VIAL

The Anatomy of an Exceptional Study Protocol

White Paper

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1. Introduction

One of the most important documents that must be drafted before beginning a clinical trial is the study protocol. The study protocol acts as a roadmap for clinical sites, principal investigators, and regulatory agencies. There are many documents that are included in an Investigational New Drug (IND) application and the sponsor or contract research organization (CRO) of the clinical trial is typically responsible for writing the study protocol. Federal guidelines outline the basic requirements for a protocol [1, 2], however, there are several strategies that sponsors and CROs can employ to improve the study design and safeguard against potential barriers.

2. Notable Sections of a Study Protocol

While each section of a protocol must be addressed at the minimum level, there are several sections that directly impact study conduct, which will be the focus of this article moving forward. Phase-specific templates provided by the Food and Drug Administration (FDA) can be used as a blueprint for drafting a comprehensive protocol [3].

Figure 1. While there are many sections within a clinical study protocol that must be addressed, these five sections significantly affect the overall study conduct.

01

Study Rationale

The problem, question, hypotesis, and intervention should be discussed along with background data the risk and benefit assessment of the clinical trial.

02

Study Population

The main portion of this section is the inclusion and exclusion criteria to detail the population to be the target of the study. Strategies for recruitment and retention are also included here.

03

Study Intervention

Information regarding the randomization schema, blinding details, administration and dosing of the investigational product is included in this section of the protocol.

04

Study Assesments

This section contains the schedule of events that includes the procedures and assessments that accompany each study visit which will translate into vital data.

05

Safety Reporting

The characteristics and distinguishments of adverse events and serious adverse events is defined in this section to ensure valuable safety information is properly reported.

3. Study Rationale

The study rationale section lays the foundation for the clinical trial. It contains necessary background information and review of published literature. First, the problem should be stated with a description of the disease, current standards of care, and limitations of available therapy. Then, background information on the proposed intervention should be discussed. In addition, all preclinical or previous study data should be included in this section to provide ample rationale for conducting the study.

Another portion of this section is a discussion of potential benefits and risks. The Investigator's Brochure (IB) should be the primary source of all risk and benefit information, but it's important to have a summary of the IB in this section of the protocol. Based on previous studies, published literature, and preclinical data, a statement of risks and benefits should be included. Similarly, a rationale for the necessity of exposing participants to the potential risks, a summary of the ways that risks are planned to be minimized, and justification of how the benefits outweigh the risks should be stated.

4. Study Population

In order for study sites to recruit participants for a clinical trial, the inclusion and exclusion criteria must be strategically developed. The inclusion and exclusion criteria are vital to clinical trial conduct and ensures each patient enrolled is in a similar state of health, which maintains validity of the data when the intervention is introduced. The inclusion and exclusion criteria should clearly define participant characteristics and be kept as minimal as possible to prevent unnecessary preclusion. Regulatory and federal agencies have policies and guidelines to ensure that women, minorities, and elderly individuals are equally accounted for, and these policies should be reflected in the inclusion and exclusion sections to promote diversity [4].

Considerations for inclusion criteria include prognostic factors, diagnoses, and previous treatments. Exclusion criteria may include concurrent medication, allergies, and underlying health conditions [5]. It is also important that one criteria does not fall under both the inclusion and exclusion section. For example, it would not be best practice to denote an age greater than or equal to 18 in the inclusion criteria and an age less than 18 in the exclusion criteria. Similarly, willingness to sign an ICF (informed consent form), comply with study procedures, and adhere to the interventional regimen is becoming increasingly common to add to the inclusion criteria. It also may be necessary to include lifestyle limitations such as the subject refraining from starting new medications or dietary supplements or taking necessary precautions against pregnancy. Lastly, there are some cases in which a patient does not qualify for the study but has already completed the informed consent process. For example, a patient may need to consent before a diagnostic test can be completed to determine if the patient is eligible. If the diagnostic test concludes that the patient is not eligible, the patient would then be a screen failure. The process for how screen failures will be defined and managed should also be discussed in this section.

5. Study Intervention

Interventional studies that are in early or pre-approval phase studies will need to clearly define the blinding and randomization scheme used. Randomization helps prevent the potential impact of selection bias by randomly assigning each clinical trial patient to either a dose of the investigational product (IP) or placebo, if applicable.

