FDA Executive Summary

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Patient Engagement Advisory Committee

Documents for

Patient Engagement in Medical Device Clinical Trials Meeting

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Introduction

The Food and Drug Administration (FDA) is responsible for protecting the public health by ensuring the safety, efficacy, and security of medical products. The Center for Devices and Radiological Health (CDRH) specifically assures that patients and providers have timely and continued access to safe, effective, and high-quality medical devices and safe radiation-emitting products. To support this mission and enable adequate evaluation of investigational medical devices, FDA requires valid scientific evidence which can include clinical trials.[1] A clinical trial or clinical study is any investigation in human subjects intended to discover or verify the effects of an investigational product. FDA believes clinical trials that better incorporate the patients' perspectives will be more likely to enroll and reach successful completion and that the information derived from those trials will be more meaningful and impactful to patients. Historically, medical device developers have worked with leading healthcare providers and researchers to design the clinical trial. This often results in clinical trials for medical devices that do not incorporate input from the patients in the design and conduct of the trial, capture outcomes important to patients, or adequately communicate trial results to the trial participants. A survey of 582 patients conducted by Avoca Quality Consortium found that on average participants did not feel that their healthcare providers had a good understanding of what it was like to be a patient with their condition.[2] Upon reviewing trials listed on ClinicalTrials.gov, Carlisle et al found that 481 (19%) of registered trials that closed or terminated in 2011 either failed to meet accrual goals (85% of expected enrollment) or were terminated early due to insufficient accrual.[3] This termination equated to more than 48,000 patients who were exposed to risk without yielding any gains in scientific knowledge. Hence, a movement is underway to include the patients'[*] voice in the development and evaluation of medical products.

Looking to implement innovative ways to improve trial participation, the clinical research industry has also been more open to engaging patients as research collaborators whose input can be essential to the overall success of the clinical trial.[4] Patient engagement refers to meaningful involvement of patients through the research cycle from the design to the implementation and dissemination of research results.[5] The goal of patient engagement is to produce clinical studies that are more patient-centric and relevant, leading ultimately to a greater trust in and uptake of study results by patients, providers and care partners making treatment decisions. Ultimately, patient-centered trials keep the things that patients value in focus during the design and conduct phase, asking what patients think, what they need, and what they want.[6] Listening effectively to patients at early stages may uncover patient-facing obstacles, facilitate effective planning and minimize cost as well as patient-burden during clinical trials.

[*] The term "patient" refers inclusively to people who receive health care services; family members, friends, and other care partners; and any consumers of health care. (http://aircpce.org/sites/default/files/PCM%20Principles_April182017_FINAL.pdf)

FDA has been actively working with patient groups as well as other stakeholders to foster the evaluation of patient preferences for benefits and the acceptability of risk to inform device-approval decisions.[7] The inaugural Patient Engagement Advisory Committee (PEAC) meeting offers another opportunity to obtain feedback and recommendations from patients and their care partners on ways to integrate the patient perspective in the conception, design, conduct of clinical trials, and dissemination of trial results.

History of Clinical Trials

The first documented clinical trials were born out of natural occurrences rather than planned experiments.[8] In 1600, James Lind noted that scurvy was prevented in one of three East India Ships that were supplied with lemon juice, thereby concluding that scurvy was caused by the absence of citrus fruit. Over time, researchers developed medical therapies such as penicillin and systematically tested the medication on themselves and a small number of patients .[8] With the introduction of the control group by Haygarth in the early 1800s and the concept of randomizing treatment assignment by Fisher in the early 1920s, additional building blocks for clinical trial designs were laid.[8] The concept of multiple investigators from different sites all following a common study protocol emerged in the 1930s-40s with studies on infectious disease conducted by the Veterans Administration in conjunction with the United States Armed Services.[8] As a result of centuries of clinical trial evolution, many approaches currently exist for evaluating investigational products, including randomized, controlled, multicenter clinical trials.

