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Rethinking the Investigator's brochure

Optimizing an essential, legacy document

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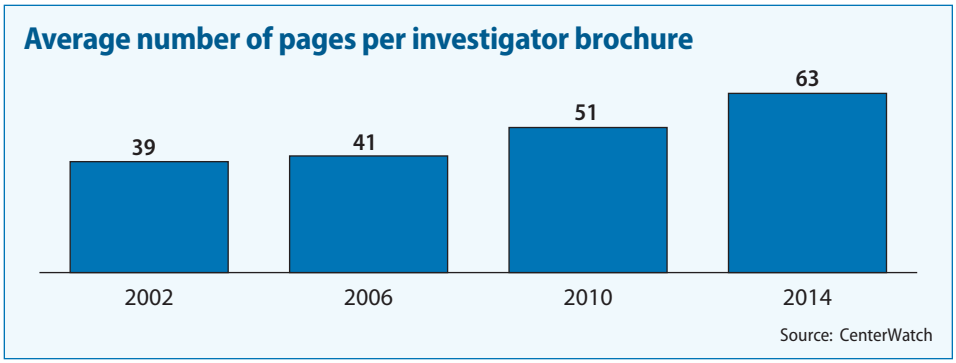


The investigator's brochure (IB) has long functioned as the main reference document for clinical trials, providing investigators with information needed to understand possible risks or adverse events (AEs) related to the investigational product and keep sites up-to-date on the study. Yet IBs are invariably lengthy, complex documents that are seldom read cover-to-cover or consulted when questions arise.

While new technology has impacted many clinical research domains to improve the usability and efficiency of documents or processes, IBs remain a relic of another era. The structure and content requirements for IBs haven't changed in more than two decades and paper copies of the document, which can run to hundreds of pages, are typically mailed to investigative sites or sent electronically as a PDF file that a staff member must print and file in a regulatory binder with other required documents.

"Often the IB is seen with a kind of checklist mentality," said Andrea Meyers, vice president, medical writing, INC Research/inVentiv Health. "The sites have it and file it away. But there is a big difference between knowing that it's there and actually using the document for its intended purpose."

Given the time and expense sponsors invest in creating these documents, which are required as part of certain regulatory submissions in the U.S. and Europe, questions have been raised about whether IBs could become a more useful resource for communicating study information to investigators and site staff, help motivate patient enrollment efforts or improve mandatory safety reporting.

Investigators and other clinical research experts interviewed by CenterWatch had divergent views on the topic. Suggestions ranged from presenting better summary information about the study's importance to integrating IBs with clinical trial technology platforms to creating more interesting documents that included color graphics or even a top 10 list of key elements.

Yet given its nature as an objective, balanced and comprehensive scientific document designed to protect the health and safety of clinical trial participants, there are limitations on how IBs could evolve and become more user-friendly going forward.

"Everybody tries to look for a panacea and to get knowledge without doing any work, but there is no such thing. Professionals need to invest the time to understand what they are doing," said Joy Frestedt, Ph.D., president and CEO of Frestedt Incorporated, which provides clinical, regulatory, quality and engineering services to drug and device companies.

Challenges in IB presentation

The IB, which compiles comprehensive information about an entire drug development program, is intended to give investigators the ability to make an unbiased risk-benefit assessment about a clinical trial and to provide practical advice for managing study participants, including information about dosing and safety monitoring procedures. Institutional Review Boards (IRBs) and ethics committees also review the

document when deciding on approval for clinical research involving human participants. IBs are required for Investigational New Drug (IND) applications in the U.S., as well as Investigational Medicinal Product Dossier (IMPD) submissions in Europe. Incomplete or missing information in an IB could delay regulatory approval or result in a clinical hold on a proposed or ongoing investigation.

The ICH E6 guideline on Good Clinical Practice (GCP), which provides the official guidance for producing an IB, contains a suggested layout for the document's required elements, which establishes a table of contents that nearly all IBs follow. In addition to describing the study drug, including its physical and chemical properties along with manufacturing information, the guidance requires that the IB include an overview of non-clinical and clinical studies conducted with the investigational product and a guidance for investigators on using the drug in clinical trials.

"The intended purpose of the document is to inform the investigator—not in layman's terms, but in scientific terms—what to expect with the drug, dosing modifications and manufacturing practices. It can be important. For example, if a patient has a known allergy to an excipient product—one of the fillers—then the PIs should be familiar enough with the manufacturing of the drug to know what the excipients are in the product. CROs, the FDA and other regulatory agencies expect PIs to be knowledgeable and have that information," said INC Research/inVentiv Health's Meyers.

