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PEER REVIEWED

## **Investigator Compensation: No One Size Fits All**

Suzanne J. Rose, MS, PhD, CCRC, FACRP



Managing investigator payments is probably one of the most challenging aspects of conducting a clinical trial, but it seems that it is the best kept secret in our industry. It is the topic that generates the most interest when discussed with colleagues, but unlike other straightforward processes in our industry, the topic of investigator compensation is one that has guidelines but no specific steadfast rules to let us know if we are compensating appropriately or inappropriately. While

there are several models that are discussed in the literature, {1–4} there is no clear consensus on which model is the best fit for each site.

The first step in de-mystifying the conversation on investigator compensation is to identify and explain key operational and compliance factors for consideration, such as fair market value (FMV) and equity across specialties. Does one or can one size fit all? How much should we pay investigators for their work on a clinical trial and what laws govern investigator compensation so that we remain compliant? While it is important to understand the Stark Law and the Anti-Kickback Statue, and the exceptions and Safe Harbor that allow physician payments, these are excellently described elsewhere. {2}

We will therefore focus on FMV because amounts paid to investigators are considered part of their overall compensation amount and therefore subject to the FMV Guidelines. Importantly, both FMV and commercial reasonableness are important concepts in the Anti-Kickback Statute Safe Harbors and Stark exceptions. {2} In addition, as most principal investigators (PIs) are physicians, the American Medical Association (AMA) provides clear guidelines on managing

conflicts of interest in the conduct of clinical trials, in that financial compensation should be at FMV and the rate of compensation per research participant should not change pursuant to the number of subjects enrolled by the physician.{5} Thus, the rate of payment for professional services should remain constant irrespective of the PI's success enrolling or completing study subjects compared to their target.

## **Background**

The concept of FMV extends back 120 years{6} and is described in the *Code of Federal Regulations* as “the price at which the property would change hands between a willing buyer and a willing seller, neither being under any compulsion to buy or to sell and both having reasonable knowledge of relevant facts.”{7} The Centers for Medicare and Medicare Services (CMS) defines market value as “the value in arm's length transactions, consistent with the price an asset would bring as the result of bona fide bargaining between well-informed buyers and sellers who are not otherwise in a position to generate business for the other party.”{8} In 2003, FMV for research studies was first included in the Office of Inspector General (OIG) regulations stating “Payments for Research Services should be fair market value for legitimate, reasonable and necessary services.”{9}

However, even with the clear instructions above, the rules do not provide advice on determining the FMV, which puts sites at risk. If the investigator is paid above FMV, it can give the appearance that it would influence his or her decision to participate in the trial or to influence the outcome of the trial, thus placing the institution at risk from legal and regulatory perspectives. If PIs are paid below FMV, they may not be willing to participate fully or enroll research participants, which could impact relationships between sites and sponsors. At the end of the day, there is no perfect percentile that exists for FMV calculation, as FMV for an investigator truly depends on medical specialty, geography, and physician experience.{10}

However, the following are helpful hints for a site to stay in line with FMV:

- Determine a pricing strategy with the billing team: Engage the billing team as partners in the pricing strategy. An important goal of any research study should be to properly compensate the hospital or private site for investigator time.

- Update the fee schedules on a yearly basis: Variations in compensation rates should be monitored closely on an annual basis to ensure FMV is appropriate by region and specialty.
- Provide full justifications for all fees charged in a clinical trials budget: The budget negotiation should not be a guessing game or contentious. Clearly outline all fees and justifications therein. Provide justifications up front, not when asked for them.
- Engage internal support or external vendor to create research and/or administrative hourly compensation fee schedules: There are several firms that can assist in developing your organization's internal compensation reference materials to be used in establishing the framework and market data consistent with your compensation philosophy related to physician research and/or administrative work effort. These firms can provide FMV payment (hourly rate) range recommendations for various physician specialties providing research and/or administrative services.

Finally, best practice is to create a FMV policy in writing to defend your site's actions and to prove transparency. In addition, please remember that a physician's "going rate" or past compensation does not necessarily constitute FMV; further, the values for administrative services most likely differ from those for clinical services. Therefore, it is important to engage a third-party vendor to clearly differentiate between research and/or administrative services.

## **PI Compensation Structure**

Investigators can contribute to study in many ways,{1} and therefore the compensation should be fair, motivational, affordable, practical, legal, and agreeable.{3,4} To structure the investigator compensation model, we should include considerations for (clinical) relative value unit (RVU)-based services vs. administrative work in these models.