The protocol and ICF should outline the ratio of patients assigned to each dose of IP and placebo so patients are fully aware of the possibility that they may not receive the novel treatment. Simple randomization is oftentime utilized where an equal number of patients are assigned by a computer program to receive a dose of IP or placebo. In this case, the probability of the machine-generated assignment can be equated to the toss of a coin. More complex randomization schemas include Block Randomization or Stratified Randomization which may take into account age or gender and require more in-depth statistical analyses [6].

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Lastly, this section should include the process for administration and dosing. Since it is imperative that administration of an IP or protocol of a procedure are done consistently, an outline of necessary details is vital. Points to consider include mixing of IP, dosing changes due to weight, method of administration whether it be intravenous, subcutaneous, intramuscular, and which type of syringe and needle is preferred. A comprehensive instruction of dosing and administration can typically be found in an accompanying Pharmacy Manual, as well.

6. Study Assessments

Based on the goals of the clinical trial, specific endpoints are drafted to concretely measure the outcome of the study. These endpoints should be clinically relevant such as overall survival, progression free survival, meaningful change in laboratory values, improvement in patient reported outcomes, or positive post-surgical changes. Similarly, the endpoints of a study are likely dictated by the data needed for a new treatment to be approved for use in a specific indication by regulatory agencies.

Once the primary and secondary endpoints are decided, the study assessments should align to gather data to sufficiently and statistically answer the overall research question. Oftentimes, the study assessments are presented in a table with the visit number in the row heading and the assessment in the column heading. This table is typically included early in the protocol since it is referenced so frequently. One example is if an endpoint predicts a drug may lower HgA1c, a plausible study assessment would be to obtain a fasting blood collection at regular intervals until the study is concluded. In this case, under the “Visit 1” column, there would be an indicator that blood collection of a fasting patient should be conducted. Visit 2 may be conducted 25 days later, with a window of +/- 5 days and would also denote fasting blood collection. This would continue for each visit along with any other assessments that should be performed at each visit. Another example of study assessments may be less quantitative and rely more on documentation of how the patients feel.

Patient-reported outcomes (PROs) are becoming increasingly more common but can be more difficult to track and quantify. One example of how PROs may impact study design is if a dermatologic cream is predicted to reduce itching or burning sensation of a rash. In this case, the patient may be asked to rate the severity of the itching or burning sensations experienced on a scale of 1 to 10 at regular intervals throughout the study. Unlike the previous example in which the patient would have to complete the visit in person to perform the blood draw, PROs can oftentimes be collected remotely. Remote collection can be done through a phone call, a survey emailed or texted to the patient, or even through a secure app. PROs may also be conducted in combination with quantitative measures, though would require an in-person visit. For example, a medical professional may measure the area of the rash and also ask the patient about itching or burning sensations. In this case, there may be a conclusion that a decrease in the area of the rash correlates with less itching or burning.

A common complaint with study design are superfluous study visits. One study found that nearly half of all patients that chose to discontinue participation in the trial did so because of lengthy or frequent study visits [7]. Reducing or minimizing the number of study visits can increase patient retention, protocol adherence, and overall data satisfaction in a trial. One example of reducing unnecessary study visits could be by combining the screening and pre-testing visits when possible [8]. This allows a reduced number of in person visits required by the patient. The number, duration, and invasiveness of study visits can greatly impact patient retention and should be designed thoughtfully and strategically based on the goals of the trial.

7. Safety Reporting

A large reason that clinical trials are conducted with such strict regulations is due to safety concerns. Regardless of phase or intervention type, every clinical trial must state the guidelines for safety reporting within their protocol and IB after consultation with regulatory officials and a medical monitor. Similarly, any adverse events or side effects observed or suspected in previous research should be stated not only in the protocol and IB but also in patient-facing material, as well, such as the ICF. The Institutional Review Board (IRB) for a study, whether it be a local or central IRB, must approve the study's plan for reporting safety concerns. In order for the reports to be as accurate as possible, it is important to educate site staff and investigators on what the criteria is for adverse events (AEs), serious adverse events (SAEs), and unanticipated problems (UPs).

