kinds of stimuli, such as light, temperature, mechanical stress, or osmotic pressure.

SIGNAL TRANSDUCTION

Some signaling chemicals directly trigger a simple response, such as the opening of a ligand-gated ion channel. Others trigger a long and complicated cascade of signals within the cell. The following are the basic elements of the signal transduction pathways:

- **A ligand** is a molecule that binds reversibly to a receptor. (See Part 2 for a discussion of ligand-receptor relationships.)
- **First messengers** are signaling compounds that come from outside the cell.
- **Signal transduction** typically begins when a receptor (the signal transducer) becomes occupied by a ligand or responds to some other stimulus. As a result, the receptor undergoes a conformational change (a change in the shape...
of the protein molecule). This conformational change then activates a primary effector.

- The primary effector may produce some direct change in the cell’s behavior, such as opening an ion channel through the cell membrane. Or the primary effector may trigger the production of another signaling chemical, called the second messenger, within the cell.
- The second messenger may then go on to activate a secondary effector, which may then produce another second messenger, and so on.
- Each component within this signaling cascade is called a node.
- An efficient node can amplify a signal (a phenomenon known as signal gain). As a result, one signaling molecule can generate a response involving hundreds to millions of molecules.
- Conversely, an intracellular signal can also be suppressed by blocking an intracellular receptor or degrading a second messenger. For this reason, these nodes and the enzymes that regulate them are becoming important as therapeutic targets.
- Each cell has many intracellular signaling pathways, and these pathways can interact in complicated ways. To describe these interactions, cell biologists have borrowed radio terminology, such as networks, noise, and crosstalk.

**TYPES OF RECEPTORS**
Receptors can be sorted into 4 broad categories: ligand-gated ion channels, G-protein–coupled receptors, kinase-linked receptors, and nuclear receptors.

**Ligand–Gated Ion Channels**
Ligand-gated ion channels are also called ionotropic receptors because they can open or close a channel that would allow some sort of ion to travel into or out of the cell (Figure 1). They typically provide a signal that lasts for only a few milliseconds.

Many postsynaptic receptors are ligand-gated ion channels. Binding to the neurotransmitter that serves as their ligand causes these receptors to undergo a conformational change that opens a channel that permits a flow of ions across the cell membrane. This flow of ions then produces either depolarization (in the case of excitatory receptors) or hyperpolarization (in the case of inhibitory receptors). Ligand-gated ion channels typically consist of an extracellular domain that includes the ligand-binding site and a transmembrane domain that includes the ion pore.

**G-Protein–Coupled Receptors**
The largest family of cell-surface receptors are called G-protein–coupled receptors (GPCRs) (Figure 2) because they are associated with guanine nucleotide-binding proteins (G proteins). The time scale of a signal produced by activation of a GPCR is typically measured in seconds.

**Figure 2. The β2 adrenergic receptor is a G-protein–coupled receptor.** This artist’s rendering shows the receptor from the N–terminus (blue) to C–terminus (red), with the extracellular surface at the top of the image. The partial inverse agonist carazolol is shown as gray sticks. Rendered using PyMol from PDB ID 2RH1. By Opabinia regalis (Own work).

GPCRs are sometimes called metabotropic receptors because their action is mediated by metabolic functions (eg, enzyme activation). They do not have ion channels. However, binding of the ligand to some GPCRs can indirectly result in the opening of an ion channel elsewhere on the membrane. Many GPCRs are activated by binding with a ligand. Others are activated by other kinds of stimuli, such as light. For
example, the light-sensing protein rhodopsin (also known as visual purple) is a GPCR.2

Because GPCRs are expressed on the outer surface of the cell, they can readily interact with water-soluble ligands, including drugs. Approximately 40% of all prescription drugs (including antihistamines and beta blockers) target a GPCR.3 Analysis of the human genome suggests that there are hundreds of different GPCRs.4 Many GPCRs have been found to respond to a particular ligand or other stimulus, whether it is an amine, an ion, a nucleoside, a lipid, a peptide, a protein, or (in the case of optical receptors) light.3 There are also many “orphan” GPCRs, which have been identified through genetic analysis but whose ligands have not been identified.

Each GPCR consists of a protein that is anchored in the cell membrane by 7 transmembrane domains (ie, the receptor crosses the cell membrane 7 times). (See Part 2 for a discussion of protein structure.) When the receptor is in the unactivated state, its intracellular portion is linked to a G protein. G proteins are heterotrimeric, which means that they consist of 3 different subunits called Gα, Gβ, and Gγ. The Gα subunit of the heterotrimeric G protein may be bound to guanosine diphosphate (GDP). When the receptor is activated, the receptor undergoes a conformational change that causes phosphorylation (addition of a high-energy phosphate group) of GDP, thus yielding guanosine triphosphate (GTP). As a result, the Gα-GTP complex and the remaining Gβγ dimer break free from the GPCR and can interact with other receptors downstream in the signal transduction cascade. Meanwhile, the intracellular portion of GPCR can bind to another heterotrimeric G protein to form a new complex that can initiate a new round of signal transduction. The signaling activity of the dissociated G protein ends when the GTP associated with Gα is degraded to GDP (often by the Gα subunit’s own GTPase activity) and the Gα subunit recombines with a Gβγ dimer to form a new heterotrimer, which can then bind to the intracellular domain of the transmembrane receptor.5

There are several different classes of G-proteins, which are defined by their different Gα subunits. Some GPCRs can activate more than one Gα subtype, but they usually have a preference for a particular subtype. The Gαs and Gα12/13 subtypes activate the enzyme adenylyl cyclase, which catalyzes the formation of a second messenger called cyclic adenosine monophosphate (cAMP). When adenylyl cyclase is activated, it can generate many molecules of cAMP thus amplifying the signal. Cyclic AMP often exerts its downstream effect by binding to and activating protein kinase A (PKA; also known as cAMP-dependent kinase), which then phosphorylates target proteins in the cell (Figure 3).

Cyclic AMP is broken down by cyclic nucleotide phosphodiesterase enzymes, which thus suppress and shorten the cAMP signal. Several drugs work by selectively inhibiting a particular cyclic nucleotide phosphodiesterase enzyme. For example, theophylline exerts its anti-inflammatory effect in the respiratory tract by inhibiting phosphodiesterase 4 (PDE4), which is found in a wide range of inflammatory cells.6 In contrast, inhibitors of PDE5 are used for the treatment of erectile dysfunction.6

Gαq/11 activates an enzyme called phospholipase C, which splits a membrane phospholipid called PIP2 into 2 second messengers: inositol triphosphate (IP3) and diacylglycerol (DAG). IP3 is water soluble and diffuses through the cytosol and binds to a ligand-gated Ca++ channel on the endoplasmic reticulum (or sarcoplasmic reticulum in muscle cells). The calcium ions that consequently enter the cytosol then bind to calcium-binding proteins such as calmodulin. In contrast, DAG is lipid-soluble and stays in the membrane. DAG activates protein kinase C, which then phosphorylates particular target proteins. There is also a Gα12/13, which binds to RhoGEF proteins, which then activate the cytosolic small GTPase Rho, which is involved in regulating the cell’s cytoskeleton.

**Kinase-Linked Receptors**

Kinase-linked receptors produce a signal that can last for hours. A kinase is an enzyme that catalyzes the transfer of a phosphate group from a high-energy, phosphate-donating
molecule to a specific substrate. Kinases play an important role in intracellular signaling cascades, and dysregulation of many kinases has been linked to the development of disease. Many kinase inhibitors are currently being investigated in clinical trials. More than two dozen have been approved for human use, mainly in oncology but some for the treatment of rheumatoid arthritis or macular degeneration. Some protein kinases serve as receptors. The insulin receptor and other growth hormone receptors are receptor tyrosine kinases (RTKs). Other protein kinases serve as secondary effectors in the intracellular signaling cascade.

**Receptor Tyrosine Kinases**
The RTKs consist of an extracellular domain that binds to a ligand and an intracellular domain that functions as a kinase (Figure 4). An RTK consists of 2 subunits, which form a dimer anchored in the cell membrane. This dimer becomes stabilized when its extracellular portion binds to its ligand. This stabilization allows the tyrosine residues of the intracellular domains to become activated through phosphorylation. Once activated, they initiate phosphorylation signaling cascades that have effects on cell metabolism and differentiation.

Activated RTKs activate small G-proteins (from the Ras, Rho, and Raf families), which in turn activate guanine nucleotide exchange factors such as SOS1. When activated, these exchange factors can activate more small G proteins, thus amplifying the signal. Raf proteins are central components of the mitogen-activated protein kinase (MAPK) pathway that regulates cell proliferation. Mutations that increase the catalytic activity of Raf proteins have been identified in many human tumors. For this reason, the Raf kinase family has emerged as a promising target in the treatment of many cancers. For example, sorafenib is used in the treatment of unresectable hepatocellular carcinoma, advanced renal cell carcinoma, and refractory thyroid carcinoma.

**JAK/STAT Pathway**
Members of the type 1 and type 2 cytokine receptor families have no catalytic kinase activity of their own. Instead, they rely on Janus kinases (JAK) to phosphorylate and activate the downstream proteins in their signal transduction pathways. When activated, the JAKs phosphorylate and activate transcription factors called STATs (signal transducer and activator of transcription). JAK inhibitors (also known as Jakinibs) are being investigated for use in the treatment of patients with autoimmune diseases. One example is tofacitinib, which is approved for the treatment of patients with rheumatoid arthritis.

**Integrins**
Integrins are transmembrane receptors that facilitate the adhesion of cells to an extracellular matrix. Epithelial cells normally have active integrins at their cell surface, which help to maintain their attachment to stromal cells. In contrast, circulating leukocytes normally have inactive integrins. However, their integrins can be activated by the inflammatory process. For example, the weak binding of a T lymphocyte to its specific antigen on the surface of an antigen-presenting cell triggers intracellular signaling pathways in the T cell that activate its β2 integrins. The activated integrins then enable the T cell to adhere strongly to the antigen-presenting cell so that it remains in contact long enough to become stimulated fully. The integrins may then return to an inactive state, allowing the T cell to disengage.

Integrins are heterodimers (ie, they consist of an α and β subunit). Integrins have no kinase activity. Instead, they transmit their
signals through various intracellular protein kinases and adaptor molecules, especially integrin-linked kinase.

**Toll-Like Receptors**

Toll-like receptors (TLRs) are named after their similarity to the toll protein identified in *Drosophila*. The TLRs are single, membrane-spanning, noncatalytic receptors that are usually expressed on sentinel cells of the immune system (e.g., macrophages and dendritic cells). The TLRs recognize molecules that are broadly shared by pathogens, such as bacteria and viruses. When activated, TLRs recruit adaptor proteins, which mediate specific protein-protein interactions that drive the formation of protein complexes. These protein complexes then activate other downstream proteins, including kinases, in a pathway that ultimately alters gene expression. The TLRs play an important role in the innate immune system and serve as an important link between innate and adaptive immunity.

**Intracellular (Nuclear) Receptors**

Intracellular (nuclear) receptors produce signals that typically last for hours. Many signaling pathways end up activating an intracellular receptor that then goes on to alter the expression of a particular gene. Some intracellular receptors are activated by lipid-soluble first messengers, such as steroid hormones and vitamins A and D, that have diffused through the cell membrane. Other intracellular receptors are activated by second messengers that are produced by an intracellular signaling cascade.

Intracellular receptors can be found in the cytosol or in the nucleus (Figure 5). Before a cytosolic receptor can interact with a gene, the cytosolic receptor-ligand complex must pass into the nucleus. In the nucleus, the DNA-binding domain of the ligand-receptor complex binds to DNA. An activated steroid receptor will generally bind to a receptor-specific hormone-responsive element (HRE) sequence in the promoter region of a gene that is activated by that hormone-receptor complex. As a result, the receptor-ligand complex can alter the expression of that gene, for example by increasing or decreasing the transcription of the gene and thus influencing the production of the protein encoded by that gene.

**CONCLUSION**

The human body is made up of trillions of cells, each of which can be viewed as a separate organism. Yet these trillions of cells coordinate their activity in ways that allow the body to function as a single entity and to react to a wide range of environmental stressors. This coordination is accomplished largely through chemical signals, which are

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*Figure 5. Nuclear receptors may be found in the cytosol. But after the receptor’s ligand-binding site binds to the ligand, the receptor-ligand complex must travel into the nucleus, where the receptor’s DNA-binding domain binds to the appropriate sequence in the promoter region of a gene that is activated by that hormone–receptor complex. Image courtesy of Boghog2.*

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**Glossary**

**Conformational change**—the change in shape (conformation) of a protein.

**Cyclic AMP**—cyclic adenosine monophosphate is an important second messenger in intracellular signaling cascades.

**First messenger**—a signaling compound that came from outside the cell.

**Kinase**—an enzyme that catalyzes phosphorylation, which is the transfer of a phosphate group from a high-energy phosphate-donating molecule (such as adenosine triphosphate) to a specific substrate.

**Ligand**—a molecule that binds reversibly to a receptor.

**Phosphodiesterases**—a class of enzymes that break down the phosphodiester bond in second-messenger molecules, such as cyclic AMP and cyclic guanosine monophosphate (cGMP).

**Protein phosphorylation**—The addition of a covalently bound phosphate group to an amino acid residue in a protein. This addition often changes the shape and function of the protein.

**Second messenger**—a signaling compound that is produced inside the cell as part of a signaling cascade.
emitted by some cells and have effects on other cells. Part 1 of this 3-part presentation described how the endocrine system helps maintain homeostasis in the body. For example, hormones produced in the pancreas regulate blood sugar by causing the liver to store or release glucose, as needed. This third and final part explains what happens when one of these chemical signals reaches its target cell and how the cell’s response to that signal can be modulated by medications that act inside the cell.

Inter- and intracellular signaling pathways play important roles in maintaining health, and disturbances in these pathways can result in disease. For example, disruptions in the pathways that regulate the activities of cells in the immune system can result in autoimmune or inflammatory diseases. Likewise, disruptions in the pathways that would ordinarily suppress a cell’s division or command the cell to commit suicide (apoptosis, or programmed cell death) can lead to cancer. For this reason, research into intracellular signaling pathways has been yielding new medications for inflammatory and neoplastic disease.

Laurie Endicott Thomas is the author of Thin Diabetes, Fat Diabetes: Prevent Type 1, Cure Type 2 (www.thindiabetes.com). She can be reached at lthomas521@verizon.net.

References
Introduction
Since its inception in 1990, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has provided detailed guidelines for the preparation of drug registration submissions to regulatory agencies across the globe, particularly with its introduction of the Common Technical Document (CTD). Medical writers rely heavily on these guidance documents to aid in the preparation of compliant submissions to regulatory agencies. In particular, guidelines such as ICH Guidance for Industry E3 “Structure and Content of Clinical Study Reports” (ICH E3) and Efficacy-M4E “Enhancing the Format and Structure of Benefit-Risk Information in ICH” are invaluable resources to medical writers, as their detailed descriptions of structure and content provide templates for the preparation of clinical study reports (CSRs) and Module 2 summary documents, respectively. While these guidelines have directed the preparation of summaries of clinical data, there has been no parallel template-like guidance for the preparation of clinical trial protocols. Though ICH Guideline E6 “Guideline for Good Clinical Practice (GCP)” (ICH E6) provides a general overview of what should be included in clinical protocols and protocol amendments, it lacks detail and a template-style format.

