

**Article Title:** Streamlining Safety Data Collection in Hospital-Acquired Bacterial Pneumonia (HABP) and Ventilator-Associated Bacterial Pneumonia (VABP) Trials: Recommendations of the CTTI Antibacterial Drug Development (ABDD) Project Team

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## **Running Head**

Streamlining Safety Data Collection in HABP/VABP Trials

## ABSTRACT

**Background:** Resistant bacteria are one of the leading causes of hospital-acquired or ventilator-associated bacterial pneumonia (HABP/VABP). HABP/VABP trials are complex and difficult to conduct due to the large number of medical procedures, adverse events, and concomitant medications involved. Differences in the legislative frameworks between different regions of the world may also lead to excessive data collection. The Clinical Trials Transformation Initiative (CTTI) seeks to advance antibacterial drug development by streamlining clinical trials to improve efficiency and feasibility while maintaining ethical rigor, patient safety, information value, and scientific validity.

**Methods:** In 2013, CTTI engaged a multidisciplinary group of experts to discuss challenges impeding the conduct of HABP/VABP trials. Separate work streams identified challenges associated with current data collection processes. Experts defined “data collection” as the act of capturing and reporting certain data on the case report form as opposed to recording of data as part of routine clinical care. The ABDD Project Team developed strategies for streamlining safety data collection in HABP/VABP trials using a Quality by Design approach.

**Discussion:** Current safety data collection processes in HABP/VABP trials often include extraneous information. More targeted strategies for safety data collection in HABP/VABP trials will rely on optimal protocol design and pre-specification of which safety data are essential to satisfy regulatory reporting requirements.

**Conclusion:** A consensus and a cultural change in clinical trial design and conduct, which involve recognition of the need for more efficient data collection, are urgently needed to advance antibacterial drug development and to improve HABP/VABP trials in particular.

**Key words:** *hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia, data collection, clinical trials, CTTI*

## **Main Text:**

### **Introduction**

The emergence of multidrug resistant (MDR) Gram-negative pathogens in hospitals is an increasing threat to public health [1-3], and in recent decades, the approval of antibacterial therapies in the United States (US) and Europe, among other countries, has lagged considerably [4-6]. Several organizations and initiatives [7-9] have begun to publicize the global crisis of MDR bacteria to foster support for efficient development of new antibacterial drugs; however, particular attention to the challenges associated with hospital-acquired bacterial pneumonia (HABP)/ventilator-associated bacterial pneumonia (VABP) trials is also needed. In addition, patients with HABP/VABP often present with infections caused by MDR Gram-negative bacteria; hence, there is an unmet public health need to develop and approve new antibiotics effective in treating HABP/VABP.

Currently, there are a very limited number of clinical trials of new drugs for HABP/VABP in progress because several scientific and regulatory issues make these trials operationally and economically challenging. Protocols are complex, and data collection is driven in part by differences in various local and international regulations that govern these multinational trials. The complexity of HABP/VABP protocols is also increased by the large amount of medical data derived from the seriously ill and heterogeneous patient population enrolled in these trials. Figure 1 outlines the challenges and burden of excessive data collection for investigators, sponsors, and regulators. Collecting, monitoring, analyzing, and reviewing these large amounts of data, which may not all be critical to determining the efficacy and safety of the treatment, is a major source of inefficiency.

Important public discussions [10, 11] with participants from a variety of stakeholder groups to address possible solutions, including reducing trial complexity, are ongoing. This manuscript primarily focuses on the challenge of streamlining safety data collection (i.e., those data that are captured and “collected” on case report forms [CRFs] as opposed to data that are recorded as part of routine clinical care, which will herein be referred to simply as “data collection”) in HABP/VABP trials to attempt to reduce the non-critical data to obtain cleaner risk/benefit profiles for investigational treatments for HABP/VABP, and may also reduce the cost and burden of collection.

### ***Safety Data Reporting***

In accordance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guideline E6, safety data should be accurately recorded and reported in a timely manner. ICH GCP outlines specific safety terminology and requirements for reporting different types of safety data [12].