The ICH E6 guidelines, however, offer only general recommendations for the outline and content of an IB and each sponsor develops its own approach for presenting the document. As a result, investigators report the quality of IBs can vary greatly from company to company. The most poorly developed IBs include those with only a very limited number of figures or graphs or that read as marketing material for venture capital investors. Other less successful IBs primarily consist of large data tables and lack sufficient summaries or analysis. Investigators also consider IBs that are disorganized or inflated with lengthy summaries of similar, unsuccessful therapies uninteresting, even though they are vested in the clinical research program.

"If I am certified as a clinical investigator, when I run a clinical trial, I want to read a brochure that doesn't waste my time. If it's well-organized, well-written and very coherent, it will make logical sense to me. It wouldn't be a bunch of fragments thrown into a book. Putting the history into a well-organized story line and then pulling forward the most important things is critical," said Frestedt.

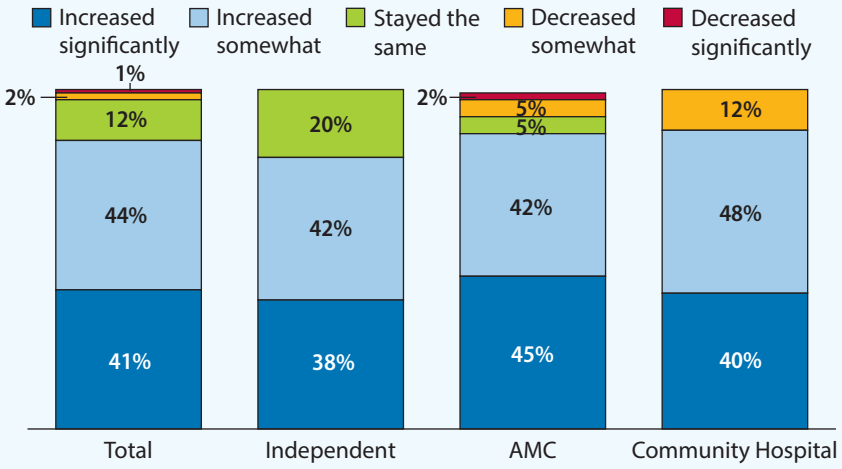
The sheer size of IBs, which can span up to 500 pages, can also make it difficult for investigators to read thoroughly. The first edition of an IB will typically focus on preclinical data and must be updated throughout the development program as new clinical data or safety information becomes available. ICH E6 recommends that an IB be reviewed at least once a year and revised when necessary. Some companies re-evaluate the IB at each update to determine if any of the existing preclinical data can be summarized or moved to an appendix, but often the new information is simply attached to the existing document, which results in not only a lengthy, but often disjointed document. Increasing regulatory requirements for more studies and safety data to bring a new drug to market have also contributed to an increase in the size of the IB over the years. CenterWatch data shows the average number of pages in an IB increased 60% from 2002 to 2014.

Ultimately, organizations face a challenge in creating an IB that meets regulatory requirements, gives investigators the information they need to ensure patient safety and isn't too difficult to read.

"It's a tough balance," said Joseph A. Franciosa, M.D., an independent pharmaceutical consultant for more than 20 years and experienced clinical trial investigator. "Who is this document for? The regulator or investigator? It comes down to how readable you make it, what the investigator needs to know and what needs to be included because the document ultimately needs to go to regulatory authorities the next time you have to submit something about the drug. You want to make sure you

Perceived increase in burden of regulatory tasks

Compared to two years ago, would you say the total cost/burden associated with regulatory tasks for a single clinical study at your investigative site has:



Source: CenterWatch-Complion Study, 2015; n= 164 investigative sites

are ahead of the game and make sure that you've got everything in it that the regulatory authorities require. You don't want to go back and do it again."

IBs rarely used as intended

Investigators should review the IB before conducting a study to become familiar with the investigational drug, its mechanism of action and what previous studies have found. Practically, however, investigators tend to read the high-level summaries for the main sections and examine particular tables and graphs. Investigators are more likely to read an IB from beginning to end for phase I or oncology clinical trials or when testing a novel compound. For phase III trials, however, investigators might not be interested in reading the sections on animal data, manufacturing or even phase I testing.