Despite the long history of clinical trial evolution, it was not until the mid-20th century that the ethical considerations in human research were addressed. Following the criminal medical experiments conducted by the Nazis on human subjects during World War II, many principles on the conduct of clinical trials were incorporated in the Nuremberg Code of 1949 and the Declaration of Helsinki in 1964. In the US, withholding therapeutic penicillin from African-American patients with syphilis during the Tuskegee syphilis experiment prompted the 1979 Belmont Report which detailed the principles of respect for persons, acting in the best interest of the patient (beneficence), and the importance of informed consent.[9] These clinical trial principles have been the tenets under which therapeutic and diagnostic devices have been evaluated in the United States.

Regulation of Medical Devices

Following the establishment of the Food, Drug, and Cosmetic Act (FD&C) in 1938 which placed medical devices under the regulatory authority of the FDA, the Medical Device Amendments of 1976 extended some of the testing requirements established for drugs to medical devices.[10,11] The FDA relies upon valid scientific evidence to determine whether there is a reasonable assurance that a medical device is safe and effective.[1] The pathway by which medical devices enter the US marketplace is largely defined and regulated by CDRH. CDRH, one of FDA's six product centers, is responsible for ensuring that safe and effective devices reach the market as quickly as possible while monitoring devices and radiological products currently on the market for continued safety and effectiveness. This legal authority to regulate both medical devices and electronic radiation-emitting products was established in the federal Food,

Drug, and Cosmetic Act. Final regulations developed to fulfill the provisions of the FD&C are codified in to the Code of Federal Regulations (CFR) [Title 21 CFR Parts 800-1299] and cover aspects of device design, clinical evaluation, manufacturing, packaging, labeling and post market surveillance of marketed products.[12] Medical devices are classified by risk as class I, II, or III, with class III devices having the highest level of risk. Class I (e.g., scalpels) or II (e.g., daily wear contact lenses) devices are lower risk devices with most class II devices requiring a premarket notification (i.e., 510(k)) for marketing in the US. Class III represents the highest risk (e.g., implantable heart valves) and is subject to the approval of a Premarket Approval Application (PMA). PMAs need to contain adequate valid scientific evidence, often including both non-clinical and clinical assessments, to provide a reasonable assurance of safety and effectiveness of the device. According to 21 CFR § 860.7(c)(2),

> valid scientific evidence is evidence from well-controlled investigations, partially controlled studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. The evidence required may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.

While well-controlled clinical trials are considered the gold standard for the evaluation of a disease intervention by the scientific community, randomization and control arms may be impractical or unethical for some device trials. For many investigational device evaluations, the device or the disease condition may warrant alternative approaches and increased flexibility in the design of the clinical investigation.[13]

Clinical Trial Design

In 21 CFR § 812.3, an investigation is defined as clinical investigation or research involving one or more subjects to determine the safety of effectiveness of a device.[14] In the US, the clinical data collected to evaluate an investigational medical device is generally conducted under an Investigational Device Exemption (IDE) clinical investigation.[†] Every clinical trial begins with the development of a clinical protocol. The protocol is a document that describes how a clinical trial will be conducted to ensure the safety of the trial subjects and integrity of the data collected. A clinical trial protocol must reflect both sound scientific rationale and local, national and, when applicable, international regulatory and human subject protection requirements. Historically, patients have entered the picture during the conduct of the trial and not during the design phase. However, a clinical trial has various design features that could

[†] The terms clinical investigation and clinical study are used interchangeably with clinical trial throughout this executive summary.

impact patient enrollment and retention in clinical trials—type of study, the enrollment criteria, study procedures and duration, and endpoints (i.e., study outcomes).

In an effort to minimize bias, negate the impact of confounders, and clearly show the effect of the experimental therapy, researchers may employ a sham-controlled, randomized, masked (i.e., blinded) clinical trial design. By randomly assigning people to the investigational device or to the control (i.e., conventional treatment or sham surgery) and not revealing the assignment to the participants or the observers (i.e., masked or blinded), the trial findings are less likely to falsely attribute benefits to the investigational device. While randomized, controlled clinical trials are methodologically preferred, oncology trials have shown that single-armed treatment trials (i.e., no control group) are often more attractive to patients who want to receive the investigational treatment and tend to accrue patients rapidly.[15] Kelly et al reported that patients were concerned that randomization may undermine "individualized care that acknowledges their unique medical histories."[16] For certain devices, a clinical trial may not be able to answer some of the critical questions related to its safety and effectiveness. Leveraging existing data sources such as registries may generate the necessary information for regulatory decisions and obviate the need for detailed clinical trials in some cases.[13] Several studies have suggested that the use of non-randomized, unmasked, or open designs may increase clinical trial enrollment.[17,18] In contrast to traditional trials, pragmatic and adaptive trial designs have been postulated as potential approaches to augment patient centeredness within a clinical trial setting.[19] Pragmatic trials recruit patients that reflect the real-world population affected by the condition addressed by the proposed treatment. Similarly, adaptive trials are thought to encourage a patient-centered focus by allowing features of the trial (e.g., target population, treatment arms, sample size, duration) to change as evidence accrues over the course of the trial. However, the impact of these designs on trial participation is unclear.[19]