In general, protocol writing can present some unique challenges. The protocol is meant to be a comprehensive outline of a clinical trial, with definitions of terms, characterization of the ideal subject, and planned procedures and assessments. Yet, brevity and readability are also critical. Concise and clear language is vital for ensuring that the implementation of the protocol is not misinterpreted by individual investigators or their staff. This is particularly important for multi-investigator alignment in multicenter studies. A carefully written protocol details objectives (with specific end points to measure their success), elucidates a well-defined study population, and is internally consistent. Often, clarity in the initial protocol can mitigate a need for subsequent changes (amendments). Thus, for those who work in clinical research, a protocol template seems long overdue.

At the level of investigator-sponsored research, a well-written template can promote consistency of protocols within institutions; lessen the chances for misinterpretation by colleagues, institutional review boards (IRBs), or governmental entities; and facilitate compliance with Section 801 of the US Food and Drug Administration Amendments (FDAAA 801). At the industry level, a consistent template can aid submissions, ensure “mapping” between the protocol and the expected data presentation within a CSR, and enhance readability and consistency for regulatory agency reviewers.

National Institutes of Health—US Food and Drug Administration Clinical Trial Protocol Template and e-Protocol Writing Tool
In an effort to provide primarily researchers, and, to a lesser degree, industry, with a more structured guidance for the design of clinical studies and their corresponding protocols and potentially to streamline their review, the National Institutes of Health (NIH) and US Food and Drug Administration (FDA) jointly developed a clinical trial protocol template for use by NIH-funded investigators writing protocols for Phase 2 and 3 clinical trials that require Investigational New Drug (IND) or Investigational Device Exemption (IDE) applications. TransCelerate BioPharma Inc., a nonprofit organization that works to accelerate research and development of new drug therapies, also recognized the need for a protocol template and released its Common Protocol Template during this same timeframe.

As the NIH-FDA protocol template attempted to synthesize input from multiple governmental organizations, we focused on this template in the discussion below.
The NIH-FDA protocol template provides structure and formatting suggestions, with definitions and instructional text. It is a Microsoft Word document containing headings for each required protocol section, accompanied with both instructional and sample text (as appropriate). In part, this template attempts to align relevant standards issued by the Centers for Medicare & Medicaid Services (CMS), Code of Federal Regulations (CFR), FDA, Department of Health and Human Services (HHS), ICH, International Organization for Standardization (ISO), NIH, Office for Human Research Protections (OHRP), and others. During the development of this protocol template, the NIH and FDA publicly released the draft template and solicited feedback from stakeholders from March 17, 2016, through April 17, 2016. The NIH reported that they received more than 200 comments from more than 60 respondents and that they used this input in the development of their final template, which was released for public use in May 2017. One of the authors and other colleagues contributed to this call for feedback.

In addition, the NIH introduced an electronic tool that uses an identical version of this template: the e-Protocol Writing Tool. This online tool is a user-friendly interface designed to collect all the relevant information that should be included in a protocol through a series of questions and fields to be populated for each of the headings and subheadings within the template. The fields can be populated with text and tables and are complete with features of word processing software, such as font formatting and the ability to add tables, images, and references. Once complete, the protocol can be exported as a Microsoft Word file. The tool is meant to allow for collaborative writing and review by investigators and other study team members.

Among the stated goals for the NIH-FDA template was alignment with ICH E6. The ICH E6 guidance addresses the broader aspects of clinical research under the umbrella of GCP. The ICH E6 includes protocol writing (as a unique section) but also outlines desired content for investigators’ brochures; defines essential documents for conducting clinical trials; and details the roles and responsibilities of clinical investigators, industry sponsors of clinical research, and IRBs.

A comparison of the sections of the NIH-FDA protocol template and the corresponding headings from ICH E6 are outlined in Table 1.

The NIH-FDA template hews closely to the requirements outlined in ICH E6. However, in some cases, aspects of the template may reflect interpretation of a requirement from a contributing body (eg, Unanticipated Problems—from OHRP within HHS interpretation of 45 CFR part 46) or “lessons learned” by the contributing authors (eg, Lost to Follow-Up).

Comparison of NIH-FDA Protocol Template with ICH E3 Guidance on Clinical Study Reports
At the outset of clinical protocol writing, the investigator and/or Sponsor should critically assess the study design, including the timing and importance of the assessments proposed. Overly complicated protocols can introduce challenges and burden for both the investigators and the study subjects, as well as unnecessary expense. Thus, an effective strategy is to consider how each study assessment will produce quality data that inform the development of the investigational product. Additionally, because the collected data are required to be reported in the CSR, how the protocol is written can influence the ease or difficulty of writing the CSR. Thus, mindfulness of the desired data output could guide the protocol author for how to obtain it. The correlation between the content of the protocol template and the required content of CSRs according to the ICH E3 guidance on writing CSRs is shown in Table 2.

Considerations for Application of NIH-FDA Protocol Template
While the protocol template introduced by the NIH and FDA was designed with NIH-funded investigators in mind, it has the potential to be widely applied in other investigator-initiated studies and studies sponsored by life science companies, particularly newer biotech companies that may not yet have standard templates for their regulatory documents. The template provides a robust framework for detailing the definitions, procedures, endpoints, and adverse events associated with clinical trials. However, there are some challenges and limitations with using the template that medical writers and investigators should consider. For example, the current template was designed for Phase 2 and 3 studies and may not be appropriate for other types of studies. However, the NIH has stated that it plans on expanding the e-Protocol Writing Tool to update the instructional and sample text to include studies that do not currently fit well in the protocol template, such as Phase 1 or behavioral studies. Another limitation of the template is that, although italicized text is used for instructional text, it can sometimes be difficult to distinguish between the instructional and sample text within the document. In addition, the template does not offer a structure or instructional text for protocol amendments.

For medical writers working within industry and intending to submit a protocol to the FDA, it is important to note that there are some headings within the protocol template that do not directly map to ICH E6 (eg, Screen Failures, Strategies for
Recruitment and Retention, and Lost to Follow-Up (Table 1). Within industry common practice, this information is typically part of a study manual or other training document outside of the clinical protocol, such as an investigative site training manual. When applying the protocol template for industry use, medical writers should consider how the template conforms to the evolving transparency landscape,4,9 which may influence the level of detail provided within a clinical protocol. Similarly, when using the data generated by the template or applying the template details to the CSR, writers need to be aware that some sections of the protocol template do not clearly map to the ICH E3 CSR template (eg, Lifestyle Considerations and Unanticipated Problems) (Table 2).

As of May 5, 2017, New Drug Applications (NDAs), Abbreviated NDAs, and Biologics License Applications must be submitted through the Electronic Submission Gateway by using standard electronic CTD (eCTD) format.10 By May 5, 2018, all Commercial Investigational NDAs and Master Files must be submitted using eCTD format.11 As these are FDA requirements, it should be noted that the template includes a font (Calibri) and formatting (shading, color, etc.) that are not compliant with the Portable Document Format (PDF) Specifications Guidance for Industry.11 Thus, prior to eCTD submission, the regulatory writer should modify the protocol to use only standard, unshaded serif-type fonts in all headings and paragraphs. In addition, appropriate styles should be used to insert caption headings and create active cross-references throughout the document.

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<tr>
<th>Section of NIH–FDA Protocol Template</th>
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<td>Section 2.1: Introduction (Study Rationale)</td>
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FDA, Food and Drug Administration; GCP, Good Clinical Practice; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; N/A, not applicable; NIH, National Institutes of Health.
Table 2. Comparison of NIH–FDA Protocol Template with ICH E3 (CSRs)

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Conclusions

The development of a clear and robust template by the NIH and FDA will greatly aid investigators and sponsors involved in clinical research. For investigators and sponsors who do not have an in-house template or resources for template development, this protocol template is a solid introduction to writing a thorough and thoughtful clinical trial protocol. Users should be aware that this protocol template is mostly aligned with ICH E3 and ICH E6, though there are noted differences. Furthermore, the protocol template has attempted to incorporate guidance from CMS, CFR, FDA, HHS, ICH, ISO, NIH, OHRP, and other influential sources. In this way, aspects of the template may differ from the goals of a potential industry user. Despite these limitations, this protocol template offers a working structure for NIH investigators and members of the life science industry and is an improvement over the broader protocol guidance offered by ICH E6. Notwithstanding limitations, alignment of protocol writing in academia and industry is a worthwhile goal and undertaking.

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References


And Laurie Endicott Thomas wraps up our clinical trials theme by sharing her opinion on why we need more natural intelligence in peer review.

But that’s not all!

In addition to these themed contributions, this issue also contains a pair of media reviews, a contribution in Practical Matters (Streamlined Notetaking: Writing Minutes and Meeting Deadlines, by Marie J. Temple, BA), another contribution In the Service of Good Writing, and AMWA News . . . including details of our new governance structure and our new president’s inaugural address.

I hope you will enjoy this special theme issue as much as we have enjoyed putting it together for you!

Yours in AMWA,

—Jim

References
The word may look like a spelling mistake, but it actually represents a new paradigm in clinical research—or, more precisely, a new and more nuanced way to look at clinical studies. With the new term comes a fully worked-out set of concepts that will change the way we perform clinical studies. Estimands are not really a statistical idea, but rather a concept that pertains more generally to the medical evaluation of clinical trial results.

Clearly the word “estimand” is related to “estimate,” a term that has a special meaning in the statistical analysis of clinical data. Counterintuitively, it does not mean an approximate judgment or an informed guess; rather, an “estimate” is the result of a defined calculation. The term is used to highlight that all clinical research can do in the evaluation of a clinical endpoint (e.g., mean level of blood sugar) is to estimate the true value in the population. That is to say that even large studies (e.g., in diabetes) can only return the results for the sample of patients in the study, not for all patients with diabetes. In that sense, all computations in clinical studies are estimating the true value in the population (which can never be known). Now, an “estimand” is a clinical entity or parameter that is estimated by performing a clinical study; in other words, an “estimand” is the target of estimation. The aim is to capture this target of estimation more precisely. The concept of estimands is the subject of lively discussion in the statistical community. It is outlined in a new Addendum to the International Council for Harmonisation (ICH) guideline on statistical principles for clinical trials, ICH E9 (ICH E9 [R1] draft, 30 August 2017).

Randomization and Intercurrent Events
Given the effort and cost involved in conducting a clinical study, we want to be sure it produces objective results that have not come about by any systematic error that shifts the results in a certain direction. A central method to avoid bias is randomization. By randomly assigning the patients in a study to 2 parallel treatment groups, we ensure that the 2 groups are comparable at the study start. Then we can safely ascribe any effect we see by the study end to the treatment we are investigating. Well, at least that is the common belief. In fact, however, that last statement is only true if the initial randomization is maintained during the study—and this is often not the case because of “intercurrent events.” These are any events that happen to patients during a study and that may affect the results. In particular, the following intercurrent events are important: patients die, they stop taking the study medication because they experience side effects or because they feel they are receiving no benefit from the treatment, or they take additional medication that will interfere with the efficacy endpoints. In any group of patients, the diversity of individuals will mean that different patients experience different intercurrent events at different points in time (Figure 1).

Randomization ensures that the variation among individuals is similar in the 2 treatment groups at baseline. However, each individual patient is likely to experience different intercurrent events depending on which treatment he or she receives. This may result in differences in the rates and timings of intercurrent events between the treatment groups. If we exclude patients who experience intercurrent events from the analysis then we may, at the time when the study results are determined, no longer have treatment groups that are comparable. This is why, until now, industry guidance (ICH E9) has recommended performing an intention-to-treat (ITT) analysis on all randomized patients, or at least as close to all randomized patients as possible. The new Addendum to ICH E9 recognizes that this guiding principle has its limitations.

Intercurrent Events: A Worked Example
The potential effect of intercurrent events is best illustrated...
with an example. Assume we have a study in patients with type 2 diabetes and we want to compare 2 treatment groups: 1 group receives wonderdrug (WD) and the other group receives a placebo, both in addition to background therapy. We want to measure the treatment effect by comparing the reduction in hemoglobin A1c (HbA1c), a long-term marker of blood glucose levels, from study start to study end (for our example, after 26 weeks of treatment).

In trials in type 2 diabetes, it is standard to make rescue medication available to patients whose blood glucose levels are not adequately controlled with the study treatment. This means that patients whose blood glucose exceeds a predefined limit are allowed to take additional antidiabetic medication alongside the study treatment and background therapy. This is done because high blood glucose increases the risk of complications such as cardiovascular problems or damage to the nerves, kidneys, or eyes. It would not be ethical to require these patients to continue in the trial with excessive blood glucose levels; thus, rescue medication is permitted.

However, from a scientific point of view, the use of rescue medication in a trial complicates evaluation of the treatment effect. The question is what to do with the data when patients start taking rescue medication. Do we continue to take efficacy measurements in these patients, and do we include such measurements when we calculate the treatment effect?

Clearly, our decision will have consequences for how we need to interpret the results. If we use the HbA1c data from patients who have started rescue medication, then the measured values will reflect both the effect of the study treatment and the effect of the rescue medication. We will end up with a comparison of WD plus rescue medication and placebo plus rescue medication. If WD is effective at lowering HbA1c, then we can expect that the use of rescue medication will be more frequent in the placebo group. The treatment effect we estimate at Week 26 will then be the difference between the effect achieved by WD, occasionally with additional rescue medication, and the average effect seen in a placebo group in which many patients are taking rescue medication known to be effective in reducing HbA1c.

As a consequence, we will lose precision with regard to the effect of WD alone because the effect of WD compared with placebo will be blurred by the effect of the rescue medication. Our estimate of the treatment effect is also likely to be a very conservative one. This means we may end up with a modest difference between the treatment groups that underestimates the true difference. On the other hand, we will obtain a result that reflects clinical practice “out there” because it is very likely that some patients in clinical practice will require additional medication, whether they are taking WD or other standard antidiabetic medications. Such an analysis is called a “treatment policy estimand,” and this analysis is likely to be of particular importance to payers and reimbursement agencies who want to know the effectiveness of WD in the real world. This is also sometimes called an “effectiveness analysis.”

Using an estimand based on treatment policy also represents an analysis strictly according to the ITT principle, as recommended by ICH E9. Analyzing all patients according to the treatment they were randomized to, rather than the treatment they actually received, helps to ensure that estimates of treatment effect are unbiased and that statistical tests produce valid results. In 2011, a US Food and Drug Administration reviewer used precisely this argument to suggest that the most valid way to analyze data for the new antidiabetic drug dapagliflozin was to use all data, including values from patients taking rescue medication, in the statistical model.

If, alternatively, we stop collecting the data of patients taking rescue medication, or ignore any data collected after rescue medication in the analysis, we may end up with a large proportion of missing data and have only a small number of patients with complete assessments. When it comes to the patients who used rescue medication, we then have various options. We can use the last value before rescue medication as a substitute for the Week 26 value (ie, the last-observation-
carried-forward [LOCF] imputation method). Alternatively we can exclude these patients from the analysis altogether and perform a completers analysis using only the data from patients with complete observations and no rescue medication use. Thirdly, we can employ sophisticated statistical modelling techniques (eg, mixed models for repeated measures [MMRM] or multiple imputation [MI]) that use the available data from all patients before rescue medication to model the results we would likely have seen for all patients at Week 26 if no patients had used rescue medication. Compared with the treatment policy estimand, these approaches have the potential to give us better estimates of the efficacy of WD itself. This may be of particular interest to a patient or her treating physician, as they both want to know what effect the patient can expect if she takes WD as prescribed.