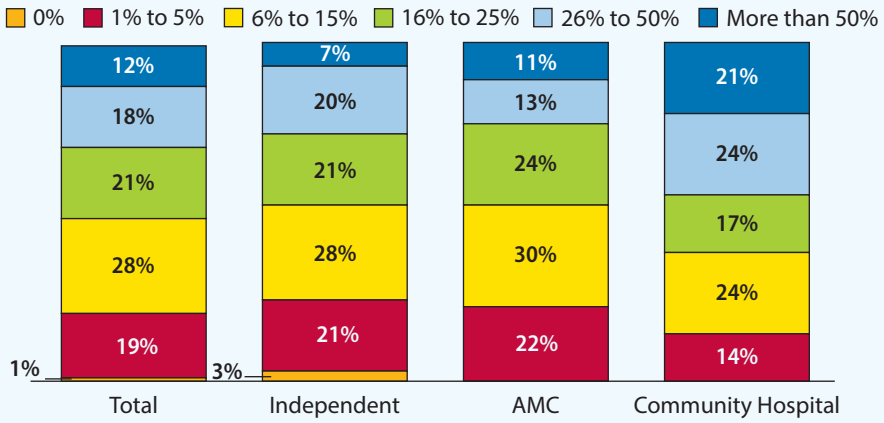
"I have actually read IBs cover to cover. I have a background in pharmacology and it doesn't take me that long to review them. But that would just be for a new molecular entity that is important to understand," said David J. Morin, M.D., director of Clinical Research at the Tennessee-based Holston Medical Group. "Otherwise, if it's a drug that belongs to the same class as another drug I am studying, I am going to look at the preclinical and human summary data in the IB. The preclinical summary will include the animal data, but I will want to hone in on the human summary data about tolerability and adverse events."

IBs are meant to be used as a reference document throughout the conduct of a clinical trial to answer questions about serious adverse events, dosing and manufacturing. In practice, however, even when IBs are distributed digitally as a PDF document, they usually lack a search function or the ability to bookmark information. In addition, IBs don't always have the most up-to-date information on questions such as dosing requirements for a specific patient subpopulation or expected serious adverse events; investigators often consult the protocol or call a study monitor to answer concerns instead. Similarly, although updating IBs has historically been a way to communicate evolving safety information to sites, investigators typically receive updated safety reports about serious and unanticipated adverse drug reactions before the information is included in a revised IB.

"A big problem with the IB is that many PIs and sites expect the protocol to be consistent with the investigator's brochure," said Meyers. "For example, the protocol may have updated safety information that is more relevant and current than the IB. Most companies adopt a strategy of updating the IB annually. By regulation, the IB should be updated anytime significant safety findings are discovered, so at a minimum, it should be updated annually. However, if a new protocol is being written for a program, often the protocol and the IB will have inconsistent information on the adverse event profile. If an auditor were to compare the expected side effects for the frequency of headache, for example, between the protocol and the IB, often they don't match because they are not updated on the same schedule."

Franciosa added, "The fundamental question is, how much do investigators use them? My guess is not very much."

Proportion of physical office space dedicated to regulatory document storage



Source: CenterWatch-Complion Study, 2015; n=164 investigative sites

Opportunities for improvement

Jeff Kingsley, D.O., chief executive officer of IACT Health, a clinical trial research company with 10 locations in the state of Georgia, said IBs could become more effective by clearly communicating in the introductory summary why investigators should care about the study drug. Particularly if the investigational product isn't a first-in-class or novel drug, investigators want to understand the rationale for the development program. What is exciting about the compound? Why should the physician care? Is it expected to be dramatically better than the standard of care? Is it being developed to go on formulary? What does the previous data or modeling show? Investigators could be more motivated to enroll patients on a clinical trial if they understood why the drug could make a difference.

"At the beginning of every trial, either I or someone on my team looks at the investigator's brochure to find out what is exciting about this research. Why should we care? Why is this research being done in the first place? Why does it matter to patients? Why should community physicians get excited? What is the walk-away message? I look at the introductory areas to

find that and they fall short. They do a very poor job of telling me why I should care," Kingsley said. "The purpose of an investigator's brochure is to teach and communicate, not just to produce data. But they don't really communicate."

William B. Smith, M.D., president and principal investigator at New Orleans Center for Clinical Research and Volunteer Research Group, multispecialty clinical research groups with headquarters in Knoxville, Tennessee, said IBs would be easier to use and save investigators time if they provided better summaries of study data. Although the documents present adverse events associated with each previous study or groups of studies, Smith also wants to see the overall incidence of AEs across the program. Similarly, other investigators reported the need for IBs to provide not only tables of data, but also analytic summaries.

"Investigator brochures have gotten bigger and have more information," said Smith. "We need all of the information and the IBs can't cull selective information, but by the same token, they would be much easier to work with if there was better summary data. If I was concerned about something, I could go back and look in more detail at certain areas, particularly as it relates to pharmacokinetics, pharmacodynamics and adverse event profiles, without having to wade through each study or group of studies, particularly those in the preclinical and early phase."

Richard Litov, Ph.D., director of Pedia Research, a dedicated site business with locations in Owensboro, Kentucky, and Evansville, Indiana, said unless IBs become more user-friendly, their value as a resource for sites isn't likely to improve. He suggests that organizations could increase the visibility of IBs and the information they contain by developing a one-page synopsis, perhaps adding color, that present key elements about the study drug in a simple bullet format. The synopsis, which could be referenced in background discussions about the drug at investigator meetings, could include information such as the number of phases in the development program, typical side effects of the investigational product or how many patients have been exposed to the drug.