The enrollment criteria for trial eligibility have also been noted as an important factor where patient input would be useful. Some healthcare providers have asserted that the enrollment criteria are needlessly narrow for many trials (e.g., excluding patients with any serious medical conditions), rendering few subjects eligible for a given trial even if there are many patients with the disease.[20] Including patients in the discussion of this trial parameter could lead to eliminating eligibility criteria that are not necessary to protect participants or to answer the research question. Broader eligibility criteria informed by patient input may increase the likelihood that clinical trial results are applicable to the general population of patients with the underlying condition.

In addition, some clinical trialists have noted that excessive data or unnecessary trial procedures are impediments to patient participation in trials. It is estimated that the median number of study procedures per protocol has almost doubled over the years, according to Getz et al.[21] In a survey of

almost 6,000 patients, 37% thought their medical care would be better if they did not enroll in a trial and 22% believed that trial participation would cause them to "be treated like a guinea pig."[22] Other trial features such as a treatment washout, a time period during which patients have their systems free of the medication, can also prohibit patient participation in the trial. Price et al reported on Parkinson's disease patients enrolled in a trial that required a washout from medication.[23] This washout led to the sudden inability to walk, leaving patients in danger and humiliated when performing daily tasks. Despite requesting hospital admission the night before, patients were denied the request due to its financial cost. This lack of incorporating patient concerns in the trial design likely impacted trial enrollment. Moreover, trials that span many years or ones that have frequent clinic visits may be too burdensome for patients and could discourage participation as well.

Another critical element of a clinical trial is the endpoint(s) of interest. An endpoint is a precisely defined variable intended to reflect an outcome of interest that is statistically analyzed to address a particular research question.[24] Despite the importance of carefully selecting trial endpoints, many of the endpoints used in trials may not reflect real-world patient care.[25] If the endpoints are not meaningful to patients, the patients may be less likely to see value in trial participation. For example, quality of life, independence, and symptom resolution are clinical endpoints cited as being important to patients.[26] However, commonly used patient-reported outcomes (PROs) such as quality of life may not relate specifically enough to the diseased population especially in rare diseases. This concern could lead to dilution of the relevant PRO effect. In addition, determining outcomes that are meaningful for children of different ages in the context of a specific study is challenging.[27] For example, patient-valued measures of function may be different in preschoolers versus high school aged children. Hence, proactively working with different patient groups could lead to an adaptation of existing PRO measures or development of new PRO measures to capture the concepts most important to patients.[28]

Informed Consent Process

Federal regulation, stipulates that all clinical trials regulated by the FDA including those that support clinical investigations for research or marketing permits for products must comply with the protection of human subjects.[29] No investigator may involve a human being as a participant in research unless the investigator has obtained the legally effective informed consent of the participant or the participant's legally authorized representative, except for emergency research.[30,31] The consent process, to be valid, must be based on factual information presented in an intelligible fashion and in a setting in which the patient or guardian is able to make a free choice, without fear of reprisal or prejudicial treatments.[8] Obtaining consent involves but is not limited to informing the participant that the trial involves research, participation is voluntary, whom to contact about the trial, the purpose of the study, the procedures performed during the trial, the potential risks and/or benefits of participation, extent of record confidentiality, compensation, and alternative treatments available.[32] There may be potential problems of understanding what the research is about, what their role in the research will be and how the research will be used. Falagas et al reported that many patients may be enrolling in clinical trials

without adequately understanding fundamental concepts such as voluntariness and the risks associated with participation.[33] However, studies have shown that too much detail in the informed consent document as well as not enough detail may decrease participant satisfaction with the consent process.[34-36] Recent clinical trials have partnered with patients and care partners to shape the informed consent process including modifying the document to foster comprehension among potential participants with a range of health literacy levels and to assuage concerns among potential control group participants about not receiving the investigational intervention.[37]