During clinical trials, any changes in severity of prior medical conditions, or medication changes, including drug dosage, are often referred to as adverse events (AEs) and usually documented in the case report forms (CRFs). Because HABP and VABP are by definition associated with another underlying illness that results in hospital admission, often of an acute and severe nature, separating complications of the underlying illness from adverse trial drug effects may be quite difficult, underscoring the importance of a proper control group. Compared to other conditions, HABP/VABP patients have a large number of medical procedures, worsening of the medical conditions independent of pneumonia treatment, and a plethora of concomitant medications needed to treat underlying conditions. This challenge results in the recording of a larger amount of data captured as part of routine clinical care than in most clinical trials targeting other conditions, leading to a temptation to capture excessive amounts of data in the CRF. These data may not contribute meaningfully to ascertainment of the risk/benefit profile of the drug. Unnecessary data collection introduces an additional layer of complexity, particularly when it includes additional procedures (e.g., blood collection), which may dissuade patients from participating in trials and can lead to a reluctance of investigators and study staff to engage in such research. The net effect is loss of patient and site participation in trials, thereby hampering the expedited antibacterial drug approval process. For these reasons, we suggest a pragmatic approach to data collection, including listing a diagnosis when possible and recording only critical data that are truly needed for regulators to assess a drug's risks and benefits.

### ***Risk / Benefit Assessments***

Despite the need to streamline data collection, full harmonization of the global requirements regarding the minimum amount or type of data collection necessary for appropriate risk/benefit assessment in clinical trials has not been reached. Safety data collection is generally tailored and informed by trial drug characteristics and experience from pre-clinical and prior clinical studies. A common concern among investigators and sponsors alike is that the multitude of data points may obscure important safety signals. Several guidance documents and guidelines from the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) exist that provide examples of important, idiosyncratic AEs [13, 14] or how to manage large datasets[15]; however, from the sponsors' standpoint, the practical reality of teasing out signal from noise is not adequately addressed. Conversely, a common concern of sponsors is that collection of too little data will limit the ability to answer post hoc questions during the regulatory review process, Advisory Committee meetings, and a peer review of publications. Striking a balance between these extremes could improve the practical feasibility of successfully completing these trials while adequately assessing the risks and benefits of the investigational drug.

HABP/VABP trials are often conducted globally, but standardizing and streamlining processes globally is difficult due to the regional variations in regulatory requirements. In particular, regulations across countries may vary in safety data requirements deemed sufficient to evaluate the risk/benefit of an investigational drug. These differences include requirements for reporting AEs and recording concomitant drug use. The perceived lack of specificity needed to identify “critical data” in the current regulatory guidelines may lead sponsors to take a more conservative approach toward premarket pharmacovigilance, which frequently involves collecting large amounts of data [16]. These differences are again magnified in complex trials for antibacterial drug development such as for HABP/VABP [17, 18]; however, these international differences are not the major obstacles that hinder global HABP/VABP trial-conduct.

### ***Benefits of Streamlining Data Collection***

From the standpoint of a sponsor, the opportunity to increase trial efficiency with use of new technologies [11], novel study designs [19], prudent selection of qualified sites, use of reliable operational alliance partners, and a risk-based monitoring approach is considerable. In addition to the advancement of technology, concentrated efforts are being made to improve many operational issues in clinical trials, including data capture and analysis [11]. Streamlined data collection plays a large role in this strategy by reducing the effort and manpower needed to accurately monitor, analyze, and review trial data. Improvements in efficient data collection will help to alleviate investigator/site work burden and fatigue and enhance data quality and patient/site retention.