### *Relative Value Units (RVUs)*

RVUs are measures constructed by Medicare to estimate productivity by calculating the relative level of physician time, skill, and expertise. Medicare relies on these measures to establish payment levels for physicians' services which are then described by Current Procedural Terminology (CPT) codes. This compensation model is typical when a hospital also employs physician-investigators as clinicians, and they earn RVU credits when they perform clinical services with CPT codes that are part of the clinical trial.

It is helpful to utilize different terminology when incorporating research RVUs into an existing electronic medical record. To this end, we have established “research RVUs,” which are calculated per hospital policy as 1.5 times the Medicare rate across all specialties with one average RVU per visit type. At the end of the day, all RVUs end up in one bucket and look like regular RVUs. This way, regular patient visits are not seen as competition with research and the physicians are motivated to perform research in an existing RVU model.

When incorporating an RVU model into your investigator compensation program, it is important to remember that the model needs to account for research time with no corresponding CPT code. In addition, for study-specific oversight and research fees without CPT codes, the investigator cannot receive RVU credit and is paid according to FMV, as discussed previously. {2}

### **Compensation Models (External to RVUs)**

*Fixed Fee or Percentage:* The site pays investigators a fixed fee or percentage for studies, regardless of their contributions. These options are simple to manage but difficult to assess if they accurately reflect the FMV of the investigators’ services.

*Research Salary:* At research sites where the investigators are employed by the site, investigators are paid a fixed salary for all their time spent working on clinical trials and all parties know the exact amount that will always be paid.

*Hourly Wage:* The site can compensate the investigator specialty-specific hourly rates for tracked time on a specific study along with activity performed. This can be seen as additional work by the investigator, who may balk at extra time spent on tracking their hours.

*Fee for Service:* The site compensates the investigator for specific services performed or time spent. This option is more time-consuming to administer, but strongly motivates investigators to perform the services they are contracted for.

*Sub-Investigators:* While the role of investigator is usually limited to a licensed physician, the sub-investigator role can be much more inclusive to include mid-level providers, such as physician assistants, nurse practitioners, and, at academic medical centers, residents and fellows.

They play various roles in a study and are often essential for success of the trial. Fee for service typically works well for sub-investigators and can be tracked inside the budget, via a spreadsheet or clinical trial management system. It is important to understand any sub-investigator's current payment structures inside the site or healthcare system and work with administration to ensure that salaried positions are capable of being compensated above and beyond their current salary structure, as well as being compensated for RVUs similar to their physician counterpart. At academic medical centers, payments to residents and fellows outside their salary will need to be carefully discussed and negotiated with the Graduate Medical Education Office and adhere to AMA guidelines.

*Hybrid Model:* In this model, a variety of the above options can be utilized. Fixed fees could be utilized for costs that are consistent from study to study, such as site initiation or monitoring visits. Fee for service would then be utilized for study procedures because they would be variable from visit to visit and study to study. An agreed-to administrative fee (in line with FMV) per visit type can also be included in this model along with research RVUs. The investigator then understands that compensation will be adjusted from study to study. This system is consistent with the financial success of the study while remaining within the regulatory guidelines.

Special considerations for all models:

- If the investigator is billing a third party/subject for routine services that are in the protocol, the site cannot also compensate for those services, meaning the physician or site cannot get paid twice.
- Ensure all investigators' work and time efforts are documented clearly.
- Written contracts and expectations are vital and should follow the guidelines set forth in The Personal Services and Management Contracts Safe Harbor or The Personal Service Exception. {2}

Regardless of the compensation structure, at the end of the day, it is important to remember that according to the tenets set forth by the International Council for Harmonization's Good Clinical Practice guidelines and the U.S. Food and Drug Administration, bonuses, finder's fees, or pay-for-performance to PIs based on the number of participants enrolled in or completing the trial are completely unacceptable. {11}

## **Compensation Models for Different Types of Physicians: Private vs. Hospital Based**

### *Hospital and Medical Group Physicians*

When working with physicians inside our system, the use of the centralized research office is required. We provide a consistent process to all studies so that all budgeting, contracting, regulatory approvals, and staffing issues are covered from study start-up to close-out to provide a concerted approach. All research funds are routed directly to the centralized research office with quarterly reimbursement made to research partnering physicians. We draft a master agreement with each physician and then utilize sub-orders to outline each study reimbursement and what payment schedule will be. The compensation follows a hybrid model approach including fixed fees, fee-for-service, RVU considerations, and administrative oversight fees.