While it is assumed that the individual who signs the consent form does so with full understanding of its content, misunderstandings can occur because of literacy challenges as well as incorrect or inadequate language translations .[38] Populations particularly vulnerable to these concerns are the elderly, children, those with learning disabilities, immigrants, and those of lower socioeconomic status. In addition, the racial and ethnic backgrounds of potential participants shape the communication needs or approach that should be considered when administering the informed consent process. For example, racially and ethnically diverse populations may have distrust of the medical establishment and clinical research, different cultural values, and language barriers that impact their perspective on the trial and the consent process. Bowers et al trained a group of racially and ethnically diverse lower income adults to review recruitment documents and the informed consent form and make recommendations to researchers on ways to make the information more understandable. Bowers et al found that when these revised documents were presented to other members of the same community, the patients were more likely to say they understood the documents, more likely to ask for more information about the study and more likely to say they would participate in the research.[39] By engaging patients from diverse backgrounds to help shape the informed consent documents as well as the recruitment materials, clinical trials may be more likely to effectively enroll participants from those communities.

For children under the age of 18, consent/permission to participate in a clinical trial has to be obtained from parents. If the child is above 7 years of age, then “child assent” is also mandatory. It can be argued that children have rights to receive information, to be listened to, have their wishes and feelings taken into account and to give or withhold consent if judged competent to do so. Difficulty arises when parents give their consent while the child refuses to assent. Attitudes towards children’s participation in health care decision making may impact decisions about their clinical trial participation.[40] Similarly, elderly participants may need care partners or other family members to aid in the consent process. Because there is no consensus on how to evaluate patient comprehension of informed consent documents, Hallinan et al recommend that sponsors should ensure the documents are at the appropriate reading level, use simplified language, include a glossary of terms in lay language, and avoid terms that confuse research with treatment.[41] By ensuring the informed consent process is personalized to patients and that they understand the informed consent document, it is likely that clinical trials would have greater retention rates and adherence to clinical trial protocols. By engaging patients at the design

phase to aid in the selection of an appropriate comparator; to discuss and mitigate concerns regarding randomization and masking; to determine the burden of various procedures and study visits; and to enhance the informed consent process, the integrity of the clinical trial results may also improve. Ignoring clinical trial design features that are important to patients may have downstream consequences such as poor study enrollment.

Trial Recruitment, Enrollment and Retention

A significant number of clinical trials fail to meet recruitment and enrollment goals, which leads to delays, early trial termination, or the inability to draw meaningful conclusions at trial completion due to loss of statistical power.[4] Poor or differential patient participation in clinical trials can lead to sampling biases, delayed trial completion, inconclusive study results, and increased study costs.[42] As a result, many clinical trials fail to accomplish the goal of demonstrating safe and effective medical products. Aggressive marketing has not worked to increase the recruitment or retention of participants.[23] For example, in the UK, 55% of trials fail to reach the required sample size. Between 2001 and 2014, Price noted that 21% fewer patients enrolled in trials and the retention rates dropped by 30% in the U.S. This decline is in contrast to the 3-fold increase in clinical trials registered at Clinicaltrials.gov during that same time period.[23] Hence, dedicated recruitment (i.e., generating interest in trial and conducting screening visit), enrollment (i.e., informed consent process), and retention (i.e., keeping patients in the trial for the duration of the trial) strategies are essential aspects of clinical trials.

The recruitment strategy must be one that reaches the greatest number of potential participants since the number of participants will decrease following screening, and progressively decrease at enrollment and still further by study conclusion. In a clinical trial of pregnant patients, 62% wanted to hear about the trial from their healthcare provider compared to 36% wanting to hear about it from research staff.[43] Another survey of 1,000 adults across the nation found that 86% of respondents believed that doctors should discuss clinical trials with patients as part of standard care; however, less than 20% report that their doctor has ever talked to them about participating in a trial.[44] Hence, successful trial recruitment involves developing and implementing a plan that allows for the most effective dissemination of research material about the clinical trial to eligible patients and healthcare providers.