AEs can be considered any untoward or unfavorable medical occurrence whether or not it is related to the subject's participation in the research study. SAEs typically meet a specific criteria such as an event that resulted in death, is considered life-threatening, resulted in inpatient hospitalization, prolonged an existing hospitalization, led to a disability, or led to a birth defect. Lastly, a UP may be based on the investigator's discretion to determine if the event is not consistent with the risk information previously described. Typically, AEs must be reported to the IRB within an appropriate time frame and SAEs must be reported within one or two business days from when staff first learned of the event. UPs must also be recorded and the IRB must be alerted within a defined timeframe. UPs often get reviewed by the medical monitor and, in some circumstances, the FDA. Reports of UPs are of the utmost importance because they may alert the sponsor to unexpected side effects and may change the course of the clinical trial.

Additionally, there are nuanced safety considerations that should be mentioned in this section of the protocol. These can include the reporting of pregnancy occurrence in a subject, adverse events of special interest, and halting rules.

There should be guidelines on documentation of the AE, how to determine severity, and how to address the likelihood that the AE was caused by the study in some way. This section should also include phone numbers, email addresses, and operating hours of regulatory agencies to ensure that safety information is sent timely and to the appropriate office. Due to its significance, all the language in this section should be developed on a study-by-study basis and in accordance with IRB officials and medical experts.

8. Consideration for the Study Review Process

FDA Review Process

After the protocol is written, it will be submitted in the IND package and reviewed by the FDA. The FDA has thirty days to review the application in which it will either approve or hold the study. The FDA may put a study on hold if there are obvious detrimental impacts if the study were to be conducted [9]. Similarly, the FDA may put a study on hold if the application is not sufficiently completed or if necessary information is not included. According to FDA research, the most common deficiencies leading to clinical holds were in product quality issues and clinical and toxicology concerns [10].

There are several steps that can be taken to avoid an FDA hold. First, including appropriate toxicology animal data for early phase studies is key. If the preclinical data was generated incorrectly, it can impede the translation of the research into human subjects. Therefore, it is critical to comprehensively evaluate the investigational treatment to determine the dose and duration in an early phase trial. Insufficient manufacturing validation can also cause a clinical hold for prospective drug trials. It is important to convey that the suggested manufacturer is reputable and will not introduce unnecessary risk such as impurities or inconsistencies into the investigational product. Lastly, sponsors should engage the right experts to fully understand all the potential risks of the study. Occasionally, smaller biotech and pharma companies are not fully staffed with subject matter experts in all disciplines which can hinder the likelihood of a federal agency approving their protocol. Therefore, sponsors oftentimes elicit help from CROs that have experience with successfully running clinical trials to draft and submit the regulatory paperwork. Engaging with a CRO who has cross-functional depth and breadth of experiencecan mitigate concerns and avoid a clinical hold [11]. The Vial CRO is a next-generation CRO powered by technology to deliver faster, cheaper, and more efficient trials. Vial also has prominent and experienced scientific advisory board members to guide clinical decision making in a vast number of treatment areas.

IRB Review Process

If the FDA does not place a hold on the study within the thirty-day period, the study will be reviewed by the IRB. An IRB may be institutional-based or a central IRB, such as Advarra. The IRB is made up of experts in clinical research, is governed by the FDA, and must also approve the protocol before the trial can begin. The IRB will either approve, request modifications, or disapprove the research plan. The FDA believes that the IRB should not make a patient-facing statement of approval since such a statement may solicit, mislead, or unduly induce subjects to participate. During this initial review, the IRB will determine how often the study must be re-reviewed, known as continuing review. The IRB's review will also comply with appropriate Code of Federal Regulations (CFR) so it would be wise for sponsors or CROs to be sufficiently familiar with appropriate guidelines prior to submission.

After the initial review, the IRB will periodically review information gleaned from the study. In addition, the IRB reviews all protocol amendments and approval must be earned before a revised protocol can go into effect. Similarly, the IRB, in addition to a Safety Review Committee or data Safety Management Board, are the primary recipients of adverse event notifications that occur during the trial. Therefore, if these regulatory committees receive information that the study is producing unanticipated or a significant amount of severe adverse events, they have the authority to halt the clinical trial. In such a case, there would likely be a meeting between the FDA and IRB to discuss the findings and move forward appropriately. Due to the large role the IRB plays through the duration of the study, it is important for the sponsor, investigator, and study staff to have a clear line of communication with the individuals that make up the board.

ICH Good Clinical Practice

A common theme that both the FDA and IRB will be considering throughout protocol review is the author's consideration of Good Clinical Practice (GCP) as established by the International Conference of Harmonization (ICH). GCP is a set of standardized guidelines that ensure all protocols meet the minimum ethical and quality principles. The standardized guidelines are extensive and should be reviewed by a member of the scientific team drafting or editing the protocol before it is reviewed by regulatory officials to avoid a clinical hold due to falling below the standards of GCP.