Recently, data collection streamlining strategies have been successfully applied to cardiovascular (CV) trials and oncology trials to improve data collection and quality [20-24]. Such streamlining effectively increased the speed and ease of recruitment as well as significantly reduced trial costs, CRF pages, monitoring visits, and site-payment amounts without a loss of patient numbers or site participation [20]. It is therefore important to consider whether similar strategies may be translated to HABP/VABP trials. For several reasons, efficiencies adopted in CV trials may not be so readily applicable to HABP/VABP trials due to the nature of their inherent, relatively small sample size in comparison to CV trials. Furthermore, patients entering CV trials have an evident primary condition whereas HABP/VABP occurs frequently as a complication of many different types of underlying illnesses or injuries and thus comprises a relatively heterogeneous patient population. However, despite these differences, many of the principles leading to the reformation of CV trials can be applied to streamlining HABP/VABP trials for optimal data collection. Oncology trials that have had success with streamlining data collection may serve as a more informative example for HABP/VABP trials, especially considering the small and heterogenous patient population also found in oncology trials. Using a statistical analysis plan (SAP) developed by

stakeholders, safety data from eight completed Phase 3 oncology trials were re-analyzed to determine an optimal approach to safety data collection. Findings from this study identified AEs that were not previously established in the safety profiles [24]. Such studies highlight the need for careful consideration of the SAP to enhance safety data collection streamlining efforts.

### ***Clinical Trials Transformation Initiative Involvement***

The Clinical Trials Transformation Initiative (CTTI) is a collaborative organization that seeks to promote practices that will increase the quality and efficiency of clinical trials. CTTI proposes to implement a Quality by Design (QbD) approach [25, 26] to prospectively examine the objectives for HABP/VABP trials and define factors critical to meeting these objectives. One identified component is to develop strategies to eliminate the collection of large amounts of non-critical data typically collected in these trials. In this paper, we consider the current issues related to safety data collection in HABP/VABP trials and outline measures to enhance efficiency in the development of antibacterial drugs, using the current US and EU regulatory pathways for clinical development [13, 27-30].

### **Methods**

A multidisciplinary group of stakeholders representing the pharmaceutical industry, government agencies, academia, and patient advocates comprised the ABDD Project Team for data collection, a workstream within the “Streamlining HABP/VABP” project of CTTI’s Antibacterial Drug Development (ABDD) program [31] (see Figure 1 in “Improving Conduct and Feasibility of Clinical Trials to Evaluate Antibacterial Drugs to Treat Hospital Acquired Bacterial Pneumonia (HABP) and Ventilator Associated Bacterial Pneumonia (VABP): Recommendations of the CTTI Antibacterial Drug Development (ABDD) Project Team”). Through discussions at a one-day conference and additional lecture sessions, the ABDD Project Team identified key issues relating to data collection that currently impede the utility and feasibility of HABP/VABP trials.

Three areas were noted to have the highest volume and burden of collection while not substantially adding to the key information required for determination of overall risk/benefit: (1) certain data included for safety considerations, (2) patient population characteristics, and (3) unnecessary scheduling of study visits/assessments. The use of data for the trial analysis was evaluated by examining both the type of data collected and the method of data collection in each category. Strategies to lessen the frequency of data collection were developed in order to mitigate some operational challenges associated with large databases and data collection while adhering to current regulatory requirements and expectations in the

US and EU. These efforts resulted in recommendations from CTTI's ABDD Project Team based on consensus statements.

## **Results**

### ***Strategies to Streamline Safety Data Collection in HABP/VABP Trials***

For HABP/VABP studies, several opportunities can be explored to address the issue of excessive safety data collection and reporting. When a drug is also being studied for multiple indications, HABP/VABP trials can be designed to limit the amount of data collected and reported provided that the drug meets 2 criteria:

- the dose and duration of the drug treatment in trials for other indications are similar to those used for HABP/VABP
- adequate pharmacokinetic/pharmacodynamic (PK/PD) data are available to accurately characterize drug exposure in critically ill patients

Because patients in HABP/VABP trials are hospitalized, often in the intensive care unit (ICU), large amounts of data are already recorded at the site as part of routine clinical care, and the challenge is to identify a subset of these data for targeted collection in the context of the clinical trial purpose and objectives. The FDA Guidance indicates that selective or targeted safety data collection is appropriate in certain situations with particular types of safety data (Table 1) [32]. According to the existing EU and US regulatory guidelines, targeted safety data collection can be implemented if the methods are pre-specified in the trial protocol, such as specifying time points that allow investigators to track and report only those events (i.e., signs, symptoms, and laboratory values) that are determined to be clinically significant over the course of the patient's illness [30, 32]. Recommendations for reporting AEs/serious adverse events (SAEs), clinical laboratory data, patient medical history, concomitant medications, vital signs, and physical examinations are described in more detail in the sections below.