Understanding clinical trials is also an important factor for recruiting, enrolling, and retaining patients in trials. Comis et al surveyed 1,000 adults and found that approximately 40% of adults do not understand clinical trials and as such may not be aware that a clinical trial is an available option for them.[45] In addition, recruitment tactics may need to be tailored based on the disease and the patient populations' demographic characteristics.[46] Crowd-sourcing, a method of soliciting contributions from a large group of people usually online, may facilitate studies with narrow inclusion criteria or in studies of patients with rare diseases. UyBico et al conducted a systematic review focused on recruiting vulnerable groups

and found that community outreach was the most effective recruitment in only two of 16 studies (13%), while mass mailings, telephone calls, and media campaigns were most successful in 8 of 18 studies (44%).[47] Mahon et al suggested that recruitment is not a "one size fits all" approach, but instead a site specific recruitment action plan to strategically apply tactics to the site's institution, community and patient population is needed. [20]

Low patient accrual rates, especially underrepresented groups (e.g., racial and ethnic minorities) impact a clinical trial's validity, the strength of the findings and the generalizability of the results to the intended use population. In some cases, studies that have not included different subgroups of patients have failed to detect potential harms or negative effects and may concomitantly magnify health inequalities. Racial and ethnic minorities bear a disproportionate burden of morbidity and mortality relative to other groups and often have limited access to care. Despite this burden, they are less likely to participate in cancer clinical trials. The National Institute of Health (NIH) Revitalization Act stipulates that every effort should be done to achieve participation rates for racial and ethnic minorities that mirror their distribution in the U.S. population or in geographic regions. In addition, Congress included section 907 in the Food and Drug Administration Safety and Innovation Act of 2012 which gives FDA direction to evaluate the issue of under-representation of racial and ethnic minorities, women, and the elderly in clinical trials and take action.[48-50] However in 2013, only 2% of National Cancer Institute (NCI) sponsored clinical trials focused on minorities which is substantially lower than their 36.3% representation of the U.S. population.[51] Individuals who participate in clinical research are more likely to be better educated and to have higher income levels than nonparticipants. Individuals of a higher socioeconomic status may be more aware of ongoing research, have more opportunities to participate, and face fewer economic and logistical barriers to participation.[51] Patients with low socioeconomic status (e.g., household income less than $50,000) often have less formal education, lower literacy, poor health care coverage, have negative experiences with the healthcare system, and have poorer health outcomes.[46] Clinical research coordinators have indicated that low literacy is a deterrent to them, preventing them from recruiting patients from that group.[52] Researchers may fail to consider the impact of child or elder care, immigration status, travel costs and the complexity of travel to the research site, job absences, and family commitments play on trial participation, particularly on patients with less financial resources.[53] Ensuring that participants are reimbursed in a timely way and avoid having them invest their own money to participate in a clinical trial would increase the likelihood of recruiting and retaining patients from diverse socioeconomic backgrounds. The delay in reimbursement could cause participants to feel undervalued or that the trial is unorganized, sparking decreased compliance and participation. By anticipating these barriers in the design of the trial, sponsors can provide reassuring messaging, establish appropriate participant expectations and decrease costs of the study.

Racial and Ethnic Minorities

Many racial and ethnic groups also have fear and distrust of the healthcare complex and the clinical trial enterprise. A survey of African-American residents of Detroit found that lack of trust of medical research and the belief that as minorities they bear most of the risks of medical research were the major impediments to clinical trial enrollment.[54] Corbie-Smith et al found that African-Americans were more likely than Whites to believe that physicians would not fully explain the details of research participation, with 25% of African-Americans voicing distrust in physicians.[55] Paskett et al also concluded that minority populations commonly cite mistrust of medical research to explain their lack of interest in clinical trials participation.[56] Among African-Americans and Latinos, trust in the health care system and their physician are strongly associated with willingness to participate in clinical trials.[57] Perceptions of the health care settings where the trial takes place can also influence the decision to participate.[58] For example, historically segregated healthcare settings may have lingering negative perceptions in local communities of color. In addition, the proposed mistrust of minority populations may be influenced by the effect of human enslavement and other historical exploitations that spill over into the healthcare experience.[59,60]