The New Approach: Estimands

These different ways of dealing with the intercurrent event “rescue medication use” represent different estimands and provide answers to different scientific questions. Rather than arriving at a particular estimand implicitly and haphazardly as a consequence of choices about data collection and statistical analyses (as has tended to be the practice up to now), looking at the problem in terms of estimands enables us to consider explicitly the various scientific questions that the trial data could be used to address. We can then choose which questions are the most meaningful in our clinical context and which are most relevant for patients, their doctors, regulators, and payers. A single estimand is unlikely to meet the different needs of all these stakeholders. In many cases, the estimand of interest will not fully reflect a strict ITT analysis.

Compared with endpoints as currently defined in clinical trial protocols, estimands are more detailed definitions of the quantity to be estimated and comprise 4 interrelated attributes:

- **Population**: which patients are targeted by the scientific question?
- **Variable/endpoint**: which quantity needs to be obtained for each patient to address the scientific question?
- **Intercurrent events**: how are these to be accounted for to reflect the scientific question?
- **Population-level summary**: which summary statistic (eg, mean or median) for the variable will be the basis for comparing the treatments?

In our diabetes example, many different estimands are possible, and the situation would become even more complicated if we were to consider other kinds of intercurrent events (eg, deaths and discontinuations due to adverse events) as well as rescue medication use. Estimands could also be defined for answering questions related to safety (eg, how long are patients able to remain on the treatment before discontinuing due to adverse events?).

To keep things simple, we will look at just 3 estimands for the treatment effect that deal with rescue medication use in different ways. All 3 estimands define the same patient population (ie, the one in which it is planned to use WD after approval, as reflected by the trial inclusion and exclusion criteria), and all use the mean difference in HbA1c values between the treatment groups as the “population-level summary.” The differences among the estimands lie in the precise definition of the variable to be used as primary endpoint and in the handling of the intercurrent event: use of rescue medication.

<table>
<thead>
<tr>
<th>Estimand</th>
<th>Endpoint Variable</th>
<th>Intercurrent Event</th>
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| **Estimand 1**  
(treatment policy) | Change in HbA1c from baseline to Week 26 | Consider all data, regardless of rescue medication use |
| **Estimand 2**  
(on treatment) | Change in HbA1c from baseline to last value before rescue medication | Data after initiation of rescue are not considered |
| **Estimand 3**  
(hypothetical) | Change in HbA1c from baseline to Week 26 | Data after initiation of rescue are modelled, as if no patients took rescue medication before Week 26 |

**Estimand 1** is the “treatment policy” estimand corresponding to an ITT analysis, as discussed above. This estimand requires that all available values are used to estimate the treatment effect at Week 26, regardless of whether patients have taken rescue medication (Figure 2).

**Estimands 2 and 3** attempt in different ways to capture the effect of WD itself without “blurring” it by the use of rescue medication.

**Estimand 2** considers all data up to the time when rescue medication is initiated (Figure 2). It estimates the effect of the treatments until rescue was needed or until Week 26 for patients who did not need rescue medication. The use of rescue medication is likely to be different between the WD group and the placebo group. If WD works, few patients will need rescue medication, and those who do need it are likely to need it late in the trial. Conversely, in the placebo group, many patients will need rescue because their background medication will not control blood sugar effectively, and they are likely
to need to initiate rescue medication soon after the study start. That means that in the placebo group, for many patients, the last recorded HbA1c value before rescue will be high. In the WD group, the majority of patients are likely to have lower values of HbA1c at Week 26 because they do not need rescue medication. This estimand will therefore likely overestimate the effect of WD.

In effect, Estimand 2 corresponds to an LOCF analysis of the kind that has often been used to deal with rescue medication use in type 2 diabetes trials. Although widely used, Estimand 2 will result in an estimate that is biased and difficult to interpret.

**Estimand 3** provides a very different and less intuitive solution. With this estimand we estimate the treatment effect that would be seen if no patients took rescue medication (Figure 2). In all probability, some patients in the trial will achieve control of their blood glucose with the randomized treatment and others will need rescue medication. The analysis for Estimand 3 will include only values from patients who have not (yet) started rescue medication; HbA1c values will be counted as missing from the point when a patient starts rescue medication. An appropriate method for handling missing data through statistical modelling (eg, MI or MMRM) will need to be used. The resulting estimate will reflect both what actually happened in patients who reached Week 26 without rescue medication and what the data collected before rescue medication suggest might have happened by Week 26 in the remaining patients if they had continued without rescue medication. This estimand is hypothetical at the level of a group of patients.

However, with the use of an appropriate statistical model, Estimand 3 is likely to provide a less biased answer than Estimand 2 to the question that is crucial to individual patients: “If I take this drug as part of my treatment regimen, without adding any further drugs, what effect can I expect to see after 26 weeks?”

**Estimands and Trial Design**

We have tried to make it clear that estimands will help clinical researchers to formulate more clearly what they really want to get out of a clinical study. The traditional approach did not adequately take into account the intercurrent events and their effect on the primary endpoint measure. As demonstrated in the example of rescue medication use in a type 2 diabetes trial, depending on how we account for such events, we may be estimating the effect of the study drug itself, or we may be shifting conceptually to an evaluation of treatment policy.

In the past, it often happened that clinical researchers tried to elucidate what exactly they had evaluated after a study had been completed. This is surely not the ideal situation because very little can be done after the fact. For example, once the decision has been taken not to collect data after initiation of rescue medication, this cannot be reversed after trial completion.

The paradigm shift introduced by the idea of estimands involves reversing this order (Figure 3). Clinical researchers first need to think about the objective of the trial (ie, what the trial is meant to show). This objective could be to demonstrate the effectiveness of a drug in reducing HbA1c in patients with type 2 diabetes. Researchers then need to consider the precise scientific question of interest to be addressed and choose an estimand that answers this question. The main measurement (eg,
HbA1c) and the main endpoint variable (change in the level of HbA1c after 26 weeks of treatment) will be defined as aspects of the estimand, alongside the target population and method of accounting for intercurrent events. Usually there will be several objectives in a study: a primary objective and several others. Once the estimands have been defined, the trial can be designed in such a way that all the necessary data are collected, and the statistical analysis methods can be chosen to address the estimands of interest.

Choosing the appropriate estimand for a given trial objective is primarily a medical and clinical question and not a statistical one. Indeed, some prominent statisticians go so far as to proclaim that estimands are not a statistical topic! In any case, discussion between medical and statistical experts will be necessary to ensure that the estimands chosen reflect questions of clinical interest and can also be estimated statistically.

In good clinical research, it was always the case that researchers started the planning of a trial by defining its objective. They also chose an endpoint and a statistical methodology. However, the potential influence of intercurrent events on the interpretation of the endpoints was rarely considered. Estimands close the gap between the trial objective and the main estimates by clarifying exactly how intercurrent events will be considered or how the interpretation changes when those events are considered in different ways.

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### READING LIST


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### STATISTICALLY SPEAKING

**Spending the Alpha: The Problem of Multiple Testing**

By William Sinkins, PhD / Scientific Director, ProEd Communications, Inc., Beachwood, OH

The randomized, double-blind, clinical trial is considered the gold standard for evaluating the safety and efficacy of new medications. In an interventional trial, eligible patients are randomly allocated to 1 of 2 or more different treatment groups, and their medical course is followed to evaluate the safety and efficacy of the potential new therapy. Depending on the therapeutic area and nature of the intervention, trial investigators may select one of a number of different endpoints as the primary outcome of the trial. A clinical study is statistically powered based on the primary end point and, therefore, can only reliably evaluate that single question. But because a single disease may have multiple, complex effects on patients, studies often evaluate secondary and exploratory end points as well. However, performing multiple statistical tests on the same data set must be approached with care to avoid reaching incorrect conclusions.

The purpose of statistical analysis is to test the null hypothesis (there is no difference in outcome between the treatment groups) compared with the alternative hypothesis (the new treatment is more effective than the comparison treatment).\(^1\) If the clinical trial has a favorable outcome for the sponsor, the null hypothesis will be rejected and the new treatment may...
be considered for regulatory approval. When performing statistical comparisons, there are 2 major potential errors. Type I error, or false positive, has occurred if the null hypothesis is rejected even though the new treatment is not better than the comparison; in other words, the difference between treatment groups was observed due to chance. Type II error, or false negative, is a failure to reject the null hypothesis even though the new treatment is better. In drug development, Type I error is the more serious condition, as it may put the public at risk of exposure to adverse events and an ineffective treatment. Type I error is referred to as alpha and, by convention, is held to a maximum value of 5%. The measure used to evaluate the experimental data with respect to the null hypothesis is the \( P \) value. If the \( P \) value is less than the maximum Type I error rate of 5% (\( P < 0.05 \)), the null hypothesis is rejected and the trial is considered to be a success.

The foregoing discussion is in the context of a single comparison, namely evaluation of the primary end point. Testing multiple comparisons presents a challenge to the trial statistician who is trying to control Type I error. If alpha is held at 5%, performing multiple comparisons on the same data set increases the risk of a false positive result. This inflation of the Type I error rate is known as the multiplicity problem. If 10 individual analyses each have an error rate of 0.05, the probability of a false positive is greater than 40%. There is frequently good reason to conduct multiple comparisons. Secondary end points, subgroup analyses, and interim analyses of the primary endpoint are examples of commonly performed and clinically relevant comparisons. Interim analyses may be performed to allow an independent data monitoring committee to evaluate the likelihood the trial will achieve its primary end point. Trials may be stopped early for benefit if the interim look at the unblinded results makes it apparent the new treatment is clearly better than the control arm, or they may be stopped for futility (little to no possibility of achieving the primary end point) to prevent continued exposure to an ineffective treatment. When dealing with multiple comparisons, it can be helpful to think of alpha as an allowance of a fixed amount of money, with some alpha being spent whenever a comparison is made. A number of methods have been developed to spend the available alpha sparingly during interim analyses. These techniques, such as those developed by O’Brien and Fleming, permit interim analyses to be performed but still allow for a statistically meaningful evaluation of the primary end point if the trial is not terminated early.

Large clinical trials are a rich source of data, and clinicians are understandably interested in identifying those patients who stand to benefit from treatment. Individual subgroup analyses are frequently used to test for associations between clinical characteristics and response. A conservative approach to control Type I error under these circumstances is the Bonferroni correction, in which alpha is divided by the number of comparisons. For example, in an analysis of 10 individual subgroups, the value of alpha would be changed to 0.05/10, or 0.005; \( P \) values >0.005 would not be considered statistically significant. An alternative approach was developed by Benjamini and Hochberg to control what they referred to as the “false discovery rate.” In this procedure, all \( P \) values from the multiple comparisons are ranked from smallest to largest, then each is compared with a calculated Benjamini-Hochberg “critical value” \((\text{illim} \times q^*)\), where \( i \) is the rank, \( m \) is the number of comparisons, and \( q^* \) is the false discovery rate. The largest \( P \) value that is smaller than the critical value is considered statistically significant, as are all smaller \( P \) values in the analysis.

Medical writers and editors should be aware of the multiplicity problem associated with the analysis of clinical trial data. If multiple comparisons were performed, were they appropriate for the study and disease setting? Were multiple comparisons prespecified in the study protocol or analysis plan? Were appropriate measures used to control the Type I error rate? Failure to adjust for multiplicity may lead to overstated statistical significance and unsubstantiated estimates of efficacy. The conclusions of the trial should be evaluated critically in light of the potential pitfalls associated with multiplicity. For further reading on this topic, please see the series of papers by Pocock and colleagues listed below.

References
A clinical trial is the sole way that new medicines come to market. Mastering the process of finding, engaging, and activating patients for enrollment into a clinical trial is a key success factor for all biopharmaceutical companies developing new treatments, yet many companies often struggle to find the required clinical trial participants within a given timeline. These delays result not only in additional development costs, but also—in more importantly—in the actual delay of innovation and treatments.

On any given day, there are more than 6000 clinical trials involving more than 1 million patients running just in the United States. The total cost of a clinical trial is $13 million for Phase 2 and $20 million for Phase 3. The industry spends more than $5.9 billion in annual expenses on patient recruitment services. In fact, roughly 80% of clinical trials fail to meet enrollment timelines, and approximately one-third (30%) of Phase 3 study terminations are due to enrollment difficulties. In addition, 15% to 20% of sites never enroll a single patient.

So how does a company reach prospective study participants in a meaningful and compliant way that spurs real action?

Online. And, in particular, via social media channels.

The average person checks social media 17 times a day—that’s nearly once every hour. During this time, they check their messages on Facebook, read news on Twitter, and share photos on Instagram. They also sometimes seek information about and support for their disease.

What if we could use just one of those 17 daily check-ins to reach them with clear and actionable information about a relevant clinical trial?

At Seeker Health, we’ve been designing and deploying institutional review board (IRB)-compliant clinical trial campaigns for serious and even rare diseases centered on social media marketing. Our process begins with a social media campaign, which takes potential participants to a powerful prescreener built specifically for that trial and then ingests the submissions into a patient-led management system called the Seeker Portal. Via this purely digital process, we’ve accelerated recruitment for dozens of clinical trials investigating new medicines for serious diseases.

Why Social Media Marketing is So Important To Clinical Trials

Efficient Targeting

Social media provide a level of efficient targeting that would rarely be accomplished by any other media. An advertisement on television, a bench advertisement, or the bus stop poster can never guarantee targeting to a certain demographic, yet a Facebook advertisement can be targeted with precision. For example, when we are recruiting for a clinical trial for women of childbearing age who suffer from uterine fibroids, as we deploy a campaign on Facebook, we can ensure the demographic is targeted to women of childbearing age. Even more precisely, we can hyper-target to the group of women of childbearing age who have behaved on the platform in a manner that demonstrates an interest in this condition.

Measurability

With social media advertising, we can measure the number of users who view an advertisement, click on it, and take an action on the website we use for prescreening. Then, via the Seeker Portal, we can follow the progress of that potential participant, all the way to screening and enrollment.

Actionable Education

In our research with patients, we often hear how frustrating it is to find a clinical trial but, when that trial is found, to be unable to press a button to self-identify for participation. At
Seeker Health, we focus on capitalizing on patients’ desire for easy access to the right information, as well as the ability for potential participants to take action. Upon seeing an advertisement that has a prescreener, the potential participant can take a definitive step toward being considered for participation in the clinical study.

Correct Demographic
The demographic in social media networks, like Facebook, is usually in the sweet spot of what biopharmaceutical companies and researchers are looking for in trial participants. Eighty-four percent of people who check Facebook are between 30 and 49 years of age, and 72% are between the ages of 50 and 64. For a clinical trial for breast cancer with a genetic modifier, we have found the highest degree of engagement on Facebook in women 50 years of age and higher.

User Disposition
A user on Facebook need not be looking for a clinical trial to see our advertising for a study. Instead, the user may be looking at his or her friends’ posts when our targeted advertisement appears on his or her news feed. We think these targeted advertisements are critical to the success that we are seeing in these campaigns. If we wait for potential participants to search for a clinical trial, we diminish our chances of finding them. In addition, if we wait for them to log in to a specific disease/patient community, we also diminish our chances of finding them. Instead, targeted advertisements allow us to intersect with potential participants on Facebook or Instagram, where they are already logged on and active most days.