### ***Safety Data Collection and Reporting***

#### **a. AEs, SAEs, and Clinical Laboratory Data**

To increase the efficiency of safety data collection in HABP/VABP trials, capturing only data that are critical and most relevant to the trial objective is advisable. Thoughtful protocol design can mitigate excessive data collection by clearly describing not only the type of events that definitely will be recorded (e.g. study end points) but also advising on which medical events are expected to occur in the study population at some frequency, independent of drug exposure, due to the study participants' medical

conditions or co-morbidities, and hence may not require expedited reporting [13]. Monitoring plans should be discussed with Regulators before starting the study. In later stages of clinical development, some aspects of a drug's safety profile may be predicted by information from non-clinical development programs, the pharmacodynamics/pharmacokinetic profile, and phase 1 and phase 2 human safety data. If this information is reassuring, then it may be possible to be more focused, and the extensive collection of safety data needed in earlier trials may no longer be viewed as necessary or appropriate.

Minimal clinically important differences (MCIDs) should be developed for clinical laboratory data in HABP/VABP trials [33]. MCIDs have been used predominantly for patient-reported outcomes but can also be used for objective data such as pulmonary function tests [34]. Collection and subsequent analysis of routinely recorded, multiple laboratory values in critically ill patients may enhance the possibility of noting differences, but such differences are frequently clinically irrelevant and hence should not warrant the time and effort associated with such data collection [35]. The process of aggregating large data sets may obscure rare but clinically important abnormalities unless the appropriate analytic techniques/tools are utilized to detect these signals [13]. Alternatively, a streamlined CRF could stipulate collection of routinely recorded values only if the laboratory values exceed this MCID during a specified time interval; the CRF may contain a simple checkbox for "no MCID abnormality." For example, an MCID for creatinine level may be twice the upper limit of normal. The statistical comparison would then be the proportion of patients in each group with changes above the MCID, rather than an average of all creatinine values. The choice of parameters which are eligible for such an approach is dependent on the candidate drug's properties (i.e., the above mentioned example may not be suitable for an overtly nephrotoxic drug). This approach may prevent the tendency to search for statistical but clinically irrelevant differences within the data and is especially relevant for laboratory tests.

Additionally, if disease conditions are clearly defined by a combination of associated signs and symptoms, individual observations that comprise a disease entity can be captured as the unified condition instead of listing them separately. This strategy should be pre-specified in the protocol along with the signs and symptoms that the unified condition will represent. For example, if safety data is being collected every third day, symptoms, signs, and hemodynamic measurements such as an increase in basal serum creatinine, a decrease in creatinine clearance, urine output of less than 400 500 mL/day, or the need for renal replacement therapy could be captured collectively in the CRF as "Acute Kidney Injury." To reduce inconsistencies in naming conventions, use of standardized Medical Dictionary of Regulatory Activities (MedDRA) queries is encouraged when possible.



The proposed approach to more limited recording of safety data is consistent with the guidances issued by the FDA [13, 27, 32, 36]. Briefly, these guidances describe and recommend the following:

(1) circumstances for which targeted safety data collection may be appropriate; (2) what sort of safety data may be suitable for abbreviated collection versus noncritical data that may not be needed (e.g. non-serious AEs not associated with drug discontinuation, routine lab monitoring, etc.) (Table 1); (3) listing in the protocol the more common SAEs likely to occur (based on past experience) in a particular trial's population; (4) rare circumstances in which submission of individual CRFs for uncommon events known to be strongly associated with trial drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson syndrome) is appropriate (rather than the more common circumstances in which cases can be aggregated and compared with those in a control group); and (5) that study endpoints should not usually be reported as investigational new drug (IND) safety reports except when evidence suggests a reasonable possibility that a causal relationship exists between the drug and the event.