Uneven or unequal recruitment may also occur due to unconscious bias by providers. Smedley et al speculated that physician biases do affect treatment decisions.[61] Similarly, van Ryn and Burke found that physicians were more likely to have negative impressions of their African-American patients than of their White patients and are likely to believe that African-American patients are less intelligent and educated than are their White patients. Their study also found that physicians believed that African-Americans are two thirds as likely to be adherent to complex therapeutic regimens compared to their White patients.[62] However, Wendler et al found that minorities were as willing to participate in clinical trials as Whites but that they are not asked to participate.[63] Some researchers suggest that White study coordinators may be afraid or anticipate a lack of trust and may avoid approaching racial and ethnic minority patients.[52]

Once enrolled in a trial, studies show that patients from various demographic groups have high attrition rates.[64] A study of community-based women which included African-Americans, non-Hispanic Whites, and Mexicans/Central Americans found that staff diversity; providing transportation, snacks or meals, and childcare; and giving reminder phone calls and emails kept the attrition rate at 10% at 12 months.[65] An academic cancer center catchment area with the highest percentage of Latinos and Native Americans in the nation was selected for strategies to increase enrollment for minorities in cancer clinical trials. Enrollment was increased dramatically by providing information and training about trial protocols and support to healthcare providers and researchers; creation of nonprofit organizations that streamline administrative and regulatory burdens; increasing research physicians and staff throughout the region and increased opportunities for patients to access trials in their own communities rather than having to travel long distances out of state; expanded medical translation services; and encouraging physicians to promote acceptance of clinical trials for their patients.[51] Strategic promoters to overcome key barriers

can increase awareness of clinical trials, and can improve the equitable representation of ethnic minorities in clinical trials. Hence, building trusting relationships with minority communities may aid in ensuring that investigational devices have adequate data to inform the entire population that will be using the devices.

Age Factors

Both children (younger than 18 years) and the elderly (age 65 years and older) react differently to therapeutic interventions, present challenges with gaining informed consent, and are subject to specific diseases. People over age 65 years make up the majority of patients with chronic conditions and are the fastest growing segment of the world population.[66] However, these patients are often under-represented in all phases of clinical trials.[67] While the elderly account for approximately 65% of all new cancer cases, only 25-36% of patients over 65 years participate in cancer trials.[68,69] By involving patients and their care partners, trials can develop a program of reminders geared toward older patients to help them improve adherence to the protocol, allow extra time for visits and recruitment, and provide communication aids such as visual images instead of text, and sound amplification devices to ensure adequate communication.[70]

Although children comprise 25% of the US population, Pasquali et al found greater than 10 times as many adult trials registered at ClinicalTrials.gov compared with pediatric trials.[71] The relatively lower number of trials in children compared with adults is likely related to the relative rarity of disease, disease heterogeneity, lack of research infrastructure, ethical issues in pediatric research, and difficulty identifying valid clinical endpoints.[72,73] Researchers have developed video games such as the "the Paper Kingdom" to teach children about clinical trials and encourage their participation (http://www.youtube.com/watch?v=_sZP18DrTZ4). Tailoring interaction methods in ways that are age appropriate (e.g., texts, social media) may lead to better engagement of pediatric patients throughout the clinical trial. Swartz et al. conducted a randomized controlled trial in inner-city children with asthma comparing environmental control education, allergen-proof encasements, pest extermination, and an air filter to a control group that only received standard therapy.[74] They used a community based participatory research approach and achieved high enrollment and retention rates, 86% and 70% respectively. Assessments of the effects on children may require lengthy follow-up studies which pose increased challenges with retaining children in clinical trials. By engaging with the children as well as their care partners during all phases of the trial, researchers can develop flexible approaches that account for both the child's and the care partner's/parents' needs.