We do have physician groups that request the money be distributed evenly across investigators or returned to their departments. Alternately, in departments where the studies might be supported by only one or two investigators, they opt to be paid individually. We always have these discussions up front, so they understand the options available to them. This model allows great flexibility amongst our physician groups, and they are able to feel engaged in the conversation from start to finish.

### *Private Physicians*

When working with private physicians, understand that they have the desire to keep their patient population yet also are aware of competitive study enrollment. Private PIs can use their own clinical research staff (if they have them) or utilize our site staff if they lack adequate study support. In this scenario, a master agreement is drafted with each private physician group and then sub-orders are utilized to outline each study reimbursement and what the payment schedule will be. Compensation is provided for specific services performed by private physicians and their research staff following a fee-for-service model.

When we work with private PIs who provide all the staffing for studies yet require the use of the physical hospital space, we draft a facility use agreement where we can charge for management

of study drug, supplies, equipment, and oversight of any research billing that may occur. Some physicians find us so helpful to work with that they have stopped performing research procedures at other hospitals, which brings in revenue for the hospital and procedures we might not have captured previously.

## Conclusion

Investigator compensation is not a one-size-fits-all model. It includes an open and honest discussion with the investigator in addition to adhering to FMV and staying within ethical guidelines. Investigators should be motivated, but not incentivized, to perform clinical trials and view this engagement as a partnership to enhance research efforts to better the lives of our patients.

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SPECIAL FEATURE

## **How and Why Bayesian Statistics Are Revolutionizing Pharmaceutical Decision Making**

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Over the past 20 years, there has been growing interest within the pharmaceutical industry in Bayesian statistics and how to apply this methodology toward reaching goals in the arenas of research, development, manufacturing, and health economics.

The Bayesian approach to pharmaceutical decision making started to gather greater momentum after the first Applied Bayesian Biostatistics conference in 2010, which brought together academicians, industry representatives, and regulatory authorities to discuss the practical implementation of Bayesian statistics in speeding up drug discovery, development, and approvals. Increasingly, pharmaceutical companies have been turning to Bayesian biostatisticians to apply probabilities to statistical problems to determine likely outcomes—in clinical trials, in product development, in manufacturing, in post-market surveillance, and in market access.

While regulatory authorities have been slower to adopt Bayesian methodologies, that is starting to change. The U.S. Food and Drug Administration (FDA), in particular, has embraced Bayesian statistics as a method for supporting clinical trials in medical devices, in adaptive clinical designs, and in rare diseases.

This paper explores the growing significance of Bayesian statistics in supporting decision making across the development and regulatory processes, and its potential to improve outcomes for the biopharmaceutical industry.

## **How an 18th Century Methodology is Gaining Traction Today**

For more than a half a century, traditional frequentist statistical methodology—where predictions are based on a fixed target of estimation—has been entrenched in clinical development and regulatory statistics. Yet, all too often drugs fail late, even in confirmatory clinical trials, at enormous cost to companies and ethical concerns for the patients, suggesting some shortcomings in these traditional methods.<sup>{ 1 }</sup> As pressure to reduce costs and improve regulatory decision making early in the process intensifies, companies have sought more efficient ways to analyze data and assess the safety and efficacy of drugs.

It turns out that one of the most effective tools for synthesizing clinical trial data is far older than even the clinical trial process itself: Bayesian statistics.

Bayes Theorem was formulated by the Rev. Thomas Bayes, an 18th century English mathematician, philosopher, and Nonconformist minister. However, it wasn't until the 1990s, when advances in computing technology emerged, that its techniques could be usefully applied.

Interest within the pharmaceutical industry in applying Bayesian methods at various stages of research, development, manufacturing, and health economics has been growing for the past 20 years because it applies the logic of probability to statistical problems, based on observed data.<sup>{ 2 }</sup>

### **Comparing Statistical Methods**

Mathematical methods have long been used to assist with decision making in clinical research, with researchers often depending on the  $p$ -value, or observed significance level, to test whether something is statistically significant. The point is to determine the significance of the results from a study in relation to the null hypothesis, which states there is no difference between two variables. If the data sample size is big enough, then the distribution of the test statistic is roughly normal (bell-shaped) and can give you the  $p$ -value. However, if there isn't a large sample of data, it becomes impossible to produce a reliable inference.