> **Figure 2. FDA review followed by IRB review of a study protocol are necessary to receive approval to begin the clinical trial. Both the FDA and IRB will expect GCP and ICH guidelines to be followed throughout the protocol.**

A few notable GCP guidelines that sponsors should take into consideration are the requirements of investigators, study staff, and site resources. For example, if a study protocol lists an echocardiogram to be performed on patients during each onsite visit, it would be important to ensure that sites initiated for this study have calibrated echocardiograms, staff trained to perform an echocardiogram, and investigators to review the echocardiogram. Another GCP consideration is in the handling of the investigative product. The protocol should maintain guidelines, consistent with GCP, to control access of the investigational product, document the quantity, and keep adequate records of the dispension of the product. In addition, there should be requirements for reporting when the protocol has been violated, often termed protocol deviations.

Protocol deviations can occur if a visit was conducted outside of the visit window, if a study assessment was not fulfilled, or if an adverse event was not reported in a timely manner. These are just a few examples of the level of detail necessary to comply with basic guidelines outlined in the World Health Organization's GCP Handbook [12].

9. Qualities of an Excellent Protocol

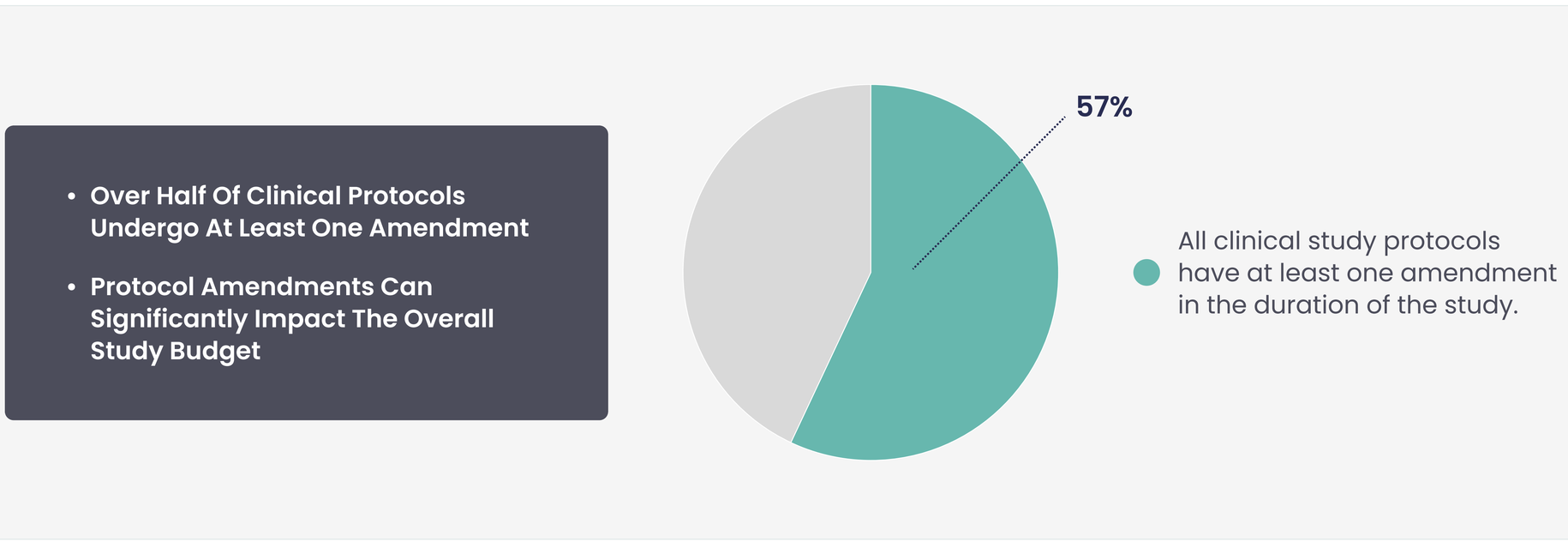
Preventative Approach

In order to draft an excellent protocol, it is important to identify and safeguard against potential pitfalls or limitations from the start. One large impact on clinical trial performance is in the frequency and significance of protocol amendments. Protocol amendments occur for many reasons such as the introduction of new standards of care, changes to permitted concomitant medications, or requested revisions from regulatory agencies. The top reason for protocol amendments was to adjust patient eligibility criteria based on changes in study design [13]. One study found that 57% of protocols had at least one substantial amendment and, of those amended protocols, 45% were found to be avoidable [14]. Depending on the phase of the trial, a protocol amendment could cost between US$141,000 and US$535,000, which can significantly impact the overall study budget.