Gender

Women have traditionally been underrepresented in clinical trials. Promoting women's participation in clinical trials better elucidates sex-specific differences in the pathogenesis, clinical presentation, and treatment response of acute and chronic diseases. Underrepresentation of women in clinical trials not only calls into question the generalizability of research findings but also fosters sex-based inequity in the

development of clinical guidelines, care delivery algorithms, and health-related public policies. Zanni et al surveyed 40 women with or at risk for HIV about factors that facilitate or impede engagement in clinical research.[75] They found that the main reasons women did not participate involved lack of information about the studies, insufficient visit payments, too many study visits, and fear and resistance to some testing or medications. These women endorsed the following factors as sustaining participation: receiving updates via website or newsletter, receiving payment for visits, good communication with staff, and having childcare during the visit.[75] By engaging with women during the design and implementation of a clinical trial, practical considerations for patient retention can be prioritized. Trial participants have busy lives and the logistics of participating can keep them from making the trial a priority. Barriers such as the inability to take off from work, transportation to and from the research site, distance from the research site, frequency of visits and the occurrence of clinic visits on holy days (e.g., Fridays) may limit the participation of certain groups of patients. Other commitments such as childcare or caregiver responsibilities can also hamper active and consistent participation in trials. Clinical trial coordinators who effectively recruit diverse patients often implement patient-sensitive changes to the trials such as extending the hours the clinical site is open, providing childcare, offering home visits, and including families and care partners in conversations about the trial. Sharma et al encourages researchers to invest time in understanding the lifestyle of the patient population that they are studying prior to designing the clinical trial protocols.[4] Patients providing input in developing study protocols which are complementary to their life experiences could lead to better trial retention rates.

Communication of Evidence

Clinical trials represent a significant investment by all involved — including trial participants, sponsors, and researchers. Data are generated throughout the clinical trial lifecycle, but results are often not published in a timely manner, and data is often not shared beyond the original investigators. Clinical trial data is considered the property of the investigators and sponsors with no real opportunity for other researchers to access the data. A recent study found that fewer than half of trials funded by the National Institutes of Health were published within 2.5 years of study completion.[76] Patients, healthcare providers, and researchers are making decisions with access to a limited number of trial data, reflecting only a fraction of the relevant clinical evidence that could be available. Data sharing is becoming increasingly more common in some areas of clinical research (e.g., genomics); however, individual, patient-level clinical trial data sharing is less common, presumably due to patient privacy concerns.[76]

The Institute of Medicine (IOM) report, *Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk*, recommends guiding principles and a practical framework for clinical trial data sharing, and making data

from scientific data available with or without restrictions—for secondary uses, which include re-analyses, new analyses and meta-analyses. The types of data the IOM recommends to share are: summary data, individual participant data, and metadata. The IOM suggests that trial participants and the general public should have available to them a "brief non-technical overview twelve months after study completion."[77] They also suggest that individual participant data (de-identified) could be released in a subset of the full data 6 months after publication and a full post-regulatory data package 18 months after product abandonment or 30 days after regulatory approval.[77] The report concludes that sharing data is in the public interest, but a multi-stakeholder effort is needed to develop a culture, an infrastructure, and policies that will foster responsible sharing.

Similarly, the International Committee of Medical Journal Editors (ICMJE) issued a requirement that the results of clinical trials must have a data sharing statement and clinical trials that begin enrollment as of January 1 ,2019 must include a data sharing plan in the trial's registration as conditions of consideration for publication in member journals, stating that it is "our ethical obligation to responsibly share data generated in clinical trials because trial participants have put themselves at risk."[78] The United States Office for Human Research Protections has indicated that when appropriate conditions are met, the sharing of de-identified individual participant data from clinical trials does not require separate consent from trial participants (https://www.hhs.gov/ohrp/). Specific elements to enable data sharing statements have been adopted at ClinicalTrials.gov (https://prsinfo.clinicaltrials.gov/definitions.html).

Not only should trial results be shared with the public, data collected during the trial should be shared with patients, according to many researchers. Participants in trials said they wanted their results to be made available to them in a portable format. In addition, they indicated that they wanted the trial result presented to them before the general public is notified of the results and to communicate with them about premature trial closure.[23] While some patients are open to sharing their data including contact information in order to help another patient make a decision about trial participation or therapeutic interventions, other patients are concerned that sharing of the data will invade their privacy.[53] Having data transparency may help build trust and confidence between trial participants, trial investigators, and industry sponsors.[4] With further discussions with patients, determining the appropriate balance among protection of patient privacy, promotion of public health, and protection of commercial interests can be accomplished.