For example, if researchers are gathering disease rates by county or state, it's relatively easy to gather good estimates in urban areas, but in sparsely populated rural areas, the estimates are not necessarily reliable. Two breast cancer cases in one small area in a year may raise suggestions of a cluster because, based on traditional statistical methods, the resulting rate is far higher than expected; seeing zero cases a year later would be just as uninformative. To make sense of the data, statisticians have to smooth the spatial maps and produce a more accurate picture of those cancer rates.

Bayesian methods help to achieve this by borrowing strength from observations across similar but not identical bits of information; for example, cancer rates across the map in question. In Bayesian statistics, previous and related information is relevant. Past information—whether from previous trials, scientific literature, or real-world data—is considered as part of an ongoing stream of data, “in which inferences are being updated each time new data become available.”<sup>{3}</sup> This allows researchers to achieve direct probability statements about unknown information, rather than settling for approximations.

### **Why Bayesian Makes Sense in the Pharmaceutical World**

What, though, does all this mean for clinical trials and drug development? As everyone in the industry knows all too well, the drug approval process is costly, complex, and time-consuming. During clinical trials, companies need to know whether a drug under development is safe and effective, as well as its likelihood of success in the marketplace. This is where Bayesian methodology comes to the fore. It addresses the probability inference: What's the probability that this new drug is safe and effective? What is the probability our current drug development program will be successful?

In most development programs, companies already have some information about a molecule or therapy from previous studies, either conducted by that company or by others. Rather than start from scratch, Bayesian statistics allow researchers to leverage this pre-existing information—including from scientific literature—to help determine the probability of success.

When a trial is conducted using Bayesian principles, initial estimates of probabilities are attributed to unknown quantities (the likelihood of a serious event, the likelihood the product will be effective for a given set of patients, etc.) using existing information (e.g., previous clinical trials) or expert opinion. These probabilities together constitute the *prior distribution* for the quantities of interest.<sup>{3}</sup>

As long as those conducting the study construct the prior distribution in an unbiased way (i.e., incorporating all existing knowledge, not merely that which is favorable to the company's position), leveraging this information to support a study can dramatically improve study accuracy and efficiency. It is also economically and ethically preferable to limit the number of in-human studies conducted whenever possible.

Regulators can sometimes be somewhat more rigorous when it comes to Bayesian analyses, because they are less familiar with it than the traditional  $p$ -value approach. However, this tends to encourage careful, less automatic analyses that are typically very robust, and more formally consider the impact of multiple different models and assumptions.

That is not to suggest that Bayesian methodologies are a replacement for  $p$ -values, which answer a fundamentally different question than Bayesian probabilities. “The  $p$ -value quantifies the discrepancy between the data and a null hypothesis of interest, usually the assumption of no difference or no effect. A Bayesian approach allows the calibration of  $p$ -values by transforming them to direct measures of the evidence against the null hypothesis, so-called Bayes factors.”<sup>{4}</sup>

For example, in a genomics experiment, researchers will put some of the drug or molecule into cells to assess the expression of different genes. The question in this case will be, is the inhibition or excitation of the genes likely linked to the treatment? Here, researchers may legitimately be interested in the  $p$ -value; they want to know if the data they see are inconsistent with the hypothesis of no differential inhibition or excitation across genes. In such cases,  $p$ -values provide fairly straightforward yes-no answers because the very question is about the observed data.

However,  $p$ -values have a number of problems that limit their effectiveness even when used correctly. This was emphasized a few years ago by the American Statistical Association (ASA), which released an official “Statement on Statistical Significance and  $P$ -Values,”<sup>{5}</sup> and later held two conferences devoted to an investigation of their problems and potential remedies—many of them Bayesian. The ASA statement emphasizes various misconceptions about  $p$ -values, including the facts that they are not the probability that the null hypothesis is true, or the probability that the data were obtained “by chance alone” (two very common though falsely held beliefs).  $P$ -values do not measure the size or importance

of an observed effect and can only provide evidence against a hypothesis of no difference, not evidence for it. As such,  $p$ -values are not useful in proving the equivalence of two treatments.