EU Regulation 536/2014 on clinical trials for medicinal products for human use [30], effective 28 May 2016, has replaced Directive 2001/20/EC (previously known as the "EU Clinical Trials Directive"). Article 41 of this regulation contains provision for some flexibility in recording and expedited reporting of AEs in clinical trials (and hence streamlined data collection) as long as this is clearly defined in the protocol. For instance, it states that investigators should "record and document AEs or laboratory abnormalities identified in the protocol as critical to the safety evaluation" and that investigators shall "record and document all AEs unless the protocol provides differently." The regulation also stipulates that SAEs should be "reported to the sponsor within 24 hours, unless, for certain SAEs, the protocol provides that no immediate reporting is required."

The US and EU regulations therefore allow for simplification of data collection, reinforcing the fact that there are valid circumstances for which streamlined safety reporting is warranted. However, it is very important that study protocol wording is carefully considered and appropriately specific to allow for such an approach [30]. For instance, a protocol might specify that AE data collection will be restricted to only those AEs that are considered to be serious (as per the standard ICH criteria) or result in discontinuation of study treatment. Equally, the protocol could stipulate which SAEs are likely to occur as part of the natural course of the disease studied in the trial and will not routinely be subject to expedited safety reporting. Additionally, in an ICU setting, clinical laboratory tests with out-of-range values or values of clinical concern may not qualify as an AE or SAE (e.g., transient asymptomatic hypokalemia, fluctuations in hemoglobin level from an abnormal baseline, and abnormal serum glucose levels). Such approaches will result in more efficient data collection and more meaningful safety data.

Ideally, harmonization of US and EU regulatory requirements would facilitate safety reporting in global trials. The *minor but important differences* in the regulations (e.g., timely reporting of SAEs or who attributes and reports AE causality) can be managed by incorporating pre-specifications in the trial protocol.

#### **b. Medical History and Concomitant Medications**

Other data, such as medical history and concomitant medications, may be collected based on the relevance to the indications studied, investigational drug/drug class, or what is deemed essential to determine the safety profile of the drug. Types of medical conditions considered relevant to the current trial should be defined in the protocol. For concomitant medications, predefining the safety concerns with certain drugs is important, such as (1) possible drug-drug or drug-disease interactions (e.g., drugs that may prolong QT interval in patients with known QT prolongation), or (2) additive toxicity. Data on the use of concomitant medications that may not impact the assessment of primary and secondary outcomes of the protocol (e.g., every dosage change with intravenous sedatives) may not warrant collection unless there is a potential safety concern.

#### **c. Vital Signs and Physical Examinations**

By defining in the protocol which physical assessments are critical to determining the safety profile of the drug, data collection can be streamlined to collect only those relevant to the trial in question. The protocol should provide direction on when certain assessments may become critical and when these should be performed. For example, if a patient is deteriorating, then obtaining blood and respiratory cultures at more frequent intervals may become important; however, these measures may not be appropriate for all patients.

### **Discussion**

#### ***Addressing the Potential Limitations of Streamlining Safety Data Collection***

When possible, the optimal approach for reliable assessment of moderate treatment effects for safety parameters is ideally through large, pre-licensure, properly randomized controlled trials (RCTs). However, considering the challenges of conducting HABP/VABP trials, it has been argued that collecting and reporting data that are not critical but easily obtained is a justifiable strategy on the basis that this may minimize the possibility of missing a safety signal. Depending on the potential benefit of the investigational drug, further evaluation of risk, including relatively rare SAEs, by conducting active post

marketing surveillance studies may be acceptable; however any safety experience that has been passively reported through such studies lack an adequate control group or ability to accurately estimate prevalence.

A frequent concern of sponsors regarding pre-defining and limiting data collection is that the ability to conduct post-hoc review of additional data requested during the approval process, but deemed unimportant initially will be restricted. However, any extraneous data lost due to streamlining could be considered a worthwhile trade-off for efficiencies gained. A recent analysis has indicated that reducing the amount of “non-core” data collected in trials can favorably impact outcomes including indirect cost, cycle time, and investigator/site work burden [16, 37].

Reducing the logistical, procedural, and operational issues that complicate these studies may help address the demand on investigators and frequent site turnover as well as alleviating the burden of maintaining, monitoring, and reviewing large databases.