Approaches to Engaging Patients

Growing awareness of the importance of patient centeredness in research has influenced the establishment of the Patient-Centered Outcomes Research Institutes (PCORI) in the U.S. which has been

at the vanguard of involving patients as research partners, alongside researchers, to set research agendas, design studies and to decide what outcomes should be measured. This emphasis on patient centeredness in research stems from a belief that involving patients in decisions about how studies are designed and conducted improves research, making it more relevant to patients and reducing waste. It is also important for moral reasons based on the principle that the people whose lives are most affected by research should have a say.[79] Patients contribute their experience-based perspective, a perspective that is not provided by industry, researchers or by healthcare providers. However, there is a lack of evidence about the most effective ways to involve patients in clinical trial development.[79] Studies have shown patients engagement at the design stage led to increased study enrollment rates, improved retention, and the addition of relevant patient outcomes.[80]

Domecq et al cited various approaches to engaging patients which include focus groups, interviews, and surveys.[80] Patients responding to a survey wanted their input to be given equal consideration with that of other external stakeholders (investigators, sponsor, monitoring boards, etc.) with an active form of engagement of serving on a study board or an advisory council. To accomplish this goal, Kirwan et al recommended a commitment to funding patient participation on working groups and at conferences as well as increasing educational support and training provided to patients to ensure they understand the research agenda and goals.[81] Although time has been identified as a challenge for researchers and patient research partners, time is essential to developing and maintaining relationships that foster effective collaboration.[82] Engaged patients can educate study personnel about the community, attend meetings to obtain necessary approvals for the study, sit on data safety monitoring boards, and even present alongside researchers. Engagement can bring a sense of patients feeling supported, included and rewarded and thus more encouraged to participate fully.[23]

Some potential downsides to engaging patients may be patient frustration with the length of training, transportation, and attendance to meetings. Researchers and patients have voiced concerns about the engagement interactions being “tokenistic” (a false appearance of inclusiveness) that could result in devalued patient input.[83] In addition, companies may be less likely to devote resources to patient engagement in the absence of a clearly defined value proposition.[84] While Levitan et al have proposed estimates of this value, follow-up work is needed to estimate the impact of different forms of patient engagement, assessments in various therapeutic areas, and comparison with real-world case studies. PCORI has asserted six principals to guide the integration of patients in the clinical trial infrastructure:

(1) establishing supportive institutional policies;

(2) fostering supportive attitudes with the understanding that optimal partnerships evolve over time and are grounded in strong communication and shared goals;

(3) adhering to principles of respect, trust, reciprocity, and co-learning;

(4) addressing training needs of all team members to ensure productive communication;

(5) identifying and providing the resources and advanced planning required for successful patient engagement; and

(6) recognizing the value that research partnerships bring across all stages of research from research conceptualization through dissemination of findings.[81,85]

The Clinical Trials Transformation Initiative (CTTI) also published recommendations for effective engagement with patient groups around clinical trials which include clearly defining the expectations, roles and responsibility of all partners, managing real or perceived conflicts, clearly identifying the resources being committed.[86] By spending adequate time to build reciprocal relationships and fostering mutual respect, Levitan et al estimated that engaging patients could bring considerable financial value to clinical trials. Using a model of expected net present value, Levitan found that engagement avoids protocol amendments and/or improve enrollment, adherence and retention.[84] While there are no consensus recommendations for engagement or robust metrics for evaluating the value of engagement, most agree that it should be done.

Conclusions

While device trials cost less than pharmaceutical trials, study costs are estimated at a minimum $1 million and a major study could cost $10 million or more.[87] Estimates vary on the cost of a failed clinical trial, but figures range anywhere from $800 million to $1.4 billion. Companies that experience a failed trial often face plummeting stock prices, workforce reductions, closed research sites, and liquidation of some assets in the portfolio in order to preserve the core business focus.[88] Failed clinical trials that have inadequate enrollment or retention of participants translate into delayed or inhibited access to high quality, safe and effective medical devices of public health importance. By understanding approaches to actively engaging patients in the design, conduct, and communication of clinical trials, we hope to generate more high quality patient-focused trial results that better inform clinical decision making.

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