How To Use Social Media For Clinical Trials
Like any worthwhile effort, an effective campaign requires a solid strategy and great execution. Message and creative development are important, as is having multiple options to test for optimization of the campaign. The following are some key considerations:

Promote the Trial Opportunity
The language of the advertisement for a clinical trial should focus on the opportunity to participate in the study of an investigational medicine (Figure). The advertisement should not make any efficacy or tolerability claims about the investigational medicine. In addition, the advertisement should not contain pointed language that could make the viewer feel targeted or identified. A great advertisement simply lets the user know that a clinical trial for an investigational treatment for a specific condition is taking place and to click on it to learn more.

Use Patient-Friendly Language
Clinical trials are full of technical language, which the average person generally does not understand. In our market research with patients, we often test language to describe clinical trials and learned that, ideally, we should be striving for a sixth-grade reading level. Technical words, such as “subject” to refer to a participant or “double-blind,” should be avoided and instead replaced with common words or definitions.

Obtain Institutional Approval
All of our campaigns to promote clinical trials receive IRB approval prior to being launched to patients. This is mandatory. Institutional review boards like to see the complete marketing package, including the controls that will be enacted for any social media campaigns.

An advertisement on television, a bench advertisement, or the bus stop poster can never guarantee targeting to a certain demographic, yet a Facebook advertisement can be targeted with precision.
Provide a Prescreener
For each clinical study, we design an online prescreener to help qualify patients on the basis of their responses. The prescreener should contain only a handful of well-written questions that provide a first level of screening against the study’s inclusion/exclusion criteria. These questions may ask whether the patient has been diagnosed with the condition, has undergone certain types of confirmatory testing and is willing to participate in a clinical trial. In addition, the prescreener should ask the user to legally opt into participating in communications related to considering enrollment in this clinical trial. Once participants sign up, thorough follow-up includes an email, text message, and/or phone call to continue pre-screening or schedule for a screening visit at the closest clinical trial site.

Design Controls and Stay Compliant
Because these advertisement products are deployed via social media channels, users are not only able to share the advertisements but are also able to include comments. From a compliance perspective, comments introduce issues. The comments may include user-generated misinformation, which remains attached to the bottom of the advertisement as it is shown to the next user. At Seeker Health, we resolve this by using a comment-suppression tool on Facebook Newsfeed Ads and by disabling comments on the Instagram advertisements prior to launch. With this approach, we’ve received 100% IRB approval of our campaigns. Comments should also be monitored for the rare possibility that an adverse event (AE) is reported by a trial participant. In the rare case an AE appears, the sponsor’s reporting procedure should be followed to begin an investigation.

Evaluating the Most Effective Platform
For biopharmaceutical companies that want to optimize clinical trial recruitment, the following social networks are the most effective marketing platforms:

Facebook
With more than 2 billion monthly active users, Facebook is the world’s biggest social media platform. It’s a great place to promote clinical trials, as there are multiple advertisement services, including videos and pictures. Here at Seeker Health, we help clients select the right demographics on Facebook on the basis of prospective patients’ behaviors and interests. We can also suppress user comments on advertisements to mitigate risk and stay compliant.

Instagram
Instagram has 700 million active monthly users and shares targeting capabilities with Facebook. Companies can advertise their clinical trials on this platform by using pictures with text. Six in 10 adults between 18 and 28 years of age use Instagram, so companies typically use this medium to advertise clinical trials for episodic conditions like acne or chronic ones like rare genetic disorders. Targeting demographics on Instagram is refined and efficient.

Twitter
With 328 million users, Twitter is a popular social network for businesses in all niches. This is an effective way to communicate with patients, post corporate updates, increase the visibility of your medical facility, and attract industry leaders. You can also use hashtags in your Twitter posts to increase referrals and sign-ups.

Snapchat
Snapchat only launched in 2011, but this social network has already garnered a loyal customer base. In fact, 166 million people use this platform every day—and many of them are under the age of 30. On Snapchat, you can create Stories for advertising purposes and increase patient engagement and enrollment.

Accelerating Clinical Trial Enrollment
Recruitment for clinical trials via social media is on the rise. In one study, 9 out of 14 medical research companies planned to use social media to boost patient enrollment. And yet, research suggests that 80 percent of clinical trials in the United States are delayed by at least 1 month because of low enrollment. Social media marketing can help accelerate clinical trial enrollment, which ultimately can help bring medicines to patients earlier.

Sandra Shpilberg is the Chief Executive Officer and Founder of Seeker Health, a digital health company innovating the process of clinical trial recruitment using technology. More information about Seeker Health is available at www.seekerhealth.com.

References
CASE STUDY
Clinical Trial Recruitment for Breast Cancer with Genetic Modifier

Genetic Modifier
A large, global pharmaceutical company enrolling a Phase 3 clinical trial in breast cancer with a genetic modifier engaged Seeker Health to create an engaging social media campaign to accelerate genetic testing, participant identification, and clinical trial enrollment.

The Challenge
Our challenge was to educate women with breast cancer about the availability of this clinical trial and the opportunity to receive genetic testing by using social and digital media, with the ultimate goal of accelerating clinical trial enrollment.

The Approach
We developed a compliant Facebook campaign focused on a subset of the Facebook user population that had previously taken actions denoting an interest in breast cancer. To optimize the campaign outcomes, A/B testing of images (comparing two versions to see which one performs better), text, and targeting were implemented. We deployed our tool for complete comment suppression on Facebook Newsfeed Ads to mitigate risk of user-generated misinformation.

The Results
This social media campaign accelerated patient enrollment in this clinical trial by 3 months, a very significant improvement, given that costs per month of trial operation run in the millions of dollars. Specifically, 9419 US patients engaged via Facebook advertising to begin online prescreening, and 866 US patients completed online prescreen and qualified for follow-up by clinical trial sites. The results were so impressive that this company engaged us to replicate this program for a clinical trial in prostate cancer.

Someone just asked you to take minutes at a meeting. You will need to document a group's decisions, recommendations, rationales, and actions. What do you do? How do you prepare? At the US Pharmacopeial Convention (USP), Technical Writers write minutes for as many as 6 meetings of our scientific groups in a month. A meeting minutes writing assignment can be a daunting responsibility. However, with preparation and organization, this task can be less stressful.

Meeting minutes document the business conducted at a meeting. They provide a record that a meeting took place and the meeting's outcomes. The writer's role is not to capture every word, but to focus on the group's decisions and action items that will help move the business forward.

Before the Meeting
Take Time to Prepare

Before the meeting, block time on your calendar to read background materials before the meeting (1 day) and to write the minutes after the meeting (1 to 2 days, depending on the length of the meeting).

Read through the briefing materials, including minutes from previous meetings, to become familiar with terms and concepts. Ask for a copy of the agenda. Then, meet with key staff members to review the agenda and objectives. The clearer you are about the proposed content, the easier it will be to write the minutes. A preliminary meeting can also help identify deliverables and the intended audience, as well as any potentially hot topics, motions and/or decision points, or confidential subjects. Also, key reviewers of the minutes can be assigned and a schedule established to share with collaborators, including due dates for review. This enables reviewers to know when to expect the draft.

Develop a Template

Write as much of the minutes ahead of time as possible. “Boilerplate” language should be included for standard items (ie, opening statements, approval of the agenda, and approval of prior meeting minutes). This can be facilitated by establishing a simple template, which can be readily adapted for new documents. The template could include the following information:

- Meeting title and organizer
- Meeting date, time, and location
- Expected attendees
- Name of facilitator
- Items on the agenda
- Other business
- Date of next meeting
- Adjournment time

Sample templates can be found online (e.g., www.agreatmeeting.com, www.effectivemeetings.com or www.smartsheet.com).

Develop a Style Guide

A style guide can help save time and eliminate inconsistency. It should include common abbreviations, numbering conventions, and desired punctuation. The style guide can also be updated periodically.

During the Meeting

Write Effective, Efficient Raw Notes

Write raw notes (short descriptive or summarized jottings) in a copy of the minutes template developed before the meeting. As to “who” and “what” to record, record the attendees (include the names of those who cannot attend) and discern what's important, highlighting key points (in bold or in color) throughout the notes. Identify decisions, recommen-
dations, and action items. Copy the action items to a list at the end of the raw notes or into a separate document. A best practice is to read the action items aloud at the end of the meeting, or even project them on a screen if available, to offer attendees an opportunity to clarify them before the meeting adjourns.

Speak Up! Interject and Clarify
If unsure about the wording of a motion, decision, or recommendation, politely interrupt and ask for clarification before the group moves on to the next topic. If needed, read what you have noted and ask if you have recorded it accurately. This is especially important for motions. Clarify and restate motions before they are voted upon to be sure all who are voting understand the exact wording of the motions. Then, clarify actions and next steps resulting from adopted motions.

If you have questions about facts or important statements made during the meeting, ask content experts to clarify them quickly during breaks, or highlight them in your notes so you remember to ask for clarification later.

Backup and Save
Save the raw notes frequently throughout the meeting. It is suggested to save consecutively numbered versions. This way, if any part of the document is inadvertently erased, it can be recovered.

After the Meeting
Email the raw notes to yourself as well as to another person as a backup. Save the raw notes to a drive that is accessible to other staff in case an emergency arises and you are unable to write the minutes.

From Draft to Distribution

Review the Raw Notes
Don’t edit the raw notes; rather, mark them up for use as an excellent content source for writing the minutes. Print the raw notes, read through them, and note key topics in the margins.

Write the First Draft
• Write the first draft (in the template) soon after the meeting, while the content is still fresh in your mind.
• Support all action items, decisions, and recommendations with rationales.
• Summarize the discussion.
• Focus on content, not on spelling or grammar.
• Write quickly, then stop.

Revise: Substantive Editing
• Be sure the information is relevant to the audience.
• Clarify the focus, meaning, and logic of key points.

• Organize paragraphs in a logical order that supports the action items or decisions.

Depending on the length of the meeting, allow 1 day to write the first draft and 1 day to copyedit.

Copyedit
Make several passes through the document, focusing on the following:
• Spelling and grammar: Check spelling and grammar at this time. Also verify the spelling of names, acronyms, websites, hyperlinks, book titles or chapters, etc.
• Style: Be sure the draft conforms to the style guide (eg, consistent formatting, fonts, spacing, indents, bolding).
• Tone: Check the tone of the draft. If the company hosting the meeting has a formal style, avoid the use of emotional language.
• Queries: If you have questions, try to answer them yourself. If this is not possible, insert comments/queries for content experts to answer.

Ask a colleague to proof the minutes before sending for content review.

Content Review
Send the draft of the minutes to the designated reviewers. If using MS Word, request that any edits be made using Track Changes. Specify the date that edits are needed. Send reminders when edits are late, and follow up by phone or in person. Always keep your supervisor apprised of the status.

Complete and Distribute
Finally, incorporate and copyedit all content edits, obtain necessary approvals, and distribute the draft minutes to attendees. Be sure to include any materials distributed at the meeting.

Conclusion
Effective minutes provide an accurate record of the decisions and action items of a group meeting. With preparation and organization, the responsibility of the minutes-taker can be less intimidating and even rewarding.

References
Clinical Trial Data Sharing Statements Required by ICMJE in 2018

By Kristina Wasson-Blader, PhD, ELS / Editor-at-Large; Clearly Communicating Science, LLC, Orchard Park, NY

During the last 20 years, significant strides have been made toward developing best practices for publishing clinical trial results, and the latest focal point of these best practices is data sharing. In January of 2016, the International Committee of Medical Journal Editors (ICMJE) published a proposal to establish the sharing of deidentified participant data from clinical trials as “the norm.”

However, the Editor-in-Chief, Dr Jeffrey Drazen, and Deputy Editor, Dr Dan Longo, of The New England Journal of Medicine (NEJM) were quick to point out that such data sharing may have two unintended and negative consequences. The first concern is the potential for use of individual participant data in systematic analyses without a thorough understanding of the protocols used to generate the data. The second concern was more headline grabbing and generated the hashtag “#researchparasites.” Drs Drazen and Longo suggested that some researchers felt that “research parasites” (aka data scientists) will emerge from this broad sharing of data. What Drs Drazen and Longo failed to recognize is that data scientists had been working with large sets of data for years, especially in the genomics field.

Given a chance by a contributor at Forbes to clarify his opinion on data scientists, Dr Drazen did not retract the original comment; however, he wrote an editorial for NEJM in May of 2016 in support of the ICJME recommendations on data sharing, provided appropriate systems are in place to release trial data within 6 months of publication within NEJM. He admitted that data scientists can improve human health but also stated that participant data from clinical trials are among the highest-quality data in medicine and should be used responsibly.

With this focus on the ethical obligation to responsibly share participant data generated by clinical trialists, ICMJE released their statements on data sharing in July 2017. The ICMJE members recognized that substantial challenges still exist to preclude the ability of clinical trialists and their sponsors to release participant data, and thus has stated that data-sharing statements will need to be included within manuscripts submitted to member journals beginning on July 1, 2018. Those statements will need to address 5 key items (see box). In addition, clinical trials that begin enrolling participants on or after January 1, 2019, must include data-sharing plans within their trial registration.

**Items Needed in Data-Sharing Statements**

- Whether deidentified participant data, including data dictionaries, will be shared
- Whether additional documents (eg, study protocol, statistical plan analysis) will be shared
- When the data will become available
- How long the data will be available
- What criteria will be used to establish access to the data (eg, who can access it, what types of analyses can be performed, and how will the investigators access the data)

Even with this clear path forward to increase the medical value of participant data from interventional clinical trials, ICMJE acknowledges that several issues remain unresolved. These include establishing transparent processes for data requests, providing appropriate scholarly credit for those who acquired the data, and data archiving. Guidance on these issues will need to be provided soon to ensure clinical trial manuscripts meet these recommendations by the 2018 deadline.

**References**

In Peer Review, We Need More Natural Intelligence

By Laurie Endicott Thomas, MA, ELS

Artificial intelligence could amplify the natural stupidity that often occurs during the peer-review process. I have seen reviewers automatically reject good articles for stupid reasons. A computer could automatically reject an article for stupid reasons much more quickly and efficiently.

Rather than trying to spend less time on peer review by having a machine do the work,1,2 editors actually should be spending more of their time on peer review. In particular, editors should review the reviewers’ reviews and should pay attention to authors’ rebuttals. For example, shortly before the fifth edition of the American Psychiatric Association’s Diagnostic and Statistical Manual (DSM-5) was published, I wrote an article that explained that the diagnoses of conversion disorder and somatization disorder should never have been included in the third edition (DSM-III) because they violated the guiding principle of the DSM-III: these diagnoses are based on unfounded speculations about etiology, as opposed to providing a case definition of a clinical syndrome. The reviewer at one journal said that my article should be rejected because conversion disorder is not an etiologic diagnosis. He or she then cited an article to support that statement. Ironically, that article said in the very first paragraph that conversion disorder is an etiologic diagnosis. I pointed out that flaw in the reviewer’s reasoning to the editor, but the editor was unfazed by my argument. The reviewer had rejected the article, and the reviewer’s decision was final. After my article was eventually published in Medical Hypotheses,3 I sent a copy to Allan Frances, who chaired the committee that compiled the DSM-IV. He then blogged about the article on the Psychology Today website,4 arguing that what I was saying was true and important. In other words, the editor at the original journal relied on a nonsensical review and thus missed the opportunity to publish an important article.

When I told this story to a friend of mine who does research in the social sciences, she had a similar story. She had done some initial research to validate a model, and then she did further research that applied the model. However, an article about her later research was rejected. The reviewer complained that the author did not understand the model and urged the author to read the earlier articles on the subject. Because the reviewer was blinded to the author’s identity, the reviewer had no idea that he or she was, in fact, urging my friend to read her own work. Yet again, the editor stood by the reviewer’s decision to reject the article, even though the reviewer’s opinion was clearly stupid. Fortunately, another journal published my friend’s article.