When conducting a clinical trial or animal study to evaluate the efficacy of a treatment, the question is not about the data itself, but rather about the treatment: Is the treatment effective? Is it safe? How likely is it that a trend emerging in the data will continue in the future? This is where Bayesian methodology has even greater usefulness. To predict a future situation, Bayesian statistics enable researchers to determine the probability of something occurring by first quantifying current uncertainty, and then propagating that into the future to get predictive probabilities. The question then is about the benefit for future patients in future trials or in the real world (i.e., not for the patients included in the past trials).

This current and future uncertainty is common in chemistry, manufacturing, and controls (CMC) applications where companies need to be able to quantify what they know now about product characteristics or manufacturing processes and combine that with additional uncertainty about what will happen in the future. It allows researchers to address the real questions of interest: Is a process comparable to a previous one? What is the probability that a development approach is on target given the observed data?

Bayesian statistics combine all that complicated and high-dimensional data, and, using 21st century computing power and experts in mathematical probability theory, develop modeling to predict a likely future outcome.

### **Supporting Decision Making in a Competitive Market**

The enormous cost of bringing drug products to market, combined with the shift away from blockbuster product development and toward personalized medicines, often targeting rare diseases, means the paradigm for product development is changing. The past practice of using trial and error to make decisions about clinical trials, manufacturing processes, regulatory practices, or any other part of the pharmaceutical value chain is proving to be highly ineffective.

Regulatory leaders also recognize the need for new methodologies to support clinical trial design. For example, the FDA has issued guidance for industry on Complex Innovative Trial Designs (CIDs) for Drugs and Biological Products, providing advice on interacting with the agency in the development and

regulatory review of such products. {6} As the guidance notes: “Bayesian approaches may be well-suited for some CIDs intended to provide substantial evidence of effectiveness because they can provide flexibility in the design and analysis of a trial, particularly when complex adaptations and predictive models are used. In addition, Bayesian inference may be appropriate in settings where it is advantageous to systematically combine multiple sources of evidence, such as extrapolation of adult data to pediatric populations, or to borrow control data from Phase II trials to augment a Phase III trial.”

Sometimes a drug might work for one patient population but fail with another, and there may be multiple reasons for that, including some tied to patients’ behaviors. As an example, at the outset of the AIDS epidemic in the 1980s, the majority of clinical trials were conducted on predominantly gay men from San Francisco and other diverse, urban areas. These men were largely compliant in their trial behavior: they stayed on their assigned treatments and dramatically reduced their risky behaviors. The result was these early trials were able to show that the drugs worked. Later in the epidemic, however, when different populations started getting HIV (for example, IV drug users from economically disadvantaged neighborhoods), these groups were sometimes less able to comply with rigid trial protocols. The result was that drugs already approved by regulators for treatment of HIV did not work in the “real worlds” of these later patients. An effective statistical approach must adjust for these differences.

What Bayesian inference allows researchers to do is, rather than keep conducting randomized trials, adjust for individual characteristics—based on where a patient lives, how old they are, their gender, their doctor, their socioeconomic status, drug use, etc. By adjusting for those real-world, confounding variables, Bayesian enables an innovative approach to data analysis with a focus on solutions.

Most important is that by leveraging prior knowledge—from previous clinical trials, scientific literature, or real-world data—Bayesian statistics allow researchers to reduce the number and size of clinical trials and help to determine the probability of success before entering Phase III trials. It does this by injecting flexibility into the way the trial is designed, to ensure projections aren’t overly optimistic, thereby accounting for the probabilities of unknown issues occurring.

Changing the paradigm of clinical trials is not only more practical and financially beneficial, but also potentially more ethical, particularly when conducting studies into treatments for rare or pediatric

diseases. Not only are researchers working with a much smaller sample size of patients, but they are also working with very vulnerable patients. In some diseases, for example, life expectancy of the patient may be very short, and including a randomized parallel control study arm would strike many as unethical. Instead, by leveraging information from past studies and the literature, researchers can eliminate or at least dramatically reduce the need for a control group and ensure new treatments are tested on the patients who really need it. Bayesian statistics support that cumulative learning process by connecting the dots across different studies to support decision making in a formal way.

Bayesian methodology can also help companies make economic decisions, such as whether to build a manufacturing line for a drug in development. This is a difficult decision: If the company decides to invest in building its facility early and a drug fails in clinical trials, that investment is wasted. On the other hand, building a plant can take several years, and if the company waits for regulatory approval to begin building the facility, it will be years before that company is able to sell the approved product. Using Bayesian statistics, it is possible to compute the future probability of success during the Phase III trial and make a risk-based economic decision from that assessment.