While a large number of protocol amendments are unavoidable, there are steps that can be taken to help prevent amendments as much as possible. Protocol design flaws can be avoided by introducing experts familiar with the disease state, patient population, and treatment landscape during the initial steps of protocol development. Similarly, these experts can assist with inconsistencies or outright errors in the protocol narrative.

Since one of the biggest reasons for protocol amendments is patient eligibility, sponsors can utilize published literature to safeguard against eligibility criteria that may be difficult to meet. If a clinical trial with a similar drug or treatment has been completed, sponsors can review that data to understand if a certain eligibility criteria was particularly difficult to recruit for. Similarly, keeping the eligibility criteria feasible is also a way to prevent protocol amendments. For example, if patients with hypertriglyceridemia typically have a fasting triglyceride value between 250-350 mg/dL, it may be difficult to have an inclusion criteria for a fasting triglyceride level of 400 mg/dL or higher. While protocol amendments can improve the quality of the study data, taking a preventative approach to avoid unnecessary amendments can save significant time and money in the long run.

Figure 3. Approximately 57% of all clinical study protocols have at least one amendment in the duration of the study. Protocol amendments can be costly and can delay study outcomes.

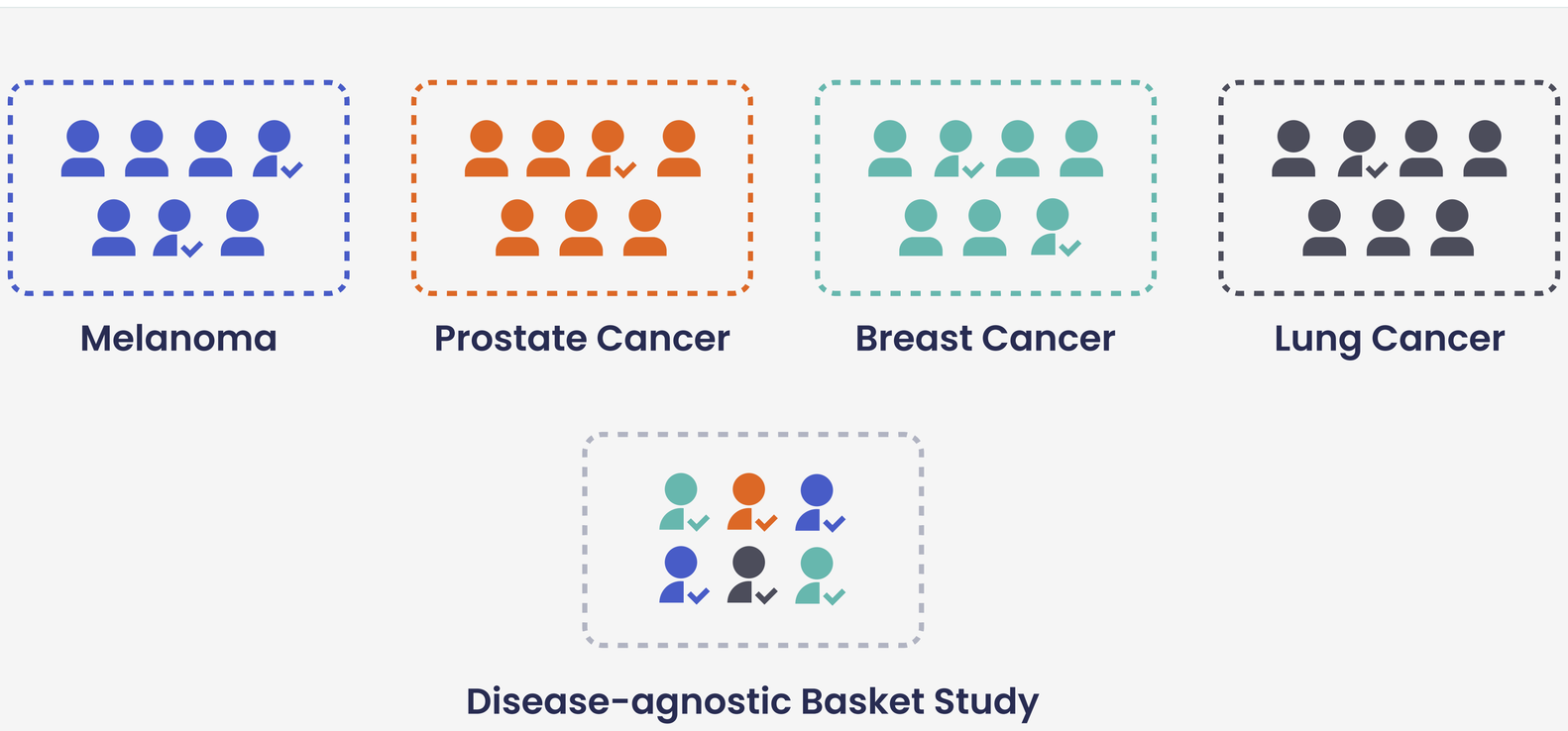


Innovative Strategies

By introducing innovative strategies into the study protocol the overall study conduct can be performed more efficiently and sponsors can receive more information about their novel treatment. One way to ensure that a protocol is set up for success is by making it as adaptive as possible [15]. The more complex and strict a protocol begins, the less adaptive it can be to the changing landscape. However, by strategically specifying the scope, risk, boundaries, and controls in the initial protocol, sponsors can submit possible planned changes that alter the study design based on preliminary data collected. The most beneficial aspect of an adaptive study design is that when a protocol amendment is made that falls within the planned changes submitted, it is considered a non-substantial or administrative amendment [16]. In this case, the amendment may not need as substantial review by regulatory committees and can be implemented much quicker.