Let me be clear: not all work that is rejected for stupid reasons is good enough for publication. However, articles that say something that is unorthodox, unexpected, or politically or commercially inconvenient are particularly likely to be rejected for stupid reasons, regardless of how important that information may be.5 One cause of this problem is the natural fallibility of human beings. Another is the tendency for our educational institutions to focus on promoting the memorization of facts and doctrines rather than on helping people cultivate skills in critical reasoning. As a result, many highly credentialed people know a great deal about the conventional wisdom of their field of expertise but are poorly equipped to evaluate groundbreaking advances, even in their own field. (This is the underlying cause of the phenomenon that Thomas Kuhn described in his book The Structure of Scientific Revolutions.)6 Worse yet, people with poor skills in critical reasoning have no way of knowing that they have poor skills in critical reasoning (a phenomenon called the Dunning-Kruger effect7). Thus, until their reasoning skills improve, they are immune to reason.

Some reviewers simply have poor skills in critical reasoning. Editors who slavishly follow the advice given by such reviewers are going to miss the opportunity to publish the very articles that are likely to make the most important contributions to science (and that may even boost their journal’s impact factor). Relying on artificial intelligence in the peer review process could amplify this problem, as the computer will be following algorithms based on conventional wisdom, rather than being able to have that “ah-ha moment” that is so thrilling to real scientists.

Laurie Endicott Thomas is the author of Not Trivial: How Studying the Traditional Liberal Arts Can Set You Free. That book explains the value of the classical liberal arts, including the trivium of grammar, logic, and rhetoric, in helping people develop skills in critical reasoning (www.nottrivialbook.com).

References

Articles about original research tend to follow a standard format, called IMRaD, which stands for introduction, methods, results, and discussion. When trying to write this kind of article, many inexperienced writers make three classic mistakes:

- They leave out something that is important.
- They put in things that are unimportant.
- They put things in the wrong section.

Fortunately, there are some rules of thumb for figuring out what is important and where it should go in the article, if it should be included at all.

**Introduction Section**

The purpose of the introduction section is to explain why the study was done. In particular, the Introduction should explain what questions the investigators attempted to answer. For example, imagine that you are writing an article about a Phase 2 clinical trial of a drug that is intended to reverse the buildup of amyloid plaque in the brains of people at risk for Alzheimer disease. In the Introduction section, you might explain that the buildup of amyloid plaque occurs at an early stage in the development of Alzheimer disease and that the amyloid itself is believed to cause the brain damage that leads to dementia. You might then explain why the investigators expected that the investigational drug would reverse the amyloid buildup. Then, you can give a simple explanation of the kind of study that was done. For example, you would state that the study is a double-blind, randomized, placebo-controlled, escalating-dose clinical trial in subjects who are at risk for the development of Alzheimer disease. However, you should not go into too much detail about the methods in the Introduction. Instead, describe the methods in the Methods section. Nor should you describe or discuss the study results in the Introduction. Present the results of the study in the Results section, and discuss the meaning of the results in the Discussion section.

Resist the temptation to put too much information in the Introduction section. An IMRaD article is a report of a particular study. It is not a review of the literature in general. The Introduction section should give just enough background information to allow an educated reader to understand why the study was done. Nor should your IMRaD article attempt to persuade people that the study should be done. By the time you are writing the IMRaD article, the study has already been done! Your Introduction should simply explain why the study has been done.

**Methods Section**

The Methods section should describe the protocol, which consists of the plans that the investigators made before they started enrolling subjects in the study. The Methods section should also mention whether any important changes were made to the protocol during the course of the study as well as describe any important post hoc analyses. **Important** is the key word. Your Methods section should describe the important methods that led to the important results that you will be reporting in your Results section and discussing in your Discussion section. If you are writing an article about a randomized controlled clinical trial, use the CONSORT checklist (http://www.consort-statement.org) to make sure that you have not left out anything important. If you are writing an article about an observational study, use the STROBE checklist (https://strobe-statement.org).

The Methods section may also describe some ethical concerns, as well as the plans for the statistical analysis. If the study involved human subjects, the Methods section should mention whether the protocol was reviewed by an ethics committee and whether the subjects provided informed consent. The Methods section should also give a basic overview of the planned statistical analysis. Usually, the statistical analyses are run after all of the data have been collected. But in some clinical trials, an interim analysis is performed after only a specified number of subjects have been treated. The study may then be stopped early if the treatment was more effective or more dangerous than expected.

Inexperienced writers often put results in the Methods section and describe methods in the Results section. They are also
often tempted to go into too much detail in the Methods section. Theoretically, the Methods section of your article should provide enough information for someone else to replicate your study. However, your study protocol may have been a hundred or more pages long, but you can devote only a few hundred words to the Methods section of your article. For this reason, the IMRaD article might be able to describe only the important aspects of the most important methods. If the study followed some standardized, validated methodology (as it generally should), then you can cite a reference that describes that methodology in detail.

**Results Section**
The Methods section describes what the investigators planned to do, and the Results section describes what actually happened. For example, the Results section of your article about the Alzheimer study would state how many subjects were enrolled, what their baseline characteristics were, how many of them received the investigational drug and how many received the placebo, and the outcome measures for the subjects in the treatment and placebo groups. If the study was stopped early, the reasons for stopping the study (e.g., the drug was more efficacious or more dangerous than expected) should be mentioned in the Results section. If the study was stopped early, make sure that the interim analysis and the stopping rules were mentioned in the Methods section.

Your Results section should report “just the facts, ma’am.” Reserve your interpretation of those facts for the Discussion section. For example, the Results section of your article about your Alzheimer clinical trial would give the test scores for the treated patients and the control patients, as well as giving the results of the statistical test for the comparison of the results between groups. In the Results section, you will mention whether the differences between groups are statistically significant, which means that they are unlikely to be due to chance. In contrast, you will discuss the clinical significance of the findings (i.e., whether the results of treatment are likely to be meaningful for the patient’s well-being) in the Discussion section.

A research study may gather a huge body of data pertaining to numerous outcome measures. However, the IMRaD article about that study might report the results for only a few of those outcome measures—the ones that pertain to the main questions that the research was intended to answer. Often, a research protocol will describe many preplanned analyses, such as comparisons of subgroups of patients. Typically, the results of these subgroup analyses are reported in a separate IMRaD article.

Often, researchers use data from a completed study to answer questions that were not asked until after the study began or even after the study was completed. These post hoc analyses are usually described in a separate article. However, if a post hoc analysis reveals something important (e.g., that the drug worked only in people who did not have diabetes), then it might be worthwhile to mention that post hoc analysis in the main article. Of course, if you do that, you will have to add the methodology of the post hoc analysis to the end of the Methods section as well as putting the results of the post hoc analysis in the Results section.

**Discussion Section**
The Discussion section of an IMRaD article is a lot like the closing argument that an attorney makes in a court case. The Results section provided the evidence (i.e., the outcome measures and statistical significance), but the Discussion section explains what that evidence means. In particular, the Discussion section should explain how well the evidence gathered during the study allows one to answer the questions posed in the Introduction. For this reason, the Discussion will have to address the strengths and weaknesses (limitations) of the study design, as well as the statistical and clinical significance of the results.

Each research study is done to answer a particular question. Often, other researchers have done similar studies to answer the same question or a similar question. For this reason, the Discussion section of your IMRaD article may have to compare the methodology and results of your study with those of similar studies. If the results of your study are different from the results of other studies, you might have to suggest an explanation for the difference.

In the Discussion section, you should also give your readers an idea of how the study you are describing fits into the overall effort to research a subject. For example, if your study showed that your drug reduced amyloid burden, you might go on to explain how the clinical significance of this finding will be addressed. Will other studies be done to see whether this decrease in amyloid burden translates into a lower risk of dementia within a few years?

Keep in mind that the purpose of the Discussion section of the IMRaD article is to discuss that particular study. The Discussion section does give you the opportunity to put the study in its larger context. However, you should resist the temptation to turn your Discussion section into a review of all of the literature on the subject. If you want to write a review article, write a separate review article!

*Laurie Endicott Thomas, MA, ELS, is the author of Not Trivial: How Studying the Traditional Liberal Arts Can Set You Free (www.nottrivialbook.com). She can be reached at lthomas521@verizon.net.*
Gene Therapy: What Is It? How Is It Different from CRISPR/Cas9? Why Is CRISPR/Cas9 Getting So Much Media Hype?

By Susan L. Towers, MS / Freelance writer, editor, and publication coordinator, Lewes, DE

Introduction
Cancer centers have been using genetic counseling and testing for years. Most of us are familiar with the much publicized BRCA1 and BRCA2 gene mutations that cause specific types of breast and ovarian cancer and with how, today, patient treatment regimens target those subtypes. Through our growing understanding of DNA sequencing, we are identifying other gene mutations that cause a multitude of diseases.

Medical researchers also are on a path to find methods to change these identified gene mutations in some way so as to eventually treat or cure the diseases they cause. This long and arduous path is gene therapy, and although the first clinical trials of gene therapy occurred more than 20 years ago, following years of preclinical research, gene therapy is still largely experimental. It includes such efforts as using vectors (made from virus or bacteria) to insert genes into cells, and sometimes into the genome, either at designated or nonselected sites, hoping that the new gene will override the mutated one with a corrected gene product. The National Institutes of Health (NIH) today reports more than 300 recruiting, active, and completed gene therapy clinical trials.1 On August 30, 2017, in a monumental decision for gene technology, the US Food and Drug Administration (FDA) approved the first therapy based on gene transfer. The FDA-approved therapy is Novartis’ Kymriah™ (tisagenlecleucel) suspension for intravenous infusion, the first chimeric antigen receptor T-cell (CAR-T) approved therapy. Kymriah is indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

Unlike chemotherapies or radiation therapies, which require multiple courses over weeks or months, Kymriah is a one-time treatment that uses a patient’s own genetically modified T cells to fight cancer. This form of gene therapy is performed outside the body, where the patients’ own cells are engineered in cell culture to arm them with the ability to fight the cancer when reinfused back into their body.

Gene editing is a technology that medical researchers use to remove and replace mutated genes. If successful, this easily adaptable technology could transform disease treatment and possibly offer a cure. While researchers have been studying genetic editing methods in laboratories for well over a decade, the method that has landed into the national limelight is CRISPR/Cas9. This method is showing great promise in guiding the targeting machinery to the desired genetic location, to remove the faulty gene, and in some cases (though this is harder to do at this time), to replace it with a normal gene template.

Children’s Hospital of Philadelphia (CHOP) is among the medical institutions at the forefront of gene therapy. Central to the work at CHOP is Beverly L. Davidson, PhD, Director of CHOP’s Raymond G. Perelman Center for Cellular and Molecular Therapeutics (CCMT). Dr Davidson has received national recognition for her research in this field (see sidebar). Under her direction, CCMT is taking a multidisciplinary approach to discover new gene and cell therapies for inherited diseases. The Clinical Manufacturing Facility at CCMT was instrumental in the early development of techniques to manufacture the viral vector component that alters the patients’ T cells, as well as in the advancement of other genetic and cellular research. (This research, in collaboration with Drs June, Grupp, and others, ultimately led to the development of Kymriah).

Dr Davidson was an invaluable resource in the development of this article to help members of the American Medical Writers Association understand gene therapy in general and the gene editing tool CRISPR specifically. In recent months, many stories have appeared in the national press about gene technology breakthroughs, with some articles and commentaries exaggerating accomplishments and
future predictions. While this article only touches the surface of the subject, its intent is to give an overall understanding of the technology: where it has been, where it is going, what it is, and what it is not.

**Gene Therapy Brings Hope**

After decades of international research and scientific collaboration, in 2003, the National Human Genome Research Institute published the complete human genome sequence. This historic occurrence opened the floodgates for medical researchers to expand their knowledge of how genes express themselves as proteins, how they interact on biological pathways, and other functional details of how diseases may occur. Understanding the part genes play meant that researchers could investigate disease at its inception.

Testing for specific gene mutations that cause disease took a dramatic step, and so, today, people diagnosed with cancer are often immediately given genetic tests to determine if the cancer is caused by an identified gene mutation. Several cancers, including breast, ovarian, and lung cancers, already have standard treatment regimens if specific known cancer-causing mutations can be matched to mutations in specific patients. These tests also give us the opportunity to identify family members who also may be carrying the mutation and are at risk for developing the disease.

Gene therapy represented a giant step toward establishing treatments to cure the diseases caused by these mutations by targeting and changing the expression of the gene mutation.

Vectors have evolved over millennia to carry genetic material into cells, and this has been harnessed to transfer genes to cells in a lab dish, or into cells residing in animal model or human tissues. In the case of some cancers, such as ALL, for example, T cells are being removed from a human body, genetically altered in a laboratory, and infused back into the body. The theory is that the bioengineered T cell will bolster the person’s immune system and attack the cancer. As of October 2017, the NIH showed that there were 154 clinical trials either ongoing or recruiting participants for these CAR-T therapies (www.clinicaltrials.gov [search: “CAR-T”]). Of those, 44 were in the United States. (With the majority of CAR-T clinical trials being conducted outside the United States, where will medical advances come from in the future? This is likely to be topic of future discussion.)

Spark Therapeutics, a publicly traded gene therapy company and commercial spinoff of CHOP, has 2 active clinical trials (one for hemophilia B and one for choroideremia) and 2 trials in the participant-recruitment stage (one for hemophilia A and one for hemophilia B), according to the NIH website. Unlike the CAR-T therapies in which cells are modified outside the body, Spark infuses the virus into patients directly, where it finds its target cells and delivers its genetic payload.

“To date, CCMT has manufactured and released 40 clinical-grade products that have been used in 20 clinical studies ranging from Phase 1 through Phase 3,” said Dr Davidson, a cofounder of Spark.

Dr Davidson specializes in inherited brain disorders, such as Huntington disease, and in the development of new therapies to treat these fatal diseases. She and her team are focused on translating their research into methods to treat patients with inherited neurodegenerative diseases, while others in CCMT continue to advance novel therapies for other blood disorders.

Huntington disease, she explains, is caused by a repeat expansion within the first exon of the huntingtin gene, and results in destruction of brain cells along with negative effects in other tissues in the body.

“Our goal is to mitigate the impact of this mutation.”

**Gene Editing Hones In on Specific Gene Mutations**

Gene editing technology is a tool medical researchers are advancing to “cut away” the mutated gene, as well as to make the manipulation of the genome easier. In short, the technology hones gene therapy. In some ways, it is a more exacting
method than most gene therapy approaches because it provides researchers with a precise way to target the problem area in specific genes. Over the years, 2 editing tools that have been used are zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs).