Similarly, in portfolio management, Bayesian methodology can help companies to compute the probability of success of each of their compounds and thus decide where to invest future resources. The point is that the methodology can assist companies with making smart investment decisions through its ability to estimate probabilities of future success.

### **Into the Future with Bayes**

The pressing needs of both companies and patients to improve the framework for making decisions has led many biopharmaceutical companies to seek out statistical experts specializing in Bayesian methodology. Many recognize the potential Bayesian statistics present to address complex problems that arise across the product lifecycle—from the probability of success with clinical trials to managing CMC and supply chains to determine the best course of action with the product portfolio.

More recently, the Bayesian momentum has gathered pace. In 2010, the first Applied Bayesian Biostatistics conference was held with a goal of stimulating the practical implementation of Bayesian statistics for the purpose of accelerating the discovery and delivery of new cures to patients.<sup>{2}</sup> That conference and others brought together a wealth of insights and knowledge that formed the basis for an

award-winning book offering an overview of Bayesian methods applied to nearly all stages of drug research and development. The book, entitled *Bayesian Methods in Pharmaceutical Research*, was announced as the 2021 winner of Best New Bayesian Statistics Book, Best New Biostatistics Books, and one of the Best Statistics eBooks of all time by BookAuthority.

Insights from the book and from experts in the field of Bayesian statistics and their applications in the pharmaceutical industry will play an important role in improving understanding of ways to apply statistical methods to pharmaceutical problem solving.

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## ACRP HOME STUDY

### CLINICAL RESEARCHER—DECEMBER 2021 (VOLUME 35, ISSUE 9)

*Parts of a Whole: Evaluating and Elevating Your Role in the Clinical Research Enterprise*

#### Article #1: Investigator Compensation: No One Size Fits All

##### LEARNING OBJECTIVES

After reading this article, the participant should be able to define fair market value and relative value units (RVUs), describe their relevance to investigator compensation for clinical trials, and cite several examples of compensation models which may be chosen as alternatives to RVU-based ones.

##### DISCLOSURES

Suzanne J. Rose, MS, PhD, CCRC, FACRP: *Nothing to disclose*

**1. What are the American Medical Association's expectations regarding financial compensation to physicians for enrollment of subjects into clinical trials?**

- a. The rate of payment changes depending on how far from the study site the subjects live.
- b. The rate of payment decreases if fewer subjects are enrolled than targeted for the study.
- c. The rate of payment does not change depending on how many subjects are enrolled.
- d. The rate of payment increases when enrollment exceeds the target for the study.

**2. Which of the following is a reason that principal investigators should not be paid above fair market value for their work on clinical trials?**

- a. It can encourage investigators to study competing products.
- b. It can give the appearance of influencing the outcome of a trial.
- c. It can persuade subjects to demand higher compensation.
- d. It can drive clinical research coordinator turnover trends.

**3. Which of the following is a reason that principal investigators should not be paid below fair market value for their work on clinical trials?**

- a. They may choose to conduct less risky studies.
- b. They may need to conduct too many studies at once to compensate.
- c. They may not receive institutional review board approvals.
- d. They may not be willing to participate fully in a study.

**4. What does the author recommend regarding fees charged by investigators in a clinical trials budget?**

- a. Provide clear and full justifications for all fees charged up front.
- b. Update the fee schedules every time a new study is performed.
- c. Keep the hospital's or private site's billing team out of the process.
- d. Do not factor in hourly rates for research and/or administrative effort.

**5. What is the purpose of relative value units?**

- a. Estimating a physician's compensation based on the number of study subjects.
- b. Estimating a physician's expertise based on the results of previous studies.
- c. Estimating a physician's productivity based on their time, skill, and expertise.
- d. Estimating a physician's skill based on feedback from study sponsors.