Another way to increase inclusivity in a study protocol is by eliminating the disease-specific aspect in a histology-agnostic clinical trial, otherwise termed a basket trial [17]. This is much more common in oncology clinical trials as sponsors aim to investigate their drug or treatment regimen against a specific genomic alteration rather than a type of cancer. For example, an oncology trial might target patients with an EGFR-mutated tumor. Since many different cancers have EGFR mutations, there would be no need to target a specific tumor type. Therefore, the inclusion criteria may simply state that a patient should have a validated EGFR-mutated solid tumor to be eligible to enroll in the study. While it's not always possible to initiate, basket trials can allow for more patients to have the opportunity to enroll and sponsors can glean data from their novel treatment in multiple different diseases.

> **Figure 4. Basket trials define eligibility based on specific genomic alterations and can investigate a drug's effectiveness in several tumor types.**



Lastly, utilizing novel health technology to monitor patients and accurately capture data can be beneficial when appropriately incorporated into a study protocol. Mobile health solutions may contribute to ease of remote patient monitoring and eliminate the need for tedious data entry [18]. One example of how mobile health technology is integrated into study protocols can be found in cardiovascular clinical trials. Issuing wearable health technology to cardiovascular patients can remotely monitor different parameters such as heart rate, blood pressure, or even arrhythmia. This example can also address any adverse events in near real-time. If information regarding the conduct of wearable technology is included in the protocol, an in-person visit can easily become remote and the data can be seamlessly integrated into the EDC.

Figure 5. Employing digital health technology can empower patients, streamline patient management, and allow for effortless data collection.

Similarly, patient reported outcomes can be done remotely as well. Surveys can be conducted over the phone or even sent to the patients via email. Completion of the surveys can also be integrated directly into the EDC without the need for extraneous data entry. For example, Vial CRO's real-time eSource, EDC, and ePRO uses integrated workflow to remove the burden of inefficiency and redundancy during data collection. This technology also eases the communication gap between sites and study teams leading to a better overall clinical trial experience.

10. Conclusion

The study protocol is arguably the most viewed document by investigators, site staff, and sponsors throughout the duration of the study. Since the protocol defines the outcomes and productivity of the clinical trial, each section must be meticulously written to provide insight into a multitude of situations. Multiple regulatory bodies will review the protocol for clarity, ethical considerations, and feasibility prior to allowing the conduct of the clinical trial. Although adverse events and unforeseen circumstances can arise, several safeguards and strategies can be implemented into the protocol to prevent avoidable amendments and increase efficiency, lower costs and improve data generation to bring better therapies to the market.

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