CRISPR, which stands for clustered regularly interspaced short palindromic repeats, is the latest of these tools and has often appeared in national news. Like the other editing methods, it too can make changes to the structure of a gene through targeting and correcting specific mutations in the DNA sequence. The difference between the CRISPR-based approaches and the other tools is the ease of its use, and in some instances, its specificity. CRISPR uses a complex of RNA and protein; the most used today is the complex CRISPR/Cas9.3

So far, on the research level, CRISPR has been used to edit nucleic acids in plants, microbes, and some animals, including mice, showing its potential as a tool for medical research and eventually therapy for humans. It has also been used to edit multiple genes at the same time to create small and large animal models. George Church, a leading geneticist and molecular engineer in the field, used CRISPR to splice genes from a frozen wooly mammoth into the DNA of Asian elephant skin cells in his lab at Harvard. The tissue culture represented the first time wooly mammoth genes have been functional since the animals became extinct 4000 years ago, according to a 2015 article in Popular Science.4

CCMT is using CRISPR as a workhorse tool for basic and translational studies. In an article published in the January 2017 issue of Molecular Therapy, Dr Davidson wrote that the technology holds promise for research into Huntington disease. According to that article, CRISPR/Cas9 "represents an exciting alternative for tackling dominantly inherited genetic disorders such as Huntington’s."5 Dr Davidson, together with the other authors, showed that CRISPR/Cas9 decreased the expression of the mutant huntingtin gene in lab animals and in cells taken from patients with Huntington disease.

As of August 2017, there still were no NIH-sponsored US human clinical trials using the direct application of CRISPR technology to patients. However, there were 5 trials in China listed on the clinicaltrials.gov site as recruiting participants. Four were for advanced cancers (leukemia/lymphoma, esophageal, metastatic non-small cell lung, and advanced Epstein-Barr virus-associated malignancies) and one was for HIV. Memorial Sloan-Kettering Cancer Center and Juno Therapeutics also are recruiting participants for a Phase 1 trial in which gene editing would make a CAR-T therapy for cancer more effective. The trial, targeting chronic lymphocytic leukemia, is called “A Trial of ‘Armored’ CAR T Cells Targeting CD19 For Patients With Relapsed CD19+ Hematologic Malignancies.”

When Will Gene Therapy Translate To Treatment?
For gene therapy and its gene editing tools, the transition from laboratory models to patient care continues to be arduous and challenging. Currently, Novartis’ Kymriah is the only FDA-approved genetic therapy available in the United States.6

In 2016, the European Commission approved GlaxoSmithKline’s gene therapy Strimvelis to treat children with severe combined immunodeficiency due to adenosine deaminase deficiency, a rare autoimmune disease. The treatment is only available in the United States and Canada to some patients through a clinical trial at the University of California, Los Angeles.7

Although neither Kymriah nor Strimvelis use the CRISPR technology, CRISPR again hit the front pages in August 2017, when a research group in Oregon reported it had used CRISPR to edit the genome of a human embryo. The announcement immediately drew concern from many in the scientific community because it represents a move to change germline genes, meaning that future generations would be affected. Gene therapy research in general, and all the research and techniques discussed in this paper thus far, has avoided changes to germline genes, with its inherent ethical and long-term safety questions. The American Society of Human Genetics (ASHG) in August 2017 published a position paper recommending against germline genome editing. “While germline genome editing could theoretically be used to prevent a child being born with a genetic disease, its potential use also raises a multitude of scientific, ethical, and policy questions. These questions cannot all be answered by scientists alone, but also need to be debated by society,” said Derek T. Scholes, PhD, ASHG Director of Science Policy.8

Conclusion
Today, we are faced with many genetic-based diseases, such as Huntington disease and other neurodegenerative diseases, hemophilia, sickle-cell anemia, blindness, cancers of all types, and autoimmune diseases, for which we have no cure. Gene therapies offer promise, although for the most part they have not reached clinical practice. Yet, researchers continue to work tirelessly to find ways to cure these diseases. Except for Kymriah, with its targeted patient group, it is difficult to predict when gene therapies will become a common tool in the physician’s armamentarium. But many significant steps in the scientific path have generated excitement and hope.

“We are at the cusp of change,” says Dr Davidson. “The challenge is getting from models to humans.”

Susan L. Towers, MS, is a freelance writer, editor, and publication coordinator in Lewes, Delaware. She can be reached at susanltowers@gmail.com.
Meet Beverly L. Davidson, PhD

Dr Davidson is Director of the Raymond G. Perelman Center for Cellular and Molecular Therapeutics; Chief Scientific Strategy Officer and holder of the Arthur V. Meigs Chair in Pediatrics at the Children’s Hospital of Philadelphia. She is also a Professor of Pathology and Laboratory Medicine at Perelman School of Medicine, University of Pennsylvania, Philadelphia.

Dr Davidson received her PhD in Biological Chemistry from the University of Michigan in 1987, and in 1994, she was recruited to the University of Iowa, where she was promoted to Associate Professor in 1999 and Professor in 2001. From 1999 to 2014, she held the Roy J. Carver Chair in Biomedical Research and was named Vice Chair for Research, Internal Medicine, from 2004 to 2014. She was named an American Association for the Advancement of Science (AAAS) Fellow in 2007, and in 2009, she received the NIH Mathilde Solowey Award and was named Member, Electorate Nominating Committee, as well as chair, Medical Sciences, AAAS. In 2011, Dr Davidson was the S.J. DeArmond Lecturer, American Association of Neuropathologists, and University of Iowa Presidential Lecturer. In 2012, she received the Carver College of Medicine Faculty Service Award and the Iowa Innovator Award. She was awarded the Leslie Gehry Brenner Prize for Innovation in Science in 2015. In April 2017, she became a member of the American Academy of Arts and Sciences.

Dr Davidson’s research is focused on inherited brain disorders and the development of novel therapies to treat these fatal diseases.

She has served on numerous National Institutes of Health (NIH) Study sections, was co-chair of the Editors Panel, Transformative Award Review Committee from the Office of the Director (NIH), and currently serves on the NIH Council for National Institute of Neurological Disorders and Stroke (NINDS). She is a member of the Scientific Advisory Board of the Huntington Study Group and the Medical Research Advisory Board of the National Ataxia Foundation.

Dr Davidson is a cofounder of Spark Therapeutics, Inc and serves on the advisory boards of Sarepta Therapeutics and Intellia Therapeutics.

References


*As we were going to press, the US Food and Drug Administration’s Cellular, Tissue, and Gene Therapies Advisory Committee voted to recommend approval of Luxturna™ (voretigene neparvovec). Spark’s lead candidate, Luxturna is indicated as a potential one-time gene therapy for the treatment of patients with vision loss due to confirmed biallelic RPE65-mediated inherited retinal dystrophies, a group of rare blinding conditions caused by one of more than 220 different genes. If approved by the FDA, Luxturna will be the first gene therapy ever authorized to treat an inherited disease in the United States.
The goal of research is publication, and for nearly 40 years, the goal of this book has been to guide researchers and medical communicators along the path of publishing their scientific work. First authored by Day, the book has been a collaborative effort with Gastel since the 6th edition, and she takes on the role of first author for this 8th edition. Both physicians have decades of experience teaching scientific writing to graduate students and early-career physicians, and these audiences, as well as beginning medical communicators, will benefit from the authors’ expertise in this book.

The term “scientific paper” most commonly refers to a journal manuscript, and the authors focus on this topic, with 20 of the 42 chapters devoted to manuscripts for scientific journals. The authors leave no stone unturned and provide practical advice for every step in the publication process, from selecting a journal to writing each section of the manuscript to submission and the review process. Readers can also learn how to effectively deal with journal editors and reviewers and how to appropriately handle proofs.

The value of the book lies in its coverage of scientific papers in a broader sense. In addition to discussing journal manuscripts, Gastel and Day provide instruction on writing other types of scientific publications, such as reviews, opinion pieces, and book chapters or books, as well as conference presentations (oral and poster presentations) and conference reports. The authors also discuss career-related topics such as writing a thesis; preparing curriculum vitae, cover letters, and personal statements; writing—and asking for—a recommendation letter; and seeking a career in scientific communication.

A section on scientific style is an essential resource for writers of all levels, with answers to questions about use and misuse of English, jargon, abbreviations, and scientific writing for non-native English speakers. The textbook also includes appendices on words and expressions to avoid, selected journal title word abbreviations, SI prefixes and their abbreviations, and helpful websites, along with a glossary and 7 pages of references. Altogether, this book is an essential resource for medical communicators at all levels.

Each chapter is short and to the point, with a generous spattering of examples and humor that make reading easy and enjoyable. The primary updates to this edition are related to our evolving electronic world, with new content on preparing digital poster presentations, using ORCID identifiers, avoiding predatory journals, and publicizing and archiving a paper after publication. A new section on editing one’s own work enhances this already comprehensive resource.

How to Write and Publish a Scientific Paper is used in teaching programs in many colleges and universities. I use it as the required text for my online course in medical writing at a major university. Students like its straightforward, practical approach, and their assignments demonstrate that the advice can be applied readily. As further testimony of the value of the book, James Jett, MD, former editor-in-chief of the Journal of Thoracic Oncology, recently recommended the book to fellows and young investigators at this year’s World Conference on Lung Cancer.

Reviewer: Lori L. Alexander, MTPW, ELS, MWC
Lori is a freelance writer/editor in North Fort Myers, FL.
An American Sickness: How Healthcare Became Big Business and How You Can Take It Back

Elisabeth Rosenthal

In America, patients are used to seeing absurd medical bills. One mother in Seattle had an emergency fallopian tube removal that resulted in a $44,873.90 bill. The cost of hospital services grew 149% from 1997 to 2012 and constitutes 40% to 50% of the $3 trillion American health industry. However, it is not just the hospitals that contribute to the high cost of care. Physicians’ bills account for 20% to 30%, drug and medical device costs account for 15%, and ancillary services account for 20% to 30%. And then there are insurance costs, which are not even included in that overall $3 trillion figure. In *An American Sickness: How Healthcare Became Big Business and How You Can Take It Back*, Dr Elisabeth Rosenthal provides an in-depth analysis of the entire health care industry and provides recommendations for patients to receive the most cost-effective medical treatment.

Dr Rosenthal attributes the dysfunctional American health care system to 10 rules:

1. More treatment is always better. Default to the most expensive option.
2. A lifetime of treatment is preferable to a cure.
3. Amenities and marketing matter more than good care.
4. As technologies age, prices can rise rather than fall.
5. There is no free choice. Patients are stuck. And they’re stuck buying American.
6. More competitors vying for business doesn’t mean better prices; it can drive prices up, not down.
7. Economies of scale don’t translate to lower prices … big providers can simply demand more.
8. There is no such thing as a fixed price.
9. There are no standards for billing.
10. Prices will rise to whatever the market will bear.

Dr Rosenthal evaluates how these rules apply to insurance, hospitals, physicians, pharmaceutical companies, medical device companies, testing and ancillary services, contractors and consultants, research, and medical conglomerates. The evaluations provide historical context and present states. Although the analysis is a harsh critique, the assessments are backed with numerous examples and references.

In the second part of the book, Dr Rosenthal gives recommendations for all health care consumers about what patients can do immediately and also recommends systematic changes in legislation and policy.

Dr Rosenthal’s ultimate goal is to inform both consumers and health care professionals about why the industry is in the state it is in and also about how the industry can be improved. This book accomplishes this goal. In fact, this book should be provided to all health care workers as a supplemental text to understand the American health care industry. Public health and public policy professionals will find this book especially helpful.

*An American Sickness* has potential to be the guidebook for American health care reform. The current system is not sustainable for patients, and the general public has the ability to fight against the industry that has capitalized on sickness. We must do so for our own health.

**Reviewer:** Patrick Kwon, MSHC
Patrick is a health care communications professional in Boston, MA.
How much clinical trial data do you typically include in sales training manuals? What are the key issues in clinical trials that require education for sales reps?

I’ve been writing sales training materials, primarily for oncology agents, for 17 years. Most of my work involves writing print or e-learning modules that sales representatives read and study on their own. Oncology sales representatives need to understand the data from clinical trials of their company’s agents as well as those of their competitors. For a given clinical trial, representatives need to be familiar with the same publicly available data that their customers—physicians—may see, which includes data presented in the primary manuscript for the trial, the agent package insert, and any data presented at meetings and congresses that have not been published elsewhere. The representatives have access to PDFs of these publications, so the purpose of training modules is to highlight the most important data and to provide definitions and explanations of the more complicated information.

In oncology clinical trial sales training modules, the content is typically divided into 3 parts: study design, efficacy, and safety. Regarding the study design, representatives need to know the inclusion/exclusion criteria, whether the study was randomized, and the number of patients and dose and schedule of treatment(s) in each arm. It is also critical that they know the trial’s primary and secondary end points and the patient baseline characteristics.

The trial’s efficacy section includes data related to the primary end point and some or all of the secondary end points. For oncology trials, this most often consists of survival outcomes and tumor response rates.

Safety data are usually presented as all-grade and grade 3-4 adverse event rates. The incidence of any serious adverse events and deaths due to adverse events are also provided. Finally, the safety section will include information about any drug discontinuations or dose interruptions, reductions, or other modifications due to adverse events.

In contrast to what some people may believe, the content in these modules is not promotional—sales representatives just need to have background knowledge about the disease, the agent, and the current treatment landscape so they can have intelligent conversations with their customers.

—Gail Flores

Every sales training manual is different, just as every client’s sales training needs and expectations are different. In my experience, a typical module educating sales representatives about a product they are responsible for selling focuses on the pivotal clinical trials included in the product labeling. Of course, in a learning module, we go into much more detail about each clinical trial than is found in the labeling. So I usually work with the clinical study report (CSR) and sometimes also with the investigator’s brochure (IB) and/or the study protocol to get all the information I need.

The sections of a clinical trial reported in a sales training manual typically include:

- Study description—a brief statement of what the trial is (eg, phase 3, randomized, placebo-controlled, multicenter trial)
- Study design—a description of how the study was conducted (often including an algorithm) and study endpoints
- Materials and methods—a summary of inclusion and exclusion criteria for patient selection and the frequency and dosing of treatments
- Results—a review of the efficacy and safety of the product for all defined end points
- Conclusion—a brief statement of the key takeaway

Learning content typically also includes insights for sales representatives to help them understand and appreciate certain aspects of the trial. For example, perhaps the enrolled patient population had an especially serious disease or some unusual or specific characteristic that is relevant to the study outcome. Or perhaps the study used a unique biomarker that

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FREELANCE FORUM

Brian Bass  Mark Bowlby  Gail Flores
the sales representatives need to learn more about so they can inform and educate their customers.

In most circumstances, sales representatives must be familiar with all aspects of the pivotal trials for their product. When they are speaking with health care professionals, having a thorough understanding of the trials and data translates into confidence, which is necessary for success.

Sales representatives should also have a solid understanding of the pivotal clinical trials for competing products. Products cannot be compared unless they have been studied in a head-to-head comparative trial, so sales training cannot compare clinical trial results. When writing sales training content on the clinical trials of competing products, medical writers will not have access to proprietary documents like CSRs, IBs, and protocols. For this content, we have to rely on published data from journal articles and the product prescribing information (PIs).

—Brian Bass

Whether freelancing or working in-house, medical writers often are asked to write the “medical backgrounder” included in sales training programs—for print media, videos/slides, and online learning. Content may include extensive educational material about the indication in question, an overview of the anatomy and physiology of the target body system, and reviews/interpretations of clinical trials that have taken place with the company’s product(s). Regarding “how much” data from clinical trials to include, this decision will be made by the company’s marketing and/or sales training department. At minimum, you must include succinct, simply written summaries of the pivotal phase 3 trials on which FDA approval was based. Also, of course, any studies that ended up published as journal articles and/or comparing the company product with competitive products should be included. Summaries of phase 4 studies are also necessary because they are pertinent to postmarketing information, and phase 1 and 2 study summaries are needed if clinical pharmacokinetics are a significant issue. Moreover, results from pivotal and other important clinical studies need to be put into perspective relative to the company’s “competitive products” so that the sales reps can answer questions intelligently and handle objections from the physicians and health care providers they call on. Details on what specific information should be included is more a “how-to” question than a “freelance” question—but if you have more questions on this topic, please feel free to contact me personally at evanscathryn@aol.com.