- 6. Who pays investigators for time spent on a clinical trial under a “research salary” compensation model?**
- Study sponsor
  - Volunteer subjects
  - Private donors
  - Study site
- 7. Which of the following is noted as a special consideration for all research compensation models?**
- Physicians cannot be paid twice for the same services.
  - Sponsors cannot support identical studies at competing institutions.
  - Subjects cannot be billed for routine services in the protocol.
  - Compliance officers cannot access data on payments to investigators.
- 8. Which of the following is deemed an unacceptable compensation practice according to ICH Good Clinical Practice guidelines and the U.S. Food and Drug Administration?**
- Fee for service arrangements with sub-investigators working on a trial.
  - Bonuses to investigators based on the number of participants enrolled in a trial.
  - Sites paying investigators a fixed fee or percentage for studies.
  - Drafting master agreements on study reimbursements with private physician groups.
- 9. How does the author’s institution manage research-related reimbursements to physicians within its own system?**
- Through an institutional review board.
  - Through an ethics and compliance office.
  - Through a centralized research office.
  - Through a third-party vendor.
- 10. What does the author’s institution utilize in cases when working with private principal investigators who provide their own staff for a study yet need to use space at the institution?**
- A fee for service agreement.
  - A relative value unit waiver.
  - A non-disclosure agreement.
  - A facility use agreement.

## **Article #2: How and Why Bayesian Statistics Are Revolutionizing Pharmaceutical Decision Making**

### **LEARNING OBJECTIVES**

After reading this article, the participant should be able to summarize the advantages of using Bayesian methodology in clinical research, compare and contrast its application with that of  $p$ -values, and cite several examples of its usefulness beyond clinical trials.

### **DISCLOSURE**

Bruno Boulanger, PhD; Bradley P. Carlin, PhD: *Nothing to disclose*

- 11. Besides clinical trials, the authors note that Bayesian statistics are being used by pharmaceutical companies in which of the following areas?**
- Placebo blinding strategies
  - Post-market surveillance
  - Bring your own device practices
  - Trial master file management
- 12. The U.S. Food and Drug Administration is noted as embracing Bayesian statistics for clinical trials in which of the following areas?**
- Medical devices, rare diseases
  - Cosmetic products, animal studies
  - Multinational studies, repurposed drugs
  - Basket studies, expanded access
- 13. Although formulated in the 18th century, the techniques of Bayes Theorem were not applied until much more recently due to the lack of which of the following?**
- Pharmaceutical firms that saw their potential.
  - Clearance from the American Statistical Association.
  - Sufficiently advanced computer technology.
  - Proper understanding of how  $p$ -values work.
- 14. A  $p$ -value helps determine the significance of results from studies in relation to which of the following?**
- Randomization
  - Adverse events
  - The null hypothesis
  - The futility threshold
- 15. What do the authors write about the relevance of previous and related information in Bayesian statistics?**
- Past information from trials is only relevant if it comes from approved products.
  - Past information from previous trials, scientific literature, or real-world data is relevant.
  - Past information can only be factored in with approval from regulatory authorities.
  - Past information is never relevant to Bayesian methodology, regardless the source.
- 16. Which of the following is given as an example of “unknown quantities” related to initial estimates of probabilities when using Bayesian principles?**
- Preferred pricing for a therapy
  - Age range of study participants
  - Experience of principal investigator
  - Likelihood of a serious event
- 17. Which of the following is cited as a shortcoming of using  $p$ -values?**
- They cannot be used effectively for medical device studies.
  - They are too difficult for most software programs to handle.
  - They do not translate well for double-blinded protocol designs.
  - They are not useful in proving the equivalence of two treatments.

**18. What does the U.S. Food and Drug Administration say about the use of Bayesian approaches for Complex Innovative Trial Designs (CIDs) for drugs and biological products?**

- a. Their ability to provide flexibility in trial design and analysis make them well-suited for some CIDs.
- b. The low costs and time demands of these approaches mainly make them suitable for CIDs at start-up ventures.
- c. The most complicated Bayesian approaches should be reserved strictly for CIDs for very risky products.
- d. They should never be used for CIDs associated with first-in-human studies of any type of drug or biologic.

**19. Leveraging prior knowledge makes Bayesian statistics very useful for which of the following goals?**

- a. Reducing the number and size of trials in advance of Phase III.
- b. Minimizing the number of staff necessary to recruit participants.
- c. Allowing sub-investigators to handle most trial responsibilities.
- d. Convincing institutional review boards to sign off on safety reports.

**20. Beyond designing clinical trials, which of the following are cited by the authors as areas in which Bayesian methodology may help drug developers make important decisions?**

- a. Media relations and community outreach.
- b. Informed consent and medication compliance.
- c. Facility investments and portfolio management.
- d. Trial registries and financial transparency.