### ***Further Considerations***

As acknowledged in 2011 by many leaders in the clinical trial enterprise [38], technology may be leveraged to enhance efficiency in data collection. Effective use of electronic data capture (EDC) systems and synchronizing SAE reporting with clinical trial databases can substantially improve the quality of data, limit redundancies, and minimize data entry errors and missing values. Recently introduced wireless technologies to improve access to electronic medical records (EMRs) may also have the potential to enhance quality and efficiency by reducing error rates, ensuring patient compliance, and enabling rapid data collection, effectively reducing the overall cost of conducting trials [39].

Although some electronic capabilities are becoming more prevalent in clinical trial conduct (e.g., use of EDC and electronic CRFs), available technology is currently not being maximally utilized in a majority of trials. Organizations such as TransCelerate and PACEr have initiatives or projects to evaluate and promote the use of electronic data sources and other technologies (e.g., electronic consent) to improve clinical trial conduct [11, 40]. Additionally, both the FDA and EMA have acknowledged the potential benefits of integrating technology into data collection practices and risk-based monitoring approaches and have released guidances or reflection papers on their use [41-44]. In regard to data collection, centralized monitoring (as opposed to on-site monitoring) that incorporates electronic capabilities can considerably reduce errors, and their use encouraged, especially as the quantity of data collected increases [41]. Finally, data reporting can be streamlined with data standardization and electronic submissions [45].

### **Conclusion**

In general, a consensus and a cultural change within the clinical research enterprise involved in antibacterial drug development is needed to adopt best practices for conducting HABP/VABP trials. Less complex trials with scientifically sound data that are easier to analyze and review will reduce the time and cost involved in bringing these much-needed drugs to patients. In tandem, such streamlining should facilitate recruitment of larger numbers of patients into such trials, meaning that the results will be statistically more reliable. With concentrated efforts from industry, regulatory agencies, and organizations like CTTI, clinical trials for antibacterial drug development for HABP/VABP can be reformed bringing us closer to attaining the goal of a steady pipeline of new antibacterial drugs for patients in need.

## NOTES

**Disclaimer:** The views expressed herein represent those of the authors and not necessarily the views or practices of the authors' employer or any other party.

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

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C. Knirsch works for and holds stocks of a pharmaceutical company, Pfizer Inc.