"It's an important and very confidential document with a lot of very useful information. But most physicians and investigators don't have time to read through it and many probably don't know what it is. IBs aren't usually reviewed at the investigator meetings," said Litov. "Companies need to make the IB interesting enough for investigators to really look at and read."

Any effort to improve the usability of IBs, however, would need to avoid introducing any bias. Regulatory guidelines require that IBs be presented in an objective, non-promotional form that allow investigators to make their own unbiased risk-benefit assessment. Some veteran investigators question whether substantive changes of IBs would be a good idea.

"I don't mind change. If you like research, you better like change. That is what you work in every day. But there are some things that we need as a solid anchor. The IB is a solid anchor," said Morin, who has been conducting research for almost 30 years. "By their nature, IBs are detailed and comprehensive. That should not change. They don't need to be made any lighter or less informative. They should be as neutral as possible and let the reader interpret what is important and what is not important."

Meanwhile, INC Research/inVentiv Health's Meyers believes the industry could better use IBs to help sites with the safety portion of clinical trials if the content was electronically integrated with other clinical trial systems to flag unexpected serious adverse events and improve the timeliness of safety reporting. Some companies have established portals that give sites access to IBs and other clinical trial information, including the protocol and training materials, but companies historically have been slow to make digital versions of IBs available or to integrate the content into clinical trial systems out of concerns about intellectual property breeches.

"I have not seen this done, and it would take a fantastic programming effort and a lot of multidisciplinary functions to do this, but one idea would be that when sites enter information about a particular adverse event, the data entry module would be smart enough to know whether it was an expected versus unexpected event," said Meyers. "There would be triggers or dingers built into the systems that intuitively know that, for this patient population in this protocol, the event is not expected in

Contents of investigator's brochure—Section 7 of ICH E6 guidance on GCP

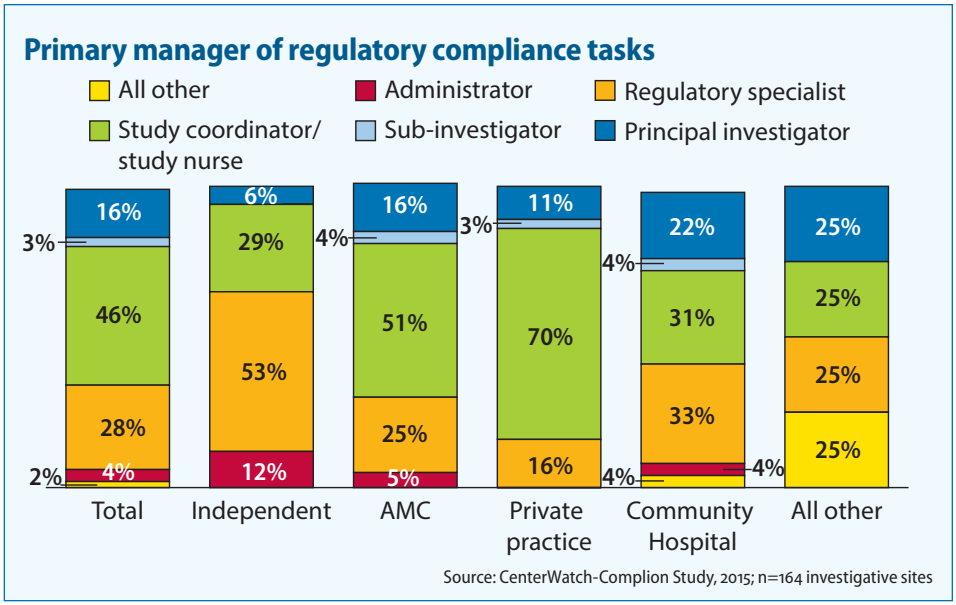
- Table of contents
- Summary
- Introduction
- Physical, chemical and pharmaceutical properties and formulation
- Non-clinical studies
- Effects in humans
- Summary of data and guidance for the investigator
- Appendix

the IB. An alert could refer the data entry person, who is usually not the PI, to the investigator's brochure."

The system would only work, Meyers added, if the IB document is maintained in a timely way. New technology platforms would also need to be designed and implemented in a way that wouldn't add to the workload at investigative sites, which already manage many disparate technology systems.

Looking ahead

While IBs compile the most comprehensive information available about an investigational product, the size and complexity of the document makes them difficult to use as intended. Addressing the way IBs are developed and leveraged in clinical research presents significant opportunities to ensure that they are not only a document that meets regulatory requirements, but can also become a more useful resource for investigators who need critical information about the study drugs in their clinical trials.



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