—Cathryn Evans

How do you use the clinical study report (CSR) to develop an outline for a manuscript?

As a freelance, you are likely to be “directed” by the client in this regard. However, according to AMWA’s Code of Ethics, presumably you, as a medical writer, will not be developing the outline for a manuscript based on a CSR unless you are (1) in close collaboration with the named author and/or (2) going to be included as a co-author. That being said, the decision about how to carry forward information from a CSR to a journal article for publication depends on the study design and objectives as well as the Instructions for Authors provided by the target journal. Caveat: You do not just automatically outline the manuscript as “Introduction, Methods & Materials, Statistical Analysis, Results, Discussion, References, Tables/Figures”—rather, you must evaluate each individual study protocol relative to the client’s intentions and, of course, to the target journal types of articles, styles, and author instructions.

In the past, companies could (and did) “cherry-pick” data from a CSR to include in a journal article; most of the time the investigators themselves were not even given a copy of the final CSR. And frequently the “authors” had little or no input to the paper (by choice, not because the company excluded them). Today, the ethical environment is quite different: companies are required to be far more transparent about all clinical-trial data. And most of the better medical journals have both print and online publication, which means you can include extended information about the methodology (and results/tables/figures) in a submission of supplemental material, which will not be printed in the journal but will be available to readers online. Hence, you can consider using a relatively large proportion of the CSR for the journal article. Again, there is more to be considered here than space allows in this column, and again, this is more a “how to” question than a “freelance” question—but if you have questions about a specific CSR/journal article, please feel free to contact me personally at evanscathryn@aol.com.

—Cathryn Evans

How can I best acquire familiarity with regulatory practices in pharma (or devices, or biologics, etc.)?

Like many aspects of life, your options depend on your circumstances. However, the first subtlety to understand is that regulatory practices applied in pharma are composed of (1) regulatory affairs and (2) regulatory writing, working in concert with a broader project team. Regulatory affairs professionals are responsible for learning the
regulations governing drug/biologic/device development and interpreting them for pharmaceutical and biotechnology companies, but it's not primarily a writing position. Regulatory writers, however, primarily report, summarize, and even interpret scientific results (usually clinical) in a format appropriate for regulatory agencies and clinical study sites. They are the primary writers of regulatory documents such as clinical protocols, investigator brochures, clinical study reports, and the many summary documents required for submission of new drug applications.

Aspiring regulatory writers coming out of college have several options for further education in medical writing, regulatory affairs, and other similar areas. These include formal graduate programs in medical or scientific writing (eg, University of the Sciences in Philadelphia) and education programs from professional organizations such as AMWA. A less well-recognized path for obtaining training, however, is to obtain a job in the pharmaceutical or biotechnology industry (including contract research organizations [CROs]) in a medical writing or regulatory affairs role. Even though it is rare to hear about this path, it is probably the dominant career path by which most current regulatory writers have gotten into the field, although many positions in industry that expose employees to project team clinical development activities can lead to regulatory and medical writing careers. Often the best teacher is experience with the team responsible for guiding a drug through the myriad of regulations governing its development.

This leads me to another large group of aspiring regulatory writers—those working in functions not associated with clinical development in pharmaceutical or biotechnology companies. Because most regulatory writing occurs during clinical development, exposure to this area is key to obtaining the experience that can lead to full-time opportunities. In these situations, you need to look for opportunities to work with a drug development team. Get in touch with others working in development in a therapeutic area that you have experience with, talk about opportunities to get involved, and add this onto your career development plan. You may be surprised at the support you receive as long as you continue to meet your main daily job expectations. It takes some perseverance and motivation, but it’s a viable method for leveraging your current position to gain experience in this area.

Last, there's the direct route of entering a regulatory writing role at a Pharma, biotech, or CRO without prior regulatory or Pharma training. This is probably the most difficult path because it places the burden for training on the employer instead of the employee. As a result, many employers prefer not to hire regulatory writers without experience, so the challenge is to seek out companies willing to train new writers. These companies do exist in both the Pharma and CRO spheres, but most don't advertise directly for writers without experience. However, if you have the right aptitude, work well in a team, and are serious about a career in regulatory or medical writing, entry-level positions do exist when the employee-employer match is right.

—Mark Bowlby

In this response, I am assuming a lack of any knowledge or experience with any aspect of Pharma/biotech/device companies. I am also assuming that the readers are experienced medical writers in other areas of health care. For the purposes of this response, I will talk about the pharmaceutical industry, but the same principles apply to biotech/device companies.

The first requirement is that you understand the industry as a whole: What is it? How/why did it come into being? What is its purpose? How does it operate? For this intelligence gathering, there are many resources. Search the internet and/or libraries if you like. One initial source might be Eisai’s “Understanding the Pharmaceutical Industry” (www.eisai.com/ir/individual/knowledge.html). It is especially important that you understand the entire process of drug development, from the bench, to animal studies, to phase 0-4 clinical trials, to mass marketing, even if you end up working only on clinical study documents.

Moreover, you must understand the industry not only as a developer and marketer of health care products but also as a business—because business (making money) is, in fact, the top priority for these companies. Nearly all major decisions made by upper management are made on the basis of profit/loss, and the prospective employee or vendor for a drug company must accept this philosophy. (Of course, this does not by any means negate the remarkable innovations and benefits to medicine and health care generated by industry; it is just a realistic understanding that I feel one needs when working for industry. About 75% of my career has been pharmaceutical-based, in both MedCom and regulatory affairs; if I did not like and respect this industry, I would not have given so much of my life to it.)

Next, read some of the regulations; the Code of Federal Regulations (CFR) is available online and can be searched by topic. Peruse the US Food and Drug Administration (FDA) websites, too—new/revised regulations, guidelines, commentaries, and examples of documents are freely available there. You can download extensively annotated outlines of International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
documents such as a Protocol or Clinical Study Report (CSR).
Complete New Drug Application (NDA) submission information (including structure and contents of the Common Technical Document [CTD]) are also easily accessed through the FDA website or via simple Google search. This is particularly important if your intention is to enter into a career in regulatory writing.

Another seriously important move would be to try to acquire and carefully read samples of specific documents that are generally written by medical writers—a few examples include (in no particular order)

- Investigational New Drug (IND) reports
- Preclinical and clinical study protocols
- Investigator Brochures (IBs)
- Clinical Study Reports (CSRs)
- Abbreviated CSRs
- Informed Consent Forms (ICFs)
- Interim reports
- Toxicology reports
- Pharmacology and/or pharmacokinetic reports
- Risk-management plans
- FDA Briefing Documents (for pre-Protocol/pre-NDA meetings and/or for pre-identified sensitive issues)
- CTD summaries (too numerous for this list but when you review the CTD outline, you will see how many types of documents need to be written for a CTD)
- Product labeling (package inserts)
- Responses to specific questions from the European Medicines Agency (EMA) and/or FDA
- Slide presentations for advisory boards (FDA and others)
- Advisory board meeting summaries

Please join the Drug Information Association (DIA)—so much can be learned about the industry from attending their meetings. Go to an annual meeting if budget permits (and it should permit, because this is an important part of your career development!); attend the larger seminars as well as the smaller breakout meetings as well as all meals and cocktail parties. Meet people in the industry—this is a critical thing to do, in my view. Equally important: pay attention to the people as individuals. Watch and listen. You can gain a lot of intelligence this way, especially a sense and feeling of what kind of people they are; do you identify with them psychologically/emotionally and do you wish to be around them every day? You should be quite certain that regulatory writing for industry is the niche you really seek. If budget permits, join the Regulatory Affairs Professional Society (RAPS) for at least a few years, as they offer meetings and educational programs of interest (they also have a RAPS educational certificate you may wish to look into, but it is not for “regulatory writing” in particular).

Of course, in my opinion, the best way to become intimately familiar with the industry is to immerse yourself in it by accepting a full-time job and staying for several years before going freelance. Do keep in mind that regulatory affairs is just one part of the arena for medical writers: MedCom, sales training, public relations (PR), marketing communications, and other departments offer scores of other interesting writing opportunities. Regardless of your choice, to work well in this industry you must understand it well—and a strong background in regulatory affairs is an excellent underpinning of a long career in this industry.

—Cathryn Evans

A Message From the Chapter Advisory Council Chair

It is my great honor to lead the efforts of the new Chapter Advisory Council as inaugural Chair. The new structure (see article on page 186) offers an opportunity for AMWA to be more strategic in its mission to its members. I look forward to working with the Chapter Advisory Council and appreciate the commitment of these chapter volunteers to advancing AMWA through their leadership.

—Katrina Burton
The Ethics of Genetics

By Tami Ball, MD / Retired

Introduction
We are long past the days when plants and animals evolved slowly, the result of random genetic mutations that lent a survival advantage to the mutated member of like species. Fast-forward to 2015: CRISPR, a relatively simple, inexpensive technique to remove and replace specific gene sequences, is introduced. Genetics has rocketed forward at an unprecedented pace ever since. This has introduced a host of new ethical questions that have left ethicists scrambling to catch up. In this piece, we’ll explore several of the key ethical issues generated by the increased use of this technology.

First Things First
Somatic cells are any body cell other than gametes (egg or sperm) and are sometimes referred to as “adult” cells. These cells are usually differentiated and do not differentiate further in vitro. When used therapeutically, they die when the patient dies and therefore pose little ethical risk beyond the usual efficacy and safety concerns extended to any individual patient.

The embryonic stem cell line results when an egg is fertilized by a sperm in vitro; the resulting embryo will proliferate without differentiation for months to years. These cells contain the complete genetic blueprint for a unique human being. Genetic manipulation of this embryo presents several ethical concerns, particularly because a baby developed from such an embryo would pass his or her modified genome on to all subsequent generations, thereby changing the gene pool. That is ethically concerning.

Human Embryo As Substrate
The pervasive question for genetic engineering had always been whether scientists should be permitted to modify the genes of human embryos or whether they should be limited to human adult cells and nonhuman embryos. We've wrestled with this question publicly; privately; in our churches, synagogues, and mosques; at academic conferences; and in the halls of government. Still, approving or not approving the use of human embryos for genetic research is an intensely personal decision. Some people feel that the embryo is endowed with the sanctity of life and see it as a potential fully unique human being, a tiny soul. “It’s not a life for us to take,” they’d argue, considering such use to be tantamount to murder. Others argue that the scientific information gleaned from the use of embryos is of greater value than the cells themselves. Besides, they might point out, most embryos used in research are the “waste product” created during in vitro fertilization. A number of choice embryos are usually selected for uterine implantation, others have been preserved for future use, and leftover embryos are discarded—or used in research. People have vigorously argued both of the views described above, and many more as well. Like most ethical questions, this one has no “correct” answer. But time marches on, compromises were reached, and decisions were made.

Embryos and the March of Time
In the United States, several technical and ethical concerns around CRISPR technology led to a 2005 policy that per-
CRISPR intervention is not 100% safe and never will be, but scientists have not understood it fully before introducing the technology clinically. The greatest peril to scientists in this field would be to introduce the technology to patients of genetically complex, poorly understood diseases like diabetes. The greatest risk is that the technology will take much of our energy in the near future.

When Will We Be Ready for a Clinical Trial?
The greatest peril to scientists in this field would be to introduce the technology clinically before they fully understood it. CRISPR intervention is not 100% safe and never will be, but how safe is safe enough? Though CRISPR has the precision of a genetic scalpel, changes to off-target loci make the results unpredictable. It would take only one human death to validate scientists and citizens opposed to this work and motivate them to demand a moratorium on further CRISPR research. But it wouldn't take a death, per se, to stop or slow progress. Unforeseen results could be judged intolerable. For example, tomatoes that have undergone selective breeding are large, uniformly red, and have a long shelf life. They also have no flavor (the unintended result). If parents have a child with lovely red hair, as intended, but the child also has a third arm, there will likely be an outcry. Moving forward, review boards will need to carefully examine all available safety data and determine what level of risk is acceptable. Ideally, safety data would include long-term observation of modified mammals and their offspring.

What Is Fair Game for Editing?
Worldwide, most researchers agree that, at this time, genetic modification of the human embryo should be limited to the correction of severe diseases for which there is no alternative treatment. The National Academy of Sciences formed an advisory committee with global representation, and the committee has drawn a red line at genetic enhancement. “Genome editing to enhance traits or abilities beyond ordinary health raises concerns about whether the benefits can outweigh the risks, and about fairness if available only to some people,” said Alta Charo, co-chair of the committee and professor of law and bioethics at the University of Wisconsin, Madison. Thus, genetic enhancements are not currently available, but their use will likely be an issue in the future. An example of how little we understand at this point is the following: scientists have identified 697 small genetic variations on 4 loci that affect our height. Where are the genes for athleticism or intelligence? Helping rid patients of genetically complex, poorly understood diseases like diabetes will likely take most of our energy in the near future.

Who Decides?
Engineering an embryo for implantation and creation of a modified human baby is a very serious business. It has the potential to change us as a species. The decision to move forward is a grave one, indeed. It should take into consideration every bit of data and take notice of red flags raised by any lab, anywhere. Ideally, this decision should be made with complete transparency by a globally representative body of individuals including scientific experts, ethicists, lawyers, religious leaders, and everyday citizens. Members should be prudent, demanding, free of conflicting interests, and unimpressed by the science. Ideally, the process would include several levels of review, and decisions would be unanimous.

What Are We Creating?
It seems that we are on our way toward germline modification, which begs the question, what exactly are we creating? Are genetically modified children still human, or has the loss of randomness changed them in some fundamental way?
Although a change in the genome is rather dramatic, it must be noted that we are always changing in small ways. All cells in our body—our brain, our heart, our bones—are continually being replaced. We are ourselves only during this exact moment in time. So perhaps the adjustment won’t be too difficult.

**How Will Society Change?**

If parents one day have the luxury of genetically modifying their children, what will it mean for society? Imagine 2 children on a swing-set. One is genetically modified (GM) and one is natural. The GM child has perfect hair; an attractive smile; perfect health; and a well-proportioned, muscular body. She attends a private school for intellectually gifted GM children. The normal child has tousled hair and a runny nose, is pudgy, and acts a bit tentative on the swing. She attends public school. How will the mothers of these children feel about their choices and how might the mother of the normal child behave when planning her next pregnancy? GM upgrades would almost certainly come at a cost. Would this further the separation between the haves and have-nots? Essentially perfect GM children would likely find doors routinely opened for them. They would go to better schools, get better jobs, enjoy greater wealth, and maybe even defy death. At the extreme, we might find ourselves in a dystopian world of duality where people were either elite, nearly identical privileged beings or commoners modified to have a durable sense of loyalty and a strong work ethic.

**Other Ethical Issues**

- Who will take responsibility for ensuring that payers, legislators, and citizens are genetically literate? Studies have shown that people understand more about genetics than previously assumed. This knowledge is seldom a result of lectures in biology and more due to documentaries, blogs, and other media that focus on the impact to specific patients and their families.
- How much should be charged for a modification that prevents a serious disease? It is a one-and-done treatment, but it results in complete cure and prevents a lifetime of resources devoted to care and a great deal of suffering.
- Does insurance pay for it and, if they do, should they have access to your DNA? Do scientists hold copyrights for genetic modifications?
- If you are the product of a genetically modified embryo, do you own your own genome or does someone else?
- At its core, is modification just a kinder, gentler form of eugenics? What forces will shape our vision of perfection and will that vision change over time?
- Along with loss of variation between people, will we lose the gifts like the creativity that often accompanies some forms of mental illness?
- Will it be necessary to study the results of pairings between GM and non-GM individuals? What about 2 individuals who have different modifications?
- How do future generations sign consent?
- Would it be possible for a fascist government to euthanize citizens who are genetically flawed? Who among us would pass the screening?
- Or could that same government request an army of soldiers optimized for aggressiveness and bravery?