D. Alemayehu works for and holds stocks of a pharmaceutical company, Pfizer Inc.

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## Figure Legends

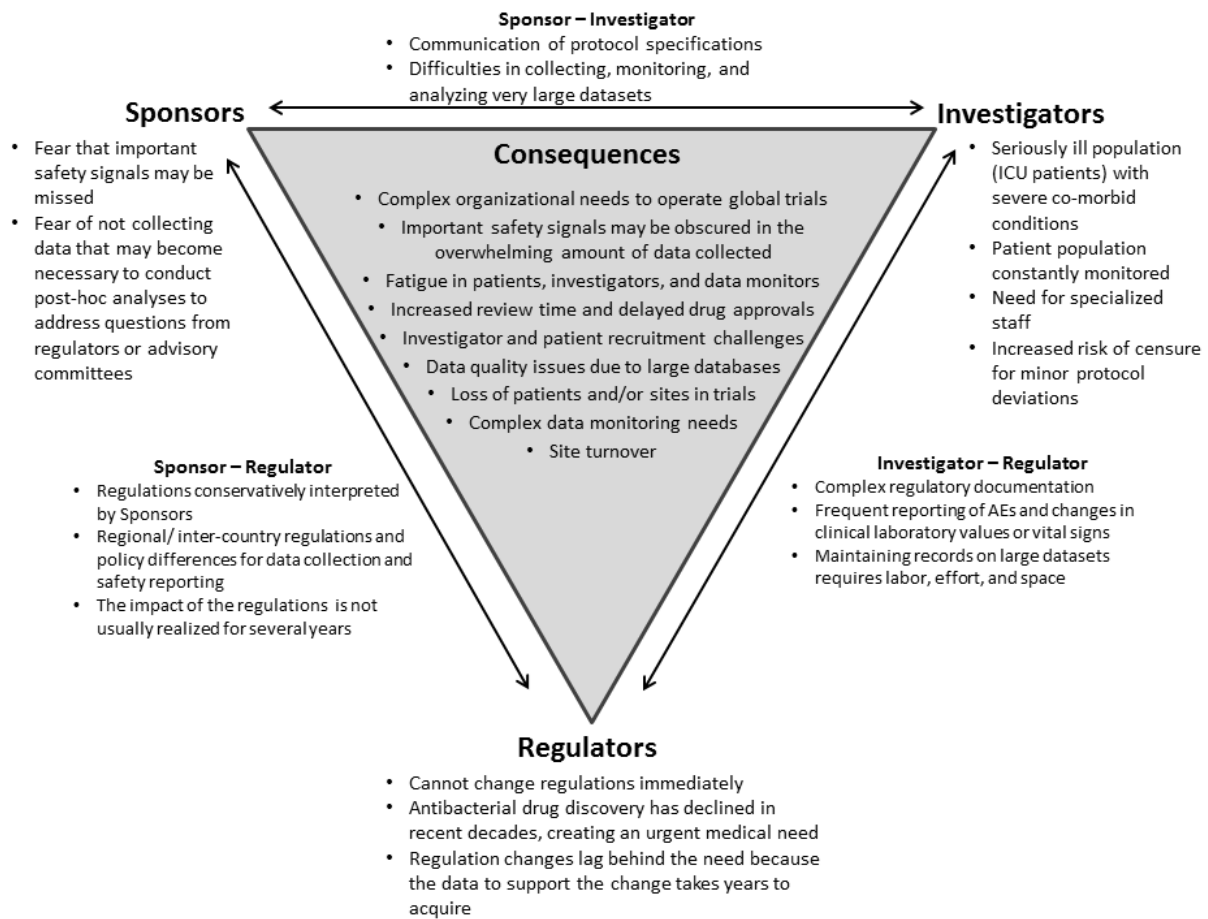
Figure 1: The Challenges and Consequences Associated with Excessive Data Collection in HABP/VABP Trials

Challenges with excessive data collection are presented at the triangle vertexes as they relate to sponsors, regulators, and investigators. Challenges associated with communication between these entities are detailed adjacent to the sides of the triangle. Consequences resulting from these challenges are noted in the center.



Figure 1: The Challenges and Consequences Associated with Excessive Data Collection in HABP/VABP

Trials



## Tables

Table 1: Summary of Considerations for Targeted Data Collection

A tabular summary of 1) circumstances in which targeted data collection is appropriate, 2) the types of safety data appropriate for abbreviated collection, and 3) the best approached to targeted safety data collection as informed by FDA guidelines.

Circumstances that are Appropriate for Targeted Data Collection	Types of Safety Data Appropriate for Abbreviated Collection*	Suggested Approaches to Targeted Safety Data Collection
<ol style="list-style-type: none"> <li>1. Number of subjects exposed to the drug in previous studies is sufficient to characterize the safety profile for all but rare events.</li> <li>2. The occurrence of AEs has generally been similar across multiple studies.</li> <li>3. There is a reasonable basis to conclude that occurrence of adverse events in the population to be studied will be similar to previously observed rates.</li> </ol>	<ol style="list-style-type: none"> <li>1. Non-serious AEs not associated with drug discontinuation.</li> <li>2. Routine lab monitoring.</li> <li>3. Information on concomitant medications.</li> <li>4. History and physical examinations.</li> </ol>	<ol style="list-style-type: none"> <li>1. Discuss the plan with the relevant regulatory body before starting the study.</li> <li>2. Include safety data collection plan in the protocol.</li> <li>3. In the protocol, specify those data fields that will not be collected.</li> <li>4. In the protocol, where applicable, specify the safety data that will be collected only from a sub-sample of the overall study population (e.g., randomly selected patients, randomly selected study sites, or only larger study sites).</li> </ol>

		5. Decrease the frequency of data collection when appropriate.
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Abbreviations: AE = adverse event