**Concluding Thoughts**

We are at a very early point in our understanding of genetic manipulation. Studies have been done on human embryos, and this will likely be the accepted form of experimentation in the future. We need to scramble to catch up with new developments. Some ethical questions are currently before us and others are not. We need to be prepared to approach issues transparently, solicit input from a variety of sources, and think globally as we move forward.

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**Would You Care to Share?**

As I mentioned in my inaugural column, a benefit of AMWA membership is being an active participant in a community of peers who are uniquely willing to share their knowledge and experience for the betterment of each other, the association, and the profession. An interactive ethics column is a new way of exercising our ethical muscle at AMWA, and the discussion may generate a renewed awareness of the ethical principles that govern our profession. Have you experienced an ethical situation relevant to the subject of this column that you would like to share for the benefit of others? Please send essential details of the situation, a list of stakeholders, proposed solutions, and, if the situation has been handled, how it was handled and the follow-up results. Please consider following the RIGHT model. Both newcomers and seasoned AMWA members are encouraged to submit thoroughly anonymized “cases” that may serve as a springboard for discussion in this column. Please send cases to tballmd@gmail.com. I may not be able to publish all cases, but I will eventually return your message.
It’s a great honor to be here addressing you at the end of another spectacular annual conference. Last year, Lori addressed us and introduced a year of magic leading up to our conference here at Disney World. But, for anyone who might think that magic is easy, think again: it was a year with a lot of hard work and AMWA passion leading up to this conference.

We are now looking forward to next year and our annual conference in Washington, DC. The DC area is home to many groups of interest to us as medical writers: the Department of Health and Human Services (including the FDA and NIH), National Patient Advocate, Physician’s Committee for Responsible Medicine, National Foundation for Cancer Research, and many prominent research universities. In other words, we have a veritable wealth of resources to call upon to make our next conference memorable. I’ll make my first plea for volunteers: we count on our members to help us create these relevant and memorable events. I particularly encourage members from the mid-Atlantic area to help us plan this conference in your backyard!

As I said, this was a year of very hard work leading up to this conference. The work really started 2 years ago, with a strategic planning initiative, which was led by our now immediate past president, Lori Alexander. The initiative involved surveys of members, hiring managers, and customers of medical writers, as well as many leadership meetings. At the end of this planning, we had several priorities identified. The first was to streamline what we were doing, and how we were doing it, so that we would have the resources to tackle the development of new educational offerings and other resources for our members.

Another important initiative that we worked on was our governance structure. Our constitution and bylaws had not had a thorough review in years, and when we instituted a legal review, we found that we were out of compliance with state and federal laws with our structure and documents. Some of these laws were new, due to increased scrutiny of nonprofits following 9/11, and enforcement of those laws was now being brought down to the level of smaller business entities such as AMWA. As a result, we established a formal chapter agreement to clarify the relationship between AMWA and its valuable chapters and to codify responsibilities. Our surveys have indicated that members value local AMWA networking, and our chapter leaders have indicated that what they enjoy most is organizing these events. We have implemented a process to empower members to organize such events. I’m very pleased to say that we already have local networking coordinators, or LNCs, both within chapter areas and in areas that do not have a formal chapter structure. There is now more activity taking place! This is another opportunity for volunteering: if you would like to coordinate please sign up on the LNC page on our website. You can volunteer to organize networking events in your area.

In addition to the changes at the chapter level, AMWA leadership voted to streamline the Board of Directors, reducing the size from nearly 40 members down to a more manageable 12 to 16. This makes our Board size in line with that of other organizations our size.

The new governance structure includes a Chapter Advisory Council, to ensure that the chapter voice remains prominent in AMWA decision making and that chapter leaders continue to have a connection to the AMWA Board. Each chapter will have a representative to the Chapter Advisory Council, and the chair will serve as a voting member to the Board of Directors. In addition, we are now striving to have a Board with a diversity of medical writing expertise as well as a geographical diversity, and representation across employer settings and career levels. We have members who have been motivated to step up to both national and chapter leadership positions, inspired by both an openness to new ways of doing things and the progress they see.

We have invested in new technologies, including the ENGAGE online community, a new Association Management System, or AMS, with a new website, and a Learning Management System, or LMS. The ENGAGE platform has been a tremendous success, and we have heard that members are happy to have such a professional forum in which to connect with colleagues. Work is ongoing to enable the LMS and AMS.
systems to share data, so that we can more easily keep track of the courses, online and in person, that each member has taken. None of these changes came easily, and I am very grateful to Lori, and Steve Palmer before her, for their leadership over the past 2 years.

Now I have talked about what we have done over the past 2 years; what about the future? We now hope to refocus our resources on new educational offerings and other resources for our members. You, our members, have told us that you value our face-to-face workshops; however, you have also said you cannot always attend the annual conference or regional conferences, and you want expanded online educational offerings. We know that AMWA is valuable for new medical writers starting out, but we also need to provide continuing education for our more experienced members. We have learned that developing online classes is neither easy nor cheap; in fact, we had a lot to learn. But we are getting better and more efficient at developing online courses. Our newest 3 online courses are Micro-editing, Macro-editing, and Evidence-Based Medicine, and they are all wonderful. I encourage you to take a look. Even if these are areas in which you have experience, I think they provide valuable refreshers.

We have gained much more experience and expertise at webinars and creating online “tips and tricks,” and we will produce more of both. We also know that we need new workshop leaders for workshops that we already have, plus we need subject matter experts to help us develop new workshops to fill needs, especially for the advanced, or more experienced, medical writer. Now we can focus on making AMWA stronger and more valuable to our members. Change is uncomfortable and some might even say scary, but change is necessary, and some may even say exciting! In the year ahead, I expect that we will see more change. It is through change that AMWA will grow, both in numbers and in value. Since in some cases we are in uncharted territory, I can’t promise that we won’t stumble along the way. However, I can promise that we will do our very best. And if we determine that we are heading in the wrong direction, we will correct course quickly. And I will make a final call: if you have ideas, if you have time, consider volunteering; at the chapter or at the national level, your contribution will be valued.

I look forward to the year ahead. I know it will be a memorable one for me and with the support of the AMWA Board, committees, chapters, and all of you, I hope it will be a memorable and valuable one for all. Thank you.

AMWA Board of Directors Approves New Bylaws and Governance Structure

By Susan Krug, MS, CAE / Executive Director

In 2016, in an effort to comply with state and federal laws and with current governance best practices for associations, the AMWA Board of Directors embarked on a journey to update AMWA’s governance documents and structure. As an important first step in updating the organization’s governance documents, a new AMWA Constitution was proposed by the Board and approved in March 2017 by vote of the membership. As the next step in updating the organization’s governance documents, new AMWA Bylaws were adopted in June 2017 by vote of the AMWA Board of Directors. As a part of that revision, the Board also voted to update the association’s governance structure (Figure).

The changes in the AMWA Constitution and Bylaws will enable the Board to be nimbler and better able to respond to the association’s opportunities and challenges. Nevertheless, the Board sought to retain the vital link between the membership, the chapters, and association governance. To ensure chapters retain a strong voice in the governance of the association, the Board implemented a new Chapter Advisory Council. This Council will play an important strategic role in the association by ensuring a continued connection between chapter leaders and the Board and by providing strategic advice, feedback, and recommendations on enhancing the member experience through the chapters. Each AMWA chapter may appoint one representative to the Council for a 1-year (renewable) term (Table), and the council chair is a voting member of the Board. The new AMWA Board of Directors is composed of the 5 officers (President, President-Elect, Immediate Past President, Secretary, and Treasurer), 6 to 8 At-Large Directors, the Chair of the Chapter Advisory Council (see sidebar on page 181), and the AMWA Executive Director (nonvoting, ex officio).

The Board approves the budget, approves the slate of nominees for elected office, approves proposed amendments to the Constitution before submitting them to the membership, approves amendments to the Bylaws, approves the appointment of members to standing committees, approves all committees and ad hoc workgroups and task forces, and fulfills such other duties as are specifically mentioned in the Constitution and Bylaws and as required by law. The Board has the power to...
establish reserve and endowment funds and approves the plans and regulations necessary to administer such funds. The Board also empowers an Executive Committee to act between meetings.

The AMWA Executive Committee consists of the President, President-Elect, Immediate Past President, Secretary, Treasurer, and Executive Director (nonvoting, ex officio).

The Executive Committee may provide consultative advice to the President and Executive Director and helps manage the flow of information to AMWA’s Board and the Chapter Advisory Council. The Executive Committee may also develop recommendations for Board consideration. When special circumstances require expeditious action between meetings of the Board, the Executive Committee has the power to take the necessary actions, subject to any prior limitation imposed by the Board. Executive Committee minutes will include a summary of the circumstances requiring any expeditious action taken by the group and will be shared with the Board.

AMWA strives to have a Board that is representative of the organization’s membership, reflecting the varied characteristics of the membership. Members interested in serving at the national level may express an interest through the annual call for volunteers. The Board candidates express their interest in serving on the AMWA Board through the Board Interest Form. Each At-Large Director is nominated by the President-Elect and approved by the Board. The slate of officer nominees is selected by the Nominating Committee, approved by the Board, and circulated to the AMWA membership at least 60 days in advance of the election. The officers of AMWA are elected at the Annual Business Meeting of the members during AMWA’s annual Medical Writing & Communication Conference.

The 2017–2018 Board of Directors began their term of service on November 4, 2017, at the conclusion of the 2017 AMWA Annual Business Meeting. AMWA members that attended the Annual Business Meeting witnessed the transition of leadership. The meeting also featured a town hall forum for members to ask questions of the AMWA Officers about the new governance structure and about the association’s initiatives.

Table. Appointed Representatives to the 2017–2018 Chapter Advisory Council

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<tr>
<th>Chapter Name</th>
<th>Chapter Representative</th>
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<tr>
<td>Carolinas</td>
<td>Jennifer Bridgers</td>
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<td>Delaware Valley</td>
<td>Julie Munden</td>
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<td>Empire State–Metro New York</td>
<td>Anjani Shah</td>
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<td>Florida</td>
<td>Irvin Peralta</td>
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<td>Greater Chicago Area</td>
<td>Sarah Prins</td>
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<td>Indiana</td>
<td>Barbara Lightfoot</td>
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<tr>
<td>Mid-America</td>
<td>Heather McNeill</td>
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<td>Mid-Atlantic</td>
<td>Jill Roberts</td>
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<tr>
<td>New England</td>
<td>Andrea Gwosdow</td>
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<td>North Central</td>
<td>Mary Knatterud</td>
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<td>Northern California</td>
<td>Barbara Arnoldussen</td>
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<td>Ohio Valley</td>
<td>Sarah Dobney</td>
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<td>Rocky Mountain</td>
<td>Brittany Hodges</td>
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<td>Southeast</td>
<td>Kim Korwek</td>
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<td>Southwest</td>
<td>Katrina Burton</td>
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Instructions for Contributors

Unless otherwise noted, submit manuscripts and suggestions for content to the Journal Editor at JournalEditor@amwa.org.

FEATURE-LENGTH ARTICLES
Feature-length articles include topical features, original research in medical communication, and Science Series articles.

Topical Features
The AMWA Journal invites manuscripts on areas of interest to medical communicators, including topics within such broad categories as regulatory writing, continuing medical education, patient education, medical marketing/advertising, public relations, medical journal management, publication ethics, health policy, etc. The AMWA Journal especially encourages the submission of articles on the theoretical underpinnings of specific types of medical communication. AMWA Journal readers are primarily practitioners (not academicians), and application of theory to practice is an essential component of manuscripts. Word Count: 3,000 words (plus an informative abstract of 250-300 words)

Original Research
The AMWA Journal invites manuscripts reporting original research on written communication, publication trends, and medical communicators’ productivity and value added. Word Count: 3,000 words (plus an informative abstract of 250-300 words)

Science Series
The Science Series accepts manuscripts that provide an overview of a specific anatomic or physiologic topic (eg, body system), disease or condition, diagnostic method (eg, laboratory tests, imaging systems), or type of treatment (eg, devices). Word Count: 3,000 words (plus an informative abstract of 250-300 words)

OTHER TYPES OF ARTICLES

Around the Career Block
The Around the Career Block section accepts manuscripts that provide advice on career-related issues, profiles of professional organizations, and first-person accounts of educational experiences.

Career-related Articles
These articles address topics that are relevant to the career development of medical communicators. Areas of interest include job hunting, developing a portfolio, interviewing techniques, hiring guidance, performance evaluation, mentoring programs, performance goals, etc. Word Count: 750-1,500 words

Profiles of Professional Organizations
These profiles help readers discover or better understand organizations that address specialty niches and may therefore be a useful supplement to AMWA membership. Word Count: 600-1,000 words

First-person Accounts of Educational Programs
These articles provide overviews of educational programs designed to enhance the knowledge and skills of medical writers and editors. Word Count: 600-1,000 words

Commonplaces
Commonplaces is devoted to the exchange of ideas between teachers of medical communication and practitioners. Contact Commonplaces Editor Lora Arduser (ardusell@ucmail.uc.edu) with article ideas.

Media Reviews
The Media Reviews section includes reviews of books, websites, and other media that are of practical value or topical interest for medical writers and editors.

Practical Matters
The Practical Matters section accepts manuscripts that provide practical guidance to medical writers and editors (at all levels of experience) for improving the skills involved in their daily work activities in a variety of medical communication settings. Word Count: 750-1,800 words

Regulatory Insights
This section provides information of particular interest to communicators who write or edit documents related to the pharmaceutical or device industries. Word Count: 750-2,000 words

Social Media
The Social Media section includes articles focusing on the use of social media and networking in the medical communication industry.

Tech Talk
The Tech Talk section includes articles about technology topics that may be of interest to biomedical communicators. Word Count: 500-1,000 words

Statistically Speaking
This section covers statistical concepts of interest to medical communicators.

Everyday Ethics
The Everyday Ethics section includes topics related to ethical situations encountered by medical communicators in any or all branches of the profession. Well-considered and professional approaches to situation management are included.

OTHER SECTIONS

Sounding Board
The Sounding Board is a forum for members’ opinions on topics relevant to medical writing and editing. Contact the Journal Editor to seek approval for the topic before preparing and submitting a manuscript. Word Count: 750-1,000 words

Letters to the Editor
Letters to the Editor provide an opportunity to comment on topics published in the Journal. Letters should refer to contents within the past two issues. Word Count Limit: 500 words

MANUSCRIPT SUBMISSION
Manuscripts are accepted for consideration with the understanding that they have not been published elsewhere and are not under review elsewhere. Submit the manuscript as an attachment to an email note to the Journal Editor (JournalEditor@amwa.org).

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Ensure a clear message with credibility and clarity.

Macroediting helps an author speak with credibility and clarity. The process works to ensure a clear message with congruent parts, coherent information, and a unified focus. Create high-quality scientific documents with the essential components of macroediting and gain the “bird’s eye